ASYMMETRIC INTRODUCTION OF NUCLEOPHILES TO THE 2-POSITION OF PYRROLIDINE RING THROUGH *N*-ACYLPYRROLIDINIUM ION

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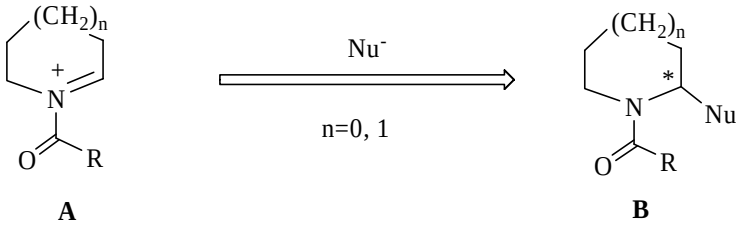
Abstract- Asymmetric carbon-carbon bond-forming reaction at the 2-position of a pyrrolidine ring was achieved. The reaction involved a chiral Ti(IV) catalyzed coupling between 1-methoxycarboyl-2-methoxypyrrolidine and silyl enol ethers to afford 2-substituted pyrrolidines with up to 53%ee.

Asymmetric introduction of carbon nucleophiles (Nu^-) onto cyclic *N*-acyliminium ions **A** (n=0, 1) has been attracting much interest because it provides an efficient route for elaboration of optically active piperidine and pyrrolidine derivatives **B** through easily available prochiral **A** (Scheme 1).[1-3] However, in contrast with some reports on the preparation of optically active piperidines **B** (n=1) by this method,[1] there have been no studies on the successful preparation of optically active pyrrolidines **B** (n=0).



A **B**

Scheme 1. Enantioselectve introduction of carbon nucleophile (Nu^-)

We report herein the result of our effort to achieve asymmetric carbon-carbon forming reaction between **A** (n=0) and Nu^- in the presence of chiral catalysts. The basic reaction we first surveyed is shown in Eq. 1 in which 1-methoxycarbonyl-2-methoxypyrrolidine (**1**)[4] as a precursor of **A** (n=0), 1-tirmethylsiloxystyrene (**2a)** as Nu^-, and (*R*)-BINOL-titanium dichloride complex (**3a**)[5] as a chiral catalyst were used (Eq 1).[6]

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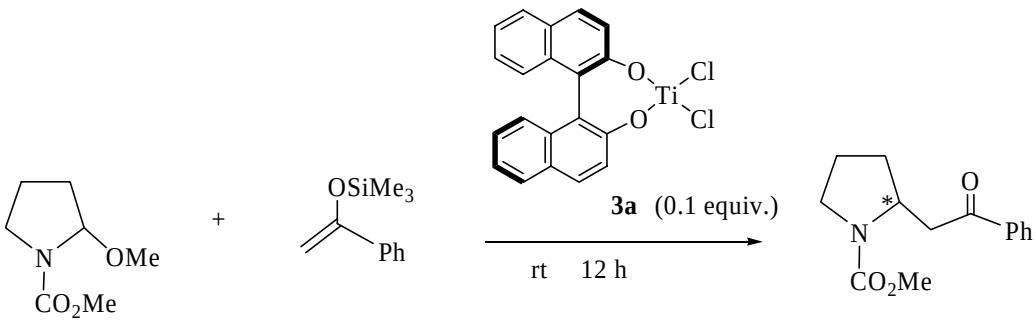
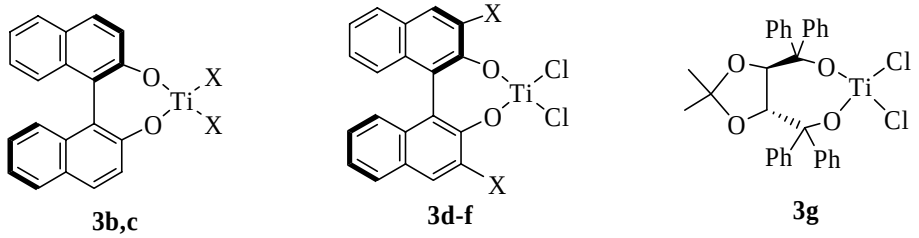


1 + **2a** (2 equiv.) → **4a**

solvent	Yield (%)	%ee
CH_2Cl_2	88	17
Et_2O	90	17
THF	90	5
MeCN	96	3

In this reaction was formed the aimed product (**4a**) in good yields with low %ee's which were dependent on the used solvent (Eq 1). The other chiral catalysts (**3b-g**)[7] in place of **3a** were also examined in CH_2Cl_2 but all of them gave disappointed %ee (Fig 1).

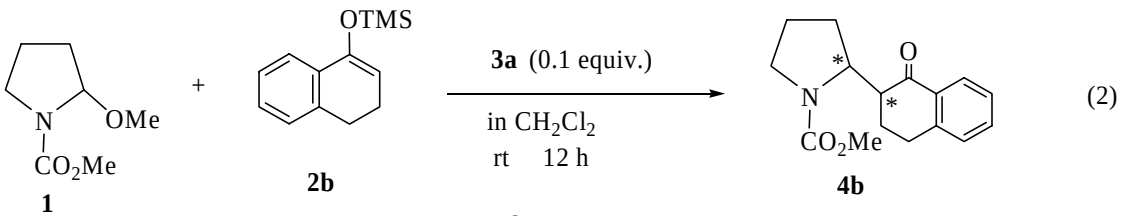


3b,c **3d-f** **3g**

	3b	**3c**	**3d**	**3e**	**3f**	
X	Br	OTf	Br	I	Ph	**3g**
Yield (%) of **4a**	96	99	93	70	9	21
%ee of **4a**	7	0	0	0	0	6

Fig. 1 Examined chiral catalysts

Then, we tried the reactions of **1** with 1-trimethylsiloxy-3,4-didehydronaphthalene (**2b**) in the presence of a chiral catalyst **3a** to afford **4b** as a mixture of diastereomers (Eq 2).

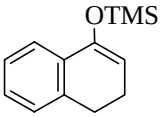
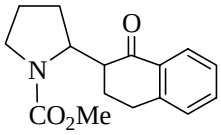
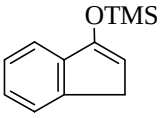
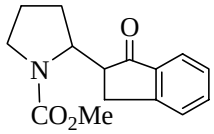
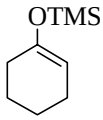
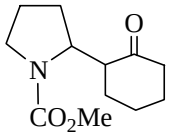
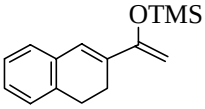
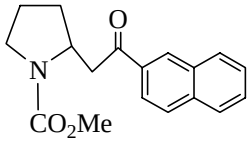
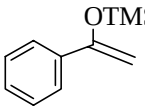
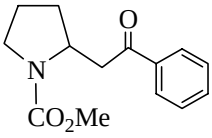
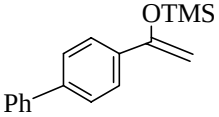
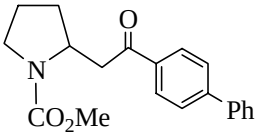
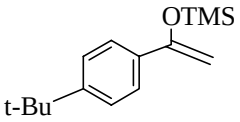
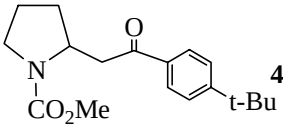
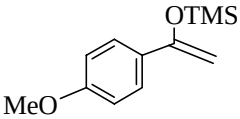
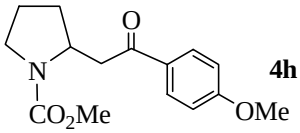


1 + **2b** → **4b**

solvent		
CH_2Cl_2	49% yield	a mixture of diastereomers 76/24 42%ee/6%ee
mesitylene	>99% yield	a mixture of diastereomers 84/16 53%ee/22%ee

Interestingly, both the yield of **4b** and the %ee of each stereoisomer were improved by carrying out the reaction in mesitylene as a solvent as shown in Eq. 2.[8] On the basis of this result, a variety of silyl enol ethers **2b-2h** was examined as Nu^- under conditions using mesitylene as a solvent. The results are shown in Table 1.

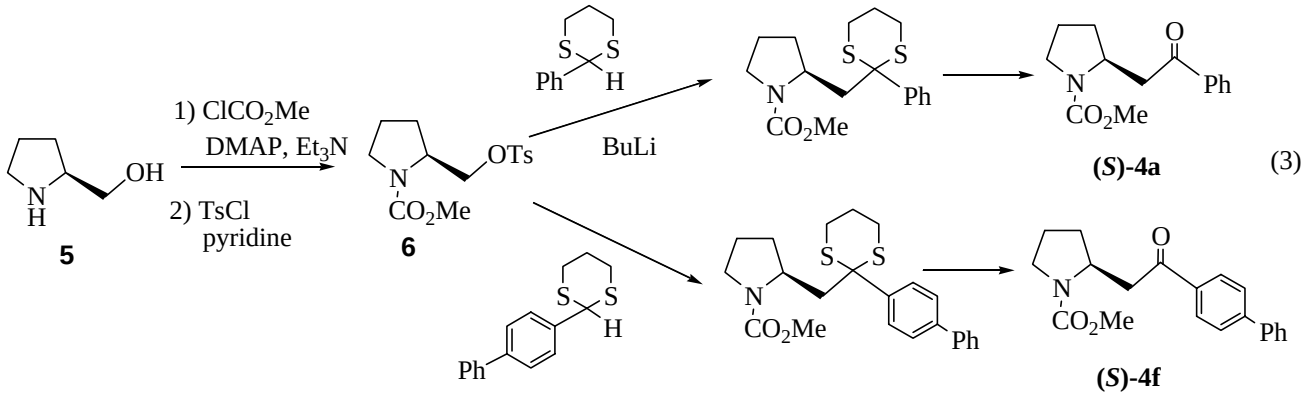
Table 1. The reaction of **1** with nucleophiles **2b-h** in mesitylene in the presence of **3a**[a]

Entry	Nucleophile	Product	Yield (%)	%de	%ee	
					Major	Minor
1	 **2b**	 **4b**	>99	68	53	22
2	 **2c**	 **4c**	98	76	33	15
3	 **2d**	 **4d**	94	50	30	13
4	 **2e**	 **4e**	84	–	36	
5	 **2a**	 **4a**	99	–	19	
6	 **2f**	 **4f**	91	–	44	
7	 **2g**	 **4g**	48	–	30	
8	 **2h**	 **4h**	78	–	33	

[a] **1** (1 mmol), **2a-h** (2 equiv.), **3a** (0.1 equiv.) in mesitylene (3 mL) at rt for 12 h.

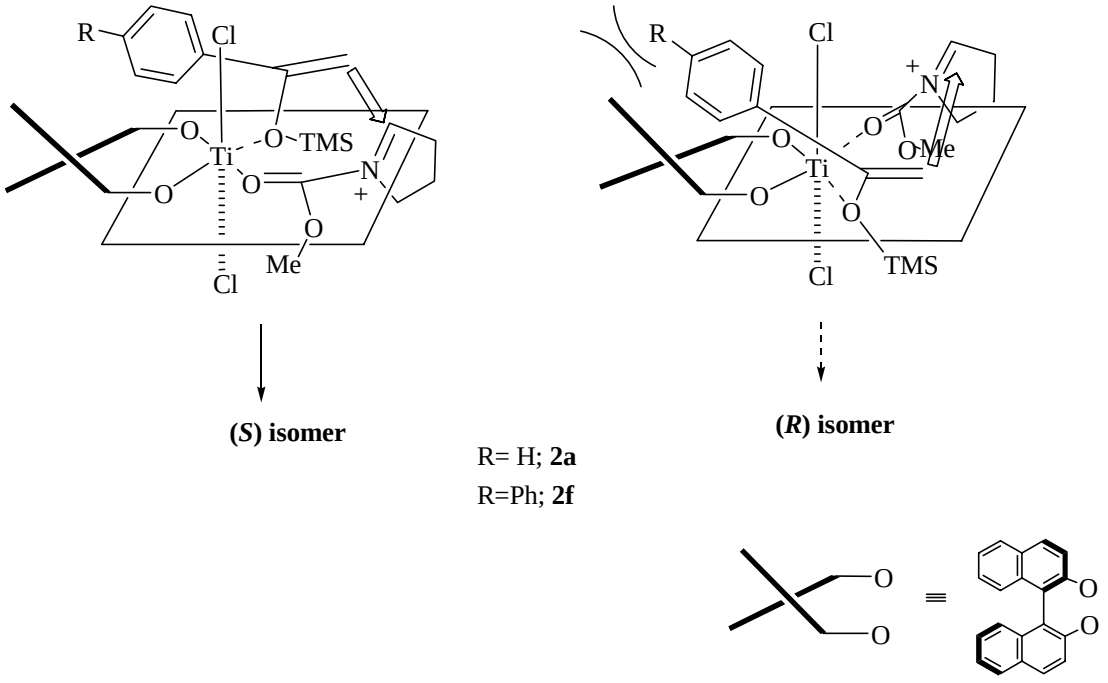
Although there was no data to speculate the absolute stereochemistry of stereoisomers of **4b-4d,** chiral chromatographic analysis showed the %de's and the %ee's of each stereoisomer as indicated in Entries 1-3 of Table 1.[9] The highest %ee so far obtained was 53% for major isomer of **4b** (Entry 1).

In order to rationalize the reaction mechanism, the absolute stereochemistry of products **4** must be clarified. Among **4a-h**, only **(*S*)-4a** and **(*S*)-4f** could be prepared from (*S*)-prolinol **5** according to the reported method (Eq 3).[10]



(3)

The enriched isomers of the products in the reaction of **1** with **2a** and **2f** in the presence of **3a** were identical with **(*S*)-4a** and **(*S*)-4f**, respectively.[11] On the basis of this result, we propose a mechanism shown in Scheme 2 for the enriched formation of **(*S*)-4a,f** in the reaction of **1** with **2a,f**.



Scheme 2. Proposed Mechanism

In conclusion, we presented herein the first method for asymmetric carbon-carbon forming reaction onto *N*-acylpyrrolidinium ion **A** (n=0, R=OMe). Although the observed enantioselectivities were low to moderate (up to 53%ee), further study to improve the stereoselectivity is under investigation on the basis of the proposed mechanism.

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5. K. Mikami and M. Terada, *Tetrahedron*, 1992, **48**, 5671; K. Mikami, Y. Motoyama, and M. Terada, *J. Am. Chem. Soc.*, 1994, **116**, 2812.
6. A typical procedure: Under an aerobic atomosphere, to a solution of *N,O*-acetal **1** (0.159g, 1mmol) and silyl enol ether **2a** (2 mmol, 385 mg) in mesitylene (3mL) was added a chiral catalyst **3a** (0.1 mmol, 0.197mL) at room temperature. After stirring for 12 h, the reaction mixture was quenched with ice-water and the organic portion was extracted with ethyl acetate. After the organic layer was dried over $MgSO_4$, the solvent was removed *in vacuo*. The residue was chromatographed on silica gel (ethyl acetate:*n*-hexane=1:3) to afford **4a** in 99% yield.
7. Catalysts **3b,c,g** were known: (**3b**)[5], (**3c**) K. Mikami, E. Sawa, and M. Terada, *Tetrahedron: Asymmetry*, 1991, **2**, 1403, (**3g**) K. Narasaka, N. Iwasawa, M. Inoue, T. Yamada, M. Nakashima, and J. Sugimori, *J. Am. Chem. Soc*., 1989, **111**, 5340; D. Seebach, R. Dahinden, R. E. Marti, A. K. Beck, D. A. Plattner, and N. M. Kuhnle, *J. Org. Chem*. , 1995, **60**, 1788. Catalysts **3d**, **3e**, **3f** were prepared from the corresponding chiral diols and dichlorotitanium diisopropoxide by the similar prosedure.
8. N. Iwasawa, J. Sugimori, Y. Kawase, and K. Narasaka, *Chem. Lett*., 1989, 1947.
9. The de's and ee's were determined by a chiral HPLC method, (**4b**) Daicel Chiralcel OD (4.6 mmϕ, 50 cm), *n*-hexane: *iso*-propanol=15:1 (v/v), flow rate: 1.0 mL/min, detection at 210 nm, retention time: 30 min and 60 min for one diastereomer and 37 min and 53 min for the other diastereomer; (**4c**) Daicel Chiralcel OD (4.6 mmϕ, 50 cm) + Chiralpak AD (4.6 mmϕ, 50 cm), *n*-hexane: *iso*-propanol=12:1 (v/v), flow rate: 1.0 mL/min, detection at 210 nm, retention time: 59 min and 73 min for one diastereomer and 64 min and 69 min for the other diastereomer; (**4d**) Daicel Chiralcel OD (4.6 mmϕ, 50 cm) + Chiralpak AD (4.6 mmϕ, 50 cm), *n*-hexane: *iso*-propanol=12:1 (v/v), flow rate: 1.0 mL/min, detection at 210 nm, retention time: 33 min and 44 min for one diastereomer and 35 min and 59 min for the other diastereomer.
10. K. Jones, K.-C. Woo, *Tetrahedron*, 1991, **47**, 7179.
11. The ee's were determined by a chiral HPLC method: Daicel Chiralcel OD (4.6 mmϕ, 25 cm), *n*-hexane: *iso*-propanol=15:1 (v/v), flow rate: 1.0 mL/min, detection at 210 nm, retention time: 10 min for (*S*)-**4a** and 12 min for (*R*)- **4a**; 19 min for (*S*)-**4f** and 28 min for (*R*)- **4f**.