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# Diastereoselective addition of some carbanions to an optically active trifluoromethyl imine derivative



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### ARTICLE INFO

### ABSTRACT

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Keywords: Trifluoromethyl 2-Ethoxy-1-phenylethyl-1-imine Trifluoroacetaldehyde Hetero Diels-Alder addition Mannich reaction Diastereoselective synthesis Optically active trifluoromethyl 2-ethoxy-1-phenylethyl-1-imine can react with various carbanions diastereoselectively, and in hetero Diels–Alder addition and in Mannich reaction, it can be derived to the corresponding products with high optical purity.

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### 1. Introduction

In recent years, various fluorinated compounds have been studied and developed in the field of pharmaceuticals [1].

Particularly, the interest for fluorinated  $\alpha$ - or  $\beta$ -amino acids has increased due to its importance for peptide synthesis [2,3].

Optically active trifluoromethylated  $\beta$ -amino acids or its derivatives were prepared by diastereoselective addition reactions of optically active imide or imine compounds with various carbanions. For example, the Mannich reaction of optically active trifluoromethyl *tert*-butylsulphinimide [4] and the Strecker reaction of optically active trifluoromethyl 2-methoxy-1-phenylmethyl-1-imine derived from optically active 2-methoxy-1-phenylethyl-1-amine (with optically active phenyl-glycinol as an ingredient) and trifluoroacetaldehyde [5] have been studied.

This paper presents a study on highly diastereoselective hetero Diels–Alder reaction and Mannich reaction by using optically active trifluoromethyl-2-ethoxy-1-phenylethyl-1-imine that is prepared from trifluoroacetaldehyde hydrate (2,2,2trifluoroethanediol) and optically active phenyglycinol in high yield (Fig. 1).

### 2. Results and discussion

### 2.1. Hetero Diels-Alder addition of the trifluoromethyl imine (S)-1

The reaction of the optically active trifluoromethyl imine **(S)-1** and 4-methoxy-2-trimethylsililoxy-1,3-butadiene (Danishefsky's diene) were reacted in the presence of Lewis acid, however in the case of Yb(OTf)<sub>3</sub> or BF<sub>3</sub>-OEt<sub>2</sub> low diastereoselectivity was observed.

On the other hand, when  $ZnCl_2$ ,  $ZnBr_2$ , or  $ZnI_2$  was used, the reaction proceeded with high diastereoselectivity and with moderate yield in non-polar solvents such as  $CH_2Cl_2$ , as shown in Table 1. However, in those cases, the absolute configuration of the 6-position on piperidine ring was reversed in the case of using Yb(OTf)<sub>3</sub>.

Table 2 shows the influence of the reaction temperature and the amount of Lewis acid for the case of  $ZnBr_2$ . No improvement of diastereoselectivity was observed in a temperature interval from -40 °C to 40 °C. Moreover, when varying the amount of the Lewis acid, yield and diastereoselectivity showed the best result at 50 mol% of  $ZnBr_2$ .

### 2.2. Mannich reaction of the trifluoromethyl imine (S)-1

As for the reaction of the optically active trifluoromethyl imine (S)-1 with corresponding lithium enolates prepared from various ester derivatives, the  $\beta$ -lactam derivatives **5** were obtained

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Fig. 1. Preparation of the optically active trifluoromethyl imine derivative (S)-1.

## Table 1 Hetero Diels-Alder addition of the optically active trifluoromethyl imine (S)-1.



Ent.	Lewis acid	Solvent <sup>a</sup>	Condition	Yield (%)	Selectivity (de %)
1	Yb(OTf) <sub>3</sub> (10 mol%)	CH₃CN	$0 {}^\circ C  imes 24  h$	60	11 <sup>b</sup>
2	Yb(OTf) <sub>3</sub> (10 mol%)	THF	$-20^{\circ}C \times 24h$	49	21 <sup>b</sup>
3	Yb(OTf) <sub>3</sub> (100 mol%)	THF	$-40^\circ C  imes 16h$	41	21 <sup>b</sup>
4	BF3 OEt2 (100 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	$-80^\circ C  imes 16h$	8	9 <sup>b</sup>
5	BF3 OEt2 (100 mol%)	Tol	$-80^\circ C  imes 16h$	Trace	_
6	BF3 OEt2 (100 mol%)	THF	$-40^\circ C  imes 16h$	62	27 <sup>b</sup>
7	$ZnCl_2$ (100 mol%) <sup>c</sup>	THF	$-20^{\circ}C  imes 16h$	8	22
8	$ZnCl_2$ (150 mol%) <sup>c</sup>	CH <sub>2</sub> Cl <sub>2</sub>	$0^{\circ}C \times 16 h$	21	50
9	ZnCl <sub>2</sub> (150 mol%) <sup>c</sup>	Tol	$-20^\circ C  imes 16h$	7	31
10	ZnCl <sub>2</sub> (150 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	$-40^\circ C  imes 16h$	22	87
11	ZnCl <sub>2</sub> (150 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	$rt \times 16 h$	39	96
12	ZnBr <sub>2</sub> (150 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	$rt \times 16 h$	39	94
13	ZnI <sub>2</sub> (150 mol%)	$CH_2Cl_2$	$rt \times 16h$	41	94

<sup>a</sup> The imene (S)-1 (1.30 mmol) in solvent(6 ml).

<sup>b</sup> Anti-form comformation.

<sup>c</sup> Used a solution of ZnCl2 in THF (0.5 M).

### Table 2

Influence of the reaction temperature and of a Lewis acid's amount.



Ent.	Lewis acid	Solvent	Condition	Yield (%)	Selectivity (de %)
14	ZnBr <sub>2</sub> (150 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	$-10^\circ C  imes 16h$	35	96
15	ZnBr <sub>2</sub> (150 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	$0^{\circ}C \times 16 h$	32	91
16	ZnBr <sub>2</sub> (150 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	rt  imes 16 h	39	94
17	ZnBr <sub>2</sub> (150 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	$40 ^\circ C  imes 16  h$	30	97
18 <sup>a</sup>	ZnBr <sub>2</sub> (150 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	$rt \times 16 h$	39	95
19 <sup>b</sup>	ZnBr <sub>2</sub> (150 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	$rt \times 16 h$	37	96
20	ZnBr <sub>2</sub> (100 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	$rt \times 16 h$	44	97
21	ZnBr <sub>2</sub> (80 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	$rt \times 16 h$	41	97
22	ZnBr <sub>2</sub> (50 mol%)	CH <sub>2</sub> Cl <sub>2</sub>	$rt \times 16 h$	46	98
23	$ZnBr_2$ (20 mol%)	$CH_2Cl_2$	$rt \times 16h$	33	96

 $^{a}$  2.0 volume of CH<sub>2</sub>Cl<sub>2</sub> was used.

<sup>b</sup> 1.5 eq. of Danishefsky's diene was used.

#### Table 3

Mannich reaction of the optically active trifluoromethyl imine (S)-1.



Ent.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Yield (%)		Selectivity (de %)		2S/2R	3S/3R
				5	6	5	6	5	6
26	Н	Н	<sup>t</sup> Bu	86	0	>99	-	-	-
30	Н	Н	<sup>i</sup> Pr	56	23	98	>99	-	-
28	Н	Cl	Me	11	0	>99	-	87/13	-
25	Н	Н	Me	0	57	-	95	-	-
24	Н	Me	Me	0	68	-	>99	-	80/20
29	Н	PhO	Et	3	72	-	>99	-	14/86



Fig. 2. Transition state models in Hetero Diels-Alder addition.

diastereoselectively as main products when the ester part was a methyl or an ethyl group (Table 3). In contrast, in case of *tert*-butyl ester, open chain  $\beta$ -amino acid derivatives **5** were obtained diastereoselectively. On the other hand, when the *iso*-propyl ester was used as substrate, a mixture of  $\beta$ -lactam derivatives **6** and open chain  $\beta$ -amino acid derivatives **5** was obtained. In the case of the reaction of the lithium enolate prepared from methyl propionate, the corresponding  $\beta$ -lactam derivative **6** was obtained with high diastereoselectivity in 68% yield, and the (3*S*, 4*S*)-configurated product was formed mainly.

### 3. Discussion

### 3.1. Hetero Diels-Alder addition of the trifluoromethyl imine (S)-1

In the case of the hetero Diels–Alder reaction using Yb(OTf)<sub>3</sub> or BF<sub>3</sub>-OEt<sub>2</sub> as a Lewis acid, the low selectivity might be explained by metal chelation only on a lone pair of the nitrogen, so the EtOCH<sub>2</sub> group does weakly shield the  $\alpha$ -face of the transition state.

On the other hand, when the zinc halide is used as the Lewis acid, the reason of high selectivity is considered that zinc was chelated on a lone pair of the nitrogen and a lone pare of oxygen as a five-membered ring system, so the phenyl group was strongly shielded at the  $\beta$ -face of the transition state (Fig. 2).

### 3.2. Mannich reaction of the trifluoromethyl imine (S)-1

As for the Mannich reaction, the high selectivity due to a sixmembered transition state of the imine **(S)-1** and the enolate **4**,  $\beta$ lactam derivatives **6** were produced from lithium amide of open chain  $\beta$ -amino acid **5**. In the case of open chain  $\beta$ -amino acid



Fig. 3. Transition state model for stereoselectivity in Mannich reaction.

derivatives as reactants, syn/anti (*S*/*R*) selectivity of the product is considered to originate from generation of E/Z mixture of the enolate anion (Fig. 3). But in the case of  $\beta$ -lactam derivative **6**, the configuration of 3-position on the  $\beta$ -lactam ring was migrated to stable conformation by the lithium amide of the product **6**. Therefore, the *trans*-configuration of the 3- and 4-position on  $\beta$ -lactam was mainly produced.

The progress of cyclization to the  $\beta$ -lactam is depended on  $R^2$  and  $R^3$  groups. For example, because the distance between anions on the nitrogen and carbon atom in the carbonyl group increases when both of  $R^2$  and  $R^3$  are bulky groups, the production of cyclic compounds is prohibited.

### 4. Conclusions

In hetero Diels–Alder addition and in Mannich reaction, optically active trifluoromethyl 2-ethoxy-1-phenylethyl-1-imine can react with high diastereoselectively.

### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2013.03.019.

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