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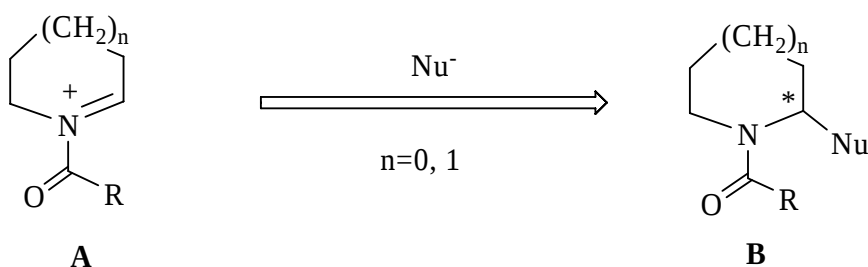
ASYMMETRIC INTRODUCTION OF NUCLEOPHILES TO THE 2-POSITION OF PYRROLIDINE RING THROUGH *N*-ACYLPYRROLIDINIUM ION

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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-methoxycarbonyl-2-methoxypyrrolidine and silyl enol ethers to afford 2-substituted pyrrolidines with up to 53 % ee.

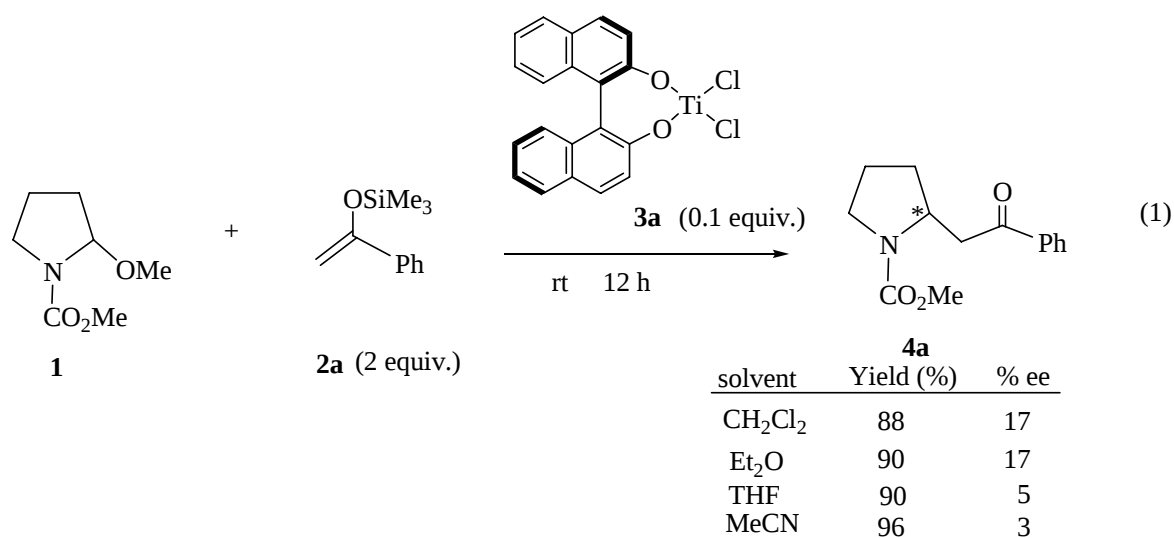
Asymmetric introduction of carbon nucleophiles (Nu^-) onto cyclic *N*-acyliminium ions (**A**) ($n=0, 1$) has been attracting much interest because it provides an efficient route for elaboration of optically active piperidine and pyrrolidine derivatives (**B**) through easily available prochiral (**A**) (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**) ($n=0$).



Scheme 1. Enantioselective 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-trimethylsiloxystyrene (**2a**) as Nu^- , and (*R*)-BINOL-titanium dichloride complex (**3a**)⁵ as a chiral catalyst were used (Eq. 1).⁶

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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 CH₂Cl₂ but all of them gave disappointed % ee (Figure 1).

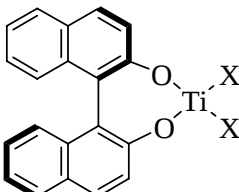
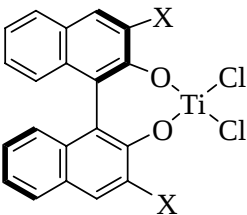
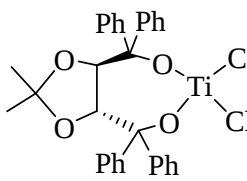
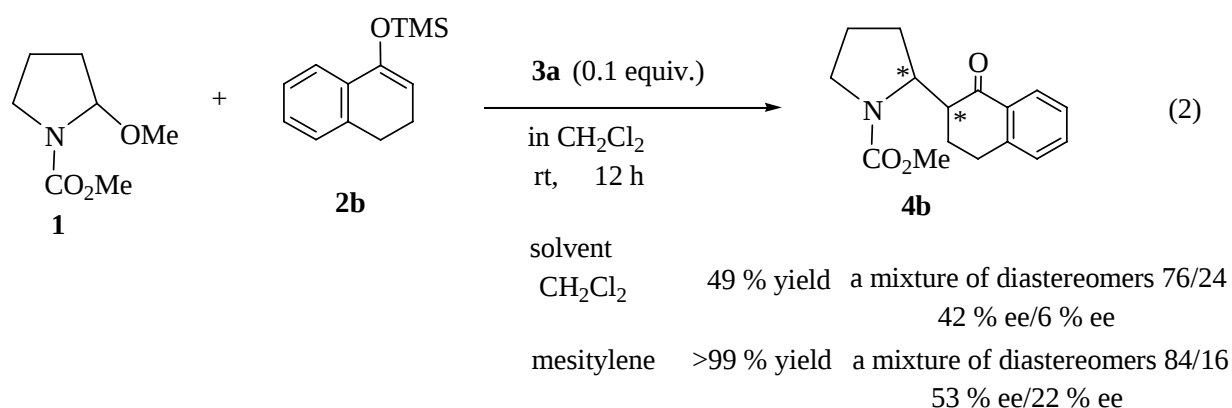
						
	3b	3c	3d	3e	3f	3g
X	Br	OTf	Br	I	Ph	
Yield (%) of 4a	96	99	93	70	9	21
% ee of 4a	7	0	0	0	0	6

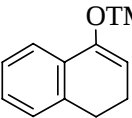
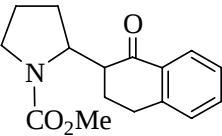
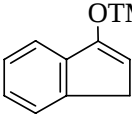
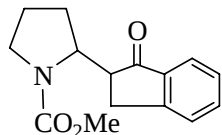
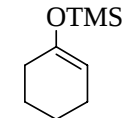
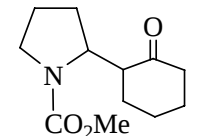
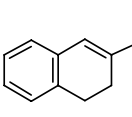
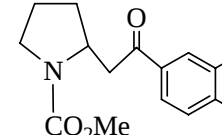
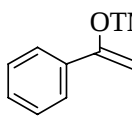
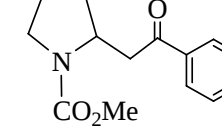
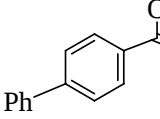
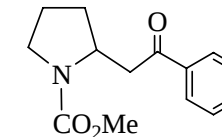
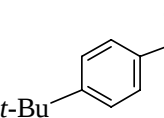
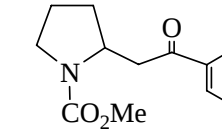
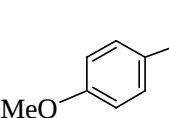
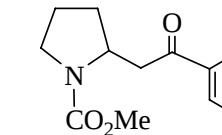
Figure 1 Examined chiral catalysts

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



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.

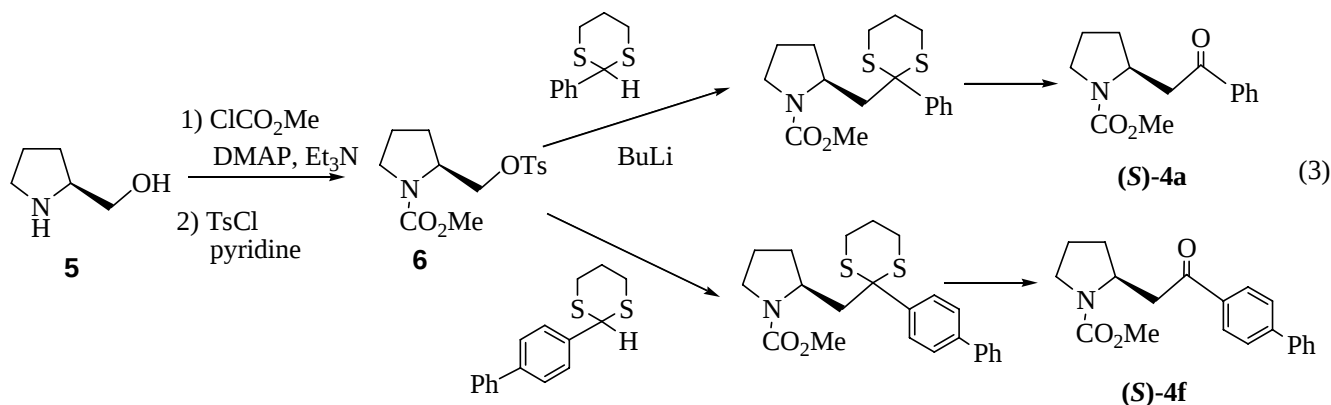
Table 1. The reaction of **1** with nucleophiles (**2b-h**) in mesitylene in the presence of **3a**^a

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

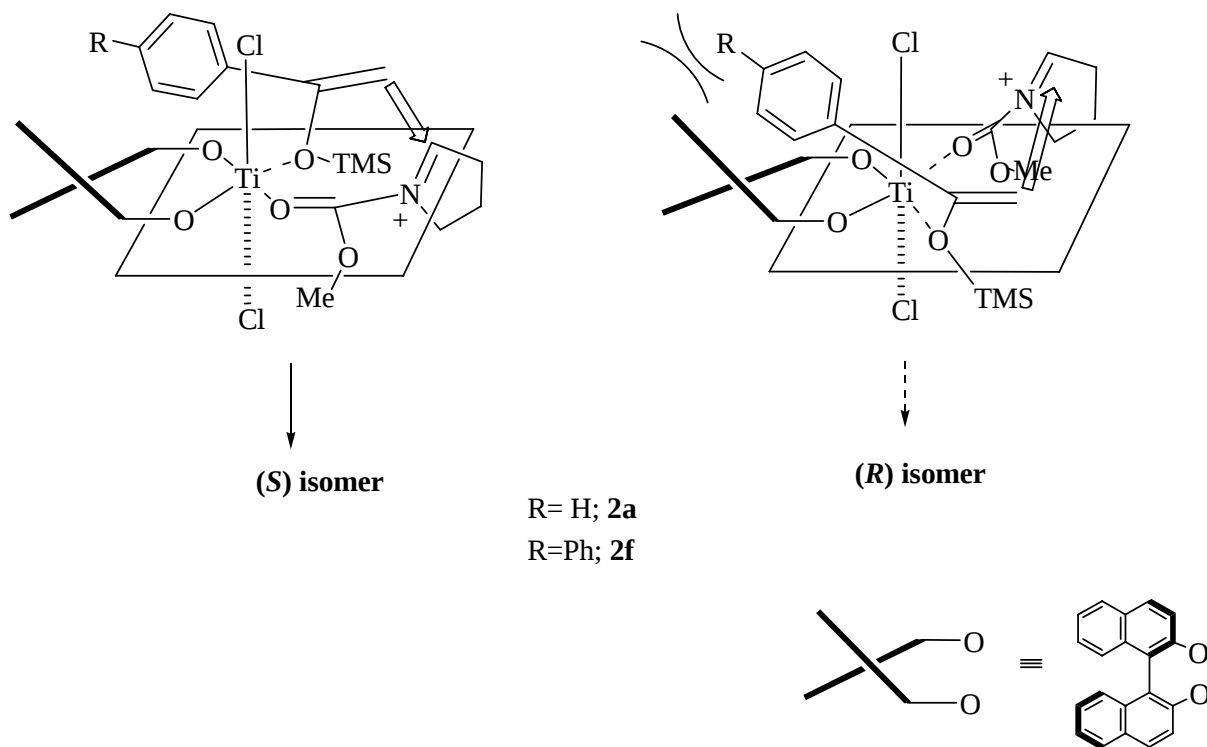
^a **1** (1 mmol), **2a-h** (2 equiv.), **3a** (0.1 equiv.) in mesitylene (3 mL) at rt for 12 h.

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**¹⁰ and (**S**)-**4f**¹⁰ could be prepared from (*S*)-prolinol (**5**) according to the reported method (Eq. 3).¹¹



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.¹² 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**.^{3,13}



Scheme 2. Proposed Mechanism

In conclusion, we presented herein the first method for asymmetric carbon-carbon forming reaction onto *N*-acylpyrrolidinium ion (**A**) ($n=0$, $R=OMe$), though 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.

ACKNOWLEDGEMENT

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6. A typical procedure: Under an aerobic atmosphere, to a solution of *N,O*-acetal (**1**) (1 mmol, 0.159 g) and silyl enol ether (**2a**) (2 mmol, 0.385 g) in mesitylene (3 mL) was added a chiral catalyst (**3a**) (0.1 mmol, 0.197 mL) 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 MgSO₄, 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.
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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 mm ϕ , 50 cm) + Chiralpak AD (4.6 mm ϕ , 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 mm ϕ , 50 cm) + Chiralpak AD (4.6 mm ϕ , 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. (**S**)-**4a**; $[\alpha]_{\text{D}}^{23}$ -23.7° (c1.1 CHCl₃). (**S**)-**4f**; $[\alpha]_{\text{D}}^{29}$ -28.4° (c 1.0 CHCl₃).
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