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Diastereoselective Introduction of an Allyl Group to the α'-Position of α-Substituted Pyrrolidines through the Intermediate Formation of *N*-Acyliminium Ions[1)]

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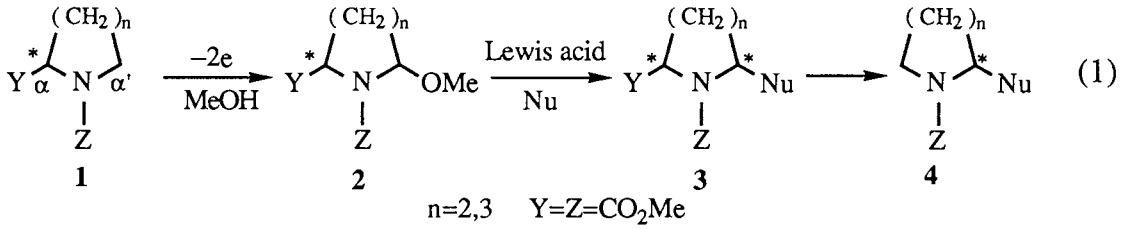
An allyl group was introduced to the α'-position of α-substituted pyrrolidines and the stereoselectivity of the allylation was investigated. High diastereoselectivities were achieved by modifying the α-substituents or the functional groups located at the nitrogen atom of pyrrolidine ring.

Regio- and stereo-selective introduction of substituents to piperidine and pyrrolidine rings is one of the current interests in the synthesis of nitrogen-heterocycles.[2)] As it has already been mentioned in the previous study, an optically active α-substituted piperidine derivative **4** (n=3) was successfully synthesized from an optically active pipecolic acid ester **1** (n=3) with high enantioselectivity. The new methodology used in the study consisted of three consecutive reactions, namely, an anodic α'-methoxylation of **1** (n=3), a stereoselective substitution of the α'-methoxy group by a nucleophile (Nu), and the removal of the α-substituent Y (a methoxycarbonyl group) of **3** (n=3) (Eq.1).[3)] This methodology was, however, not effective to the transformation of proline ester **1** (n=2) (46% e.e.) due to the low diastereoselectivity in the second step [from **2** (n=2) to **3** (n=2)].

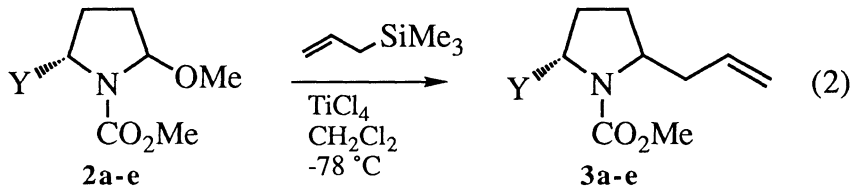
In the present study, the influences of α-substituents Y and the functional groups Z located at the nitrogen atom of **2** (n=2)[4)] on the stereochemistry of the second step were studied in detail in order to improve the diastereoselectivity and found that the substituents Y and Z possessed indeed remarkable influences on the selectivity.



(1)

Allyltrimethylsilane was used as the nucleophile since the stereochemistry of the products **3a-j** was able to be determined easily. The influences of α-substituents Y are shown in Table 1.[5)] The diastereoselectivity was not improved (d.e. 40%) even in the case in which Y was isopropoxycarbonyl group, namely, a group bulkier

than methoxycarbonyl group (runs 1 and 2). When Y was a carboxy group, the diastereoselectivity increased to 80% d.e. with almost exclusive formation of *cis* isomer (run 3), while the formation of *trans* isomer was dominant with 20% d.e. (run 4) in the case where Y was an acetoxymethyl group. Replacing the acetoxymethyl group by a bulky pivaloxymethyl group made the formation of the *trans* isomer predominant (40% d.e.)(run 5).



(2)

Table 1. Diastereoselectivity (d.e.) of allylation of **2a-e**

Run	**2a-e**	Y	**3a-e**	*cis* : *trans*	d.e./%	Yield/%
1	**2a**	CO_2Me	**3a**	73 : 27 [a)]	46	80
2	**2b**	CO_2 iso-Pr	**3b**	70 : 30 [a,b)]	40	80
3	**2c**	CO_2H	**3c**	90 : 10 [a,b)]	80	56
4	**2d**	CH_2OCOMe	**3d**	40 : 60 [c)]	20	58
5	**2e**	CH_2OCO t-Bu	**3e**	30 : 70 [c)]	40	58

a) The ratio was determined by GLC.
b) The products **3b,c** were transformed to **3a** in order to determine the *cis* /*trans* ratios.
c) See Ref. 6.

The *cis* selectivity is easily explainable by depicting an intermediate indicated in Fig.1a in which Z is imposed to be located on the *trans* position with respect to the substituent Y due to the steric repulsion between Y and Z. Nucleophiles may approach the intermediate advantageously from the direction *trans* with respect to Z. When Y is a carboxy group, its association with titanium tetrachloride results in formation of a bulkier group than an alkoxycarbonyl group and hence increasing in the diastereoselectivity (80%). On the other hand, when Y is an acetoxymethyl group, it interacts with the iminium cation at its carbonyl oxygen. Then, nucleophiles approach the cation center preferentially from the side opposite to the acetoxymethyl group (Fig.1b).

These results suggest that the functional groups Z on the nitrogen atom will show a larger influence on the diastereoselectivity than Y. The effects of Z are shown in Table 2[5)] where it is clearly shown that using bulkier Z makes the configuration shown in Fig.1a more favorable and hence brings about higher diastereoselectivity. The best selectivity was obtained in the case where was a pivaloyl group.

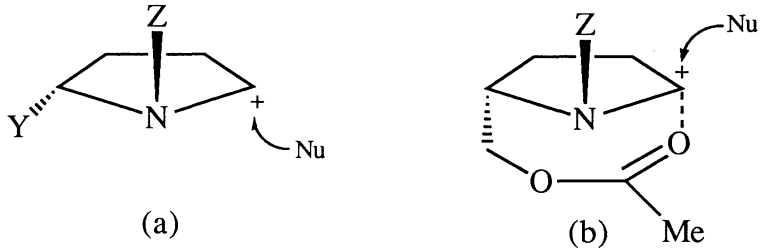
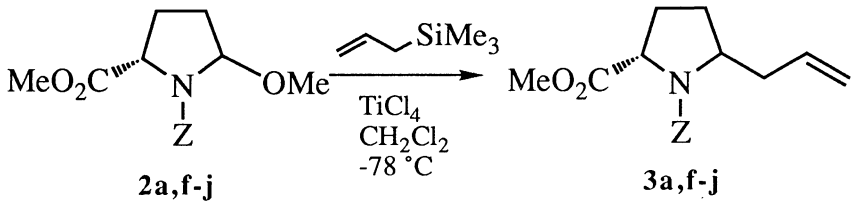


Fig. 1.



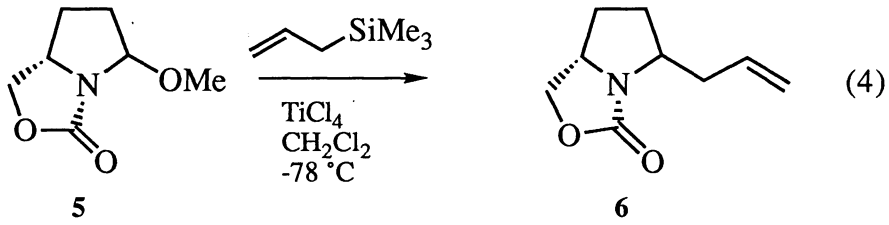
2a,f-j **3a,f-j** (3)

Table 2. Diastereoselectivity of allylation of **2a,f-j**

Run	**2a,f-j**	Z	**3a,f-j**	*cis* :*trans* [a]	d.e./%	Yield/%
1	**2a**	CO_2Me	**3a**	73 : 27	46	80
2	**2f**	CO_2CH_2Ph	**3f**	70 : 30 [b]	40	70
3	**2g**	CO_2 t-Bu	**3g**	95 : 5 [b]	90	35
4	**2h**	CHO	**3h**	80 : 20 [b]	60	80
5	**2i**	COMe	**3i**	90 : 10 [b]	80	70
6	**2j**	CO t-Bu	**3j**	≈100 : 0 [b]	≈100	75

a) The ratio was determined by GLC.
b) The products **3f-j** were transformed to **3a** in order to determine *cis* / *trans* ratios.

As shown in Table 1 and Fig.1b, using acyloxymethyl groups as Y resulted in the dominant formation of the *trans* isomer but with lack of perfectness. On the other hand, it was found that the connection of Z with Y by a chemical bonding was able to fix both Z and Y groups on the same side of the pyrrolidine ring and hence nucleophiles approached the cation center from the other side of the ring with almost exclusive *trans* selectivity (94% d.e.)(Eq.4).[4,7]



5 6 (4)

cis : *trans* = 3 : 97

Yield ; 70%

The enantioselective synthesis of 2-alkyl-substituted pyrrolidines will be achieved by using the new methodology found in this study.

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3) T.Shono, Y.Matsumura, K.Tsubata, and K.Uchida, *J. Org. Chem.*, **51,** 2590 (1986).

4) The stereochemistry of **2a-j** and **5** was not identified.

5) The identification of *cis* and *trans* of **3a** was carried out by converting **3a** to *N*,α-bismethoxycarbonyl-α'-acetonylpyrrolidine of which stereochemistry has been known.[3)]

6) The ratios of stereoisomers of **3d,e** were determined by HPLC after the substituent Y was hydrolyzed to a hydroxymethyl group. The identification of the structure of each stereoisomer was achieved by its conversion to **3a** through successive Jones oxidation and esterification.

7) The ratio of stereoisomers of **6** was determined after **6** was transformed to **3a** through successive hydrolysis, *N*-methoxycarbonylation, Jones oxidation and esterification.

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