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Stereoselective Synthesis of Optically Active Substituted Piperidines and Pyrrolidines from Amino Acid Derivatives by Titanium(II)-Mediated Intramolecular Cyclization Reaction

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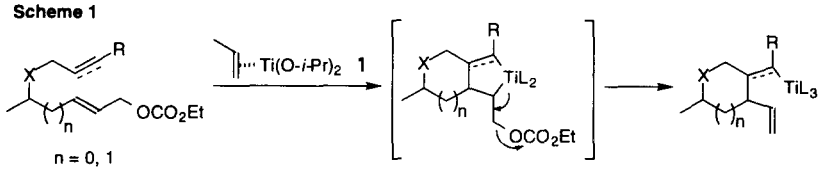
Abstract *: A versatile and high-yielding synthesis of optically active substituted piperidines and pyrrolidines from amino acid derivatives employing titanium(II)-mediated intramolecular cyclization of bis-unsaturated carbonates was developed.*

Recent publication from this laboratory has demonstrated the cyclization reaction of 2,7- or 2,8-bis-unsaturated carbonates mediated by titanium(II) complex (η^2-propene)Ti(O-*i*-Pr)$_2$ (**1**) which formally resembles the well-established metallo-ene reaction but most likely follows another reaction mechanism as shown in Scheme 1 (X = CH_2).[1] The ease of this intramolecular cyclization reaction and ready availability of **1**[2] led us to consider the feasibility of the reaction shown in Scheme 1 where X is NR, because the starting substrates might be easily synthesized in optically active form from readily available α- or β-amino acids (or their esters); thus, the reaction might open up an access to optically active piperidines and pyrrolidines.[3] Particularly, our concern was the stereoselectivity of the reaction, since the substituted piperidine and pyrrolidine moieties are found in a large number of naturally occurring alkaloid skeletons.[4]

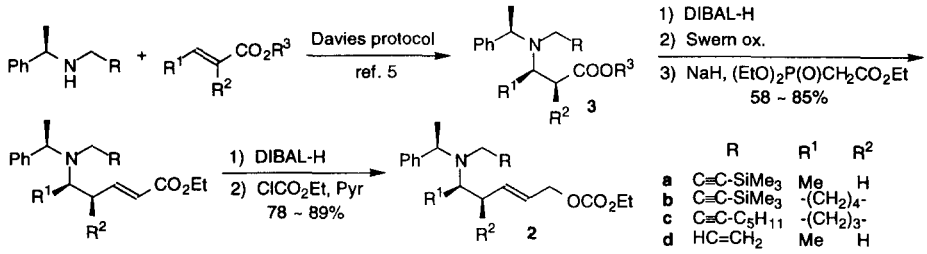
Scheme 1



The optically active N-propargylated or -allylated starting substrates **2a-d** for synthesizing piperidines were prepared according to the conventional reaction sequence shown in Scheme 2 from optically active N-propargylated or -allylated β-amino esters **3a-d** which were readily obtained by the Davies protocol.[5,6] The results of the reaction of **2** thus prepared with **1** are summarized in Table 1 (entries 1- 7).

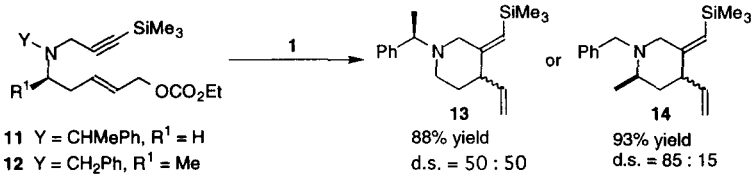
As shown in entry 1 in Table 1, the reaction of **2a** with **1** and the following hydrolysis provided the expected piperidine derivative **4** in excellent yield.[7] To our delight, the reaction proceeded with excellent diastereoselectivity of more than 90 % in favor of the cis diastereomer. Instead of hydrolysis, treatment with I_2 or benzaldehyde of the resulting alkenyltitanium intermediate afforded the expected **5** (entry 2) and **6** (entry 3),

Scheme 2



respectively. Similarly, high diastereoselective cyclization was attained with **2b** and **2c** providing, after hydrolysis, **7** (entry 4) and **8** (entry 5), respectively: thus, the reaction furnishes a new efficient method for constructing chiral cis-fused decahydroquinoline ring systems, which occur as subunits of natural products.[8] The cyclization of olefinic substrate **2d** also proceeded as expected, providing **9** by hydrolysis (entry 6) and **10** by iodolysis (entry 7) with 72% selectivity, respectively.

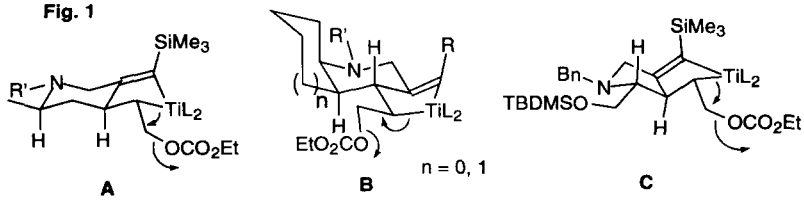
As shown below, we found that the cyclization reaction of **11** proceeded with 50:50 diastereoselectivity to afford **13**, while the reaction with **12** afforded **14** as two diastereomers in a ratio of 85:15. These findings strongly indicated that the stereogenic center having a R^1 group, but not an α-phenylethyl moiety, in **2** plays an important role in controlling the stereochemistry of the reaction.



Next, we investigated the feasibility of the reaction for the synthesis of pyrrolidines from α-amino acids by using L-serine as a substrate. Thus, N-propargylated compound **2e** and N-allylated compound **2f** were prepared from L-serine by the conventional reaction sequence shown in Scheme 3 and were subjected to the reaction with **1**. The reaction of **2e** and **2f** with **1** also proceeded with similar high diastereoselectivity as was observed for **2a** and **2d** to afford **15** (entry 8 in Table 1) and **16** (entry 9), respectively. Thus, the titanium(II)-mediated cyclization also furnished an efficient method for preparing optically active pyrrolidine derivatives from α-amino acids.

The stereochemical outcome of the reactions shown in Table 1 can be explained by assuming that the reaction proceeds *via* the transition state **A**, **B** or **C** shown in Fig. 1, *i. e.*, **A** for entry 1, **B** for entries 4 and 5 and **C** for entry 8.

Fig. 1



Scheme 3

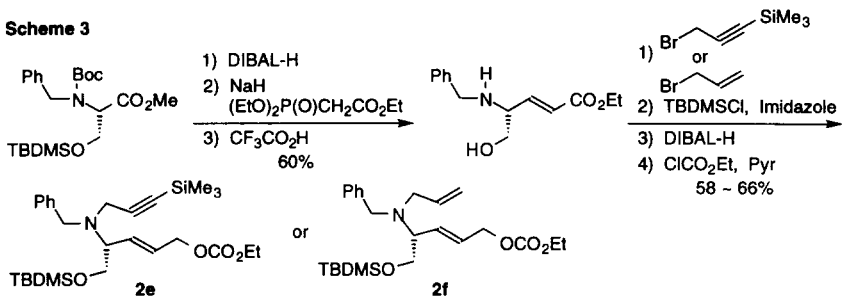
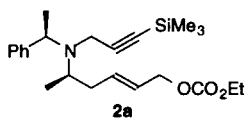
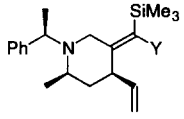
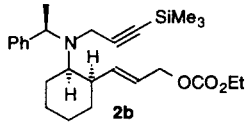
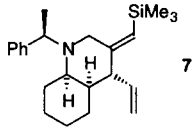
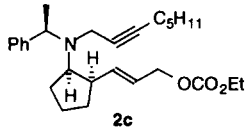
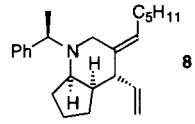
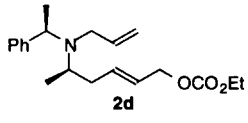
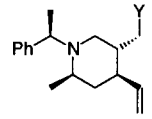
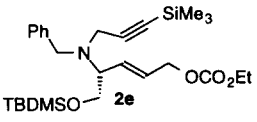
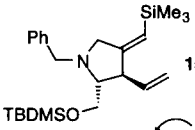
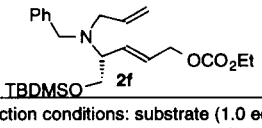
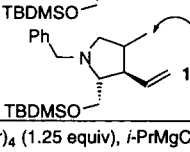


Table 1.[a] Synthesis of Optically Active Pyrrolidines and Piperidines from **1** and **2**

Entry	Substrate	Electrophile	Product: Main Product [b]		Isolated Yield [c] %	D.s. [d] (main : other)
	 **2a**					
1		H_2O	Y = H	**4**	93 (75)	91 : 9
2 [e]		I_2	Y = I	**5**	73 (60)	
3 [f]		PhCHO	Y = PhCH(OH)	**6**	68 [g]	
4	 **2b**	H_2O		**7**	90 (76)	92 : 8
5	 **2c**	H_2O		**8**	85 (71)	95 : 5
	 **2d**					
6		H_2O	Y = H	**9**	71 (42)	72 : 28 [h]
7 [e]		I_2	Y = I	**10**	55 (37)	
8	 **2e**	H_2O		**15**	77 (62)	87 : 13
9	 **2f**	H_2O	 N.D.[i]	**16**	76 [g]	74 : 26 [j]

[a] Reaction conditions: substrate (1.0 equiv), Ti(O-*i*-Pr)$_4$ (1.25 equiv), *i*-PrMgCl (2.4 equiv), -50 °C ~ r.t., 1h. [b] Stereochemistry was verified by ^{1}H NMR analysis (see ref. 9). [c] Total yield. Yield of the main product was given in parentheses. [d] Determined by ^{1}H NMR and/or GC analysis of the crude mixture. [e] 3.0 equiv of I_2 was used (r.t., 1 h.). [f] 1.5 equiv of PhCHO was used (r.t., 24 h). [g] The diastereomers could not be separated by column chromatography. [h] Four diastereomers were detected on GC analysis (ratio = 72 : 12 : 9 : 7). [i] Not determined. [j] Only two diastereomers were observed by ^{1}H NMR spectroscopy.

In summary, the cyclization reaction mediated by **1** provides an efficient and practical method for synthesizing optically active piperidines and pyrrolidines from readily available amino acid derivatives. Noteworthy is the fact that the products thus synthesized have olefinic substituent(s), thus allowing further structural manipulation.

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5. For the synthesis of **3a** and **3d**, see: Davies, S. G.; Fenwick, D. R. *J. Chem. Soc., Chem. Commun.* **1995**, 1109-1110. For the synthesis of **3b** and **3c**, see: Davies, S. G.; Ichihara, O.; Lenoir, I.; Walters, I. A. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1411-1415. The yield and diastereoselectivity are as follows; For **3a** (R^3 = Et); yield 97%, d.s. 95%; For **3b** (R^3 = *t*-Bu); 69%, 94%; For **3c** (R^3 = *t*-Bu); 80%, 83%; For **3d** (R^3 = Et); 93%, 97.5%.
6. Reaction of **3** with **1** resulted in the intramolecular nucleophilic acyl substitution reaction providing optically active piperidines or pyrrolidines having 1-hydroxybicyclo[n.1.0]alkane or a conjugated enone moiety, respectively, see ref 3h.
7. A typical procedure is as follows; To a solution of **2a** (67 mg, 0.17 mmol) and Ti(O-*i*-Pr)$_4$ (0.062 mL, 0.21 mmol) in ether (1.6 mL) was added *i*-PrMgCl (0.36 mL, 1.13 M in ether, 0.41 mmol) at -50 °C, and the reaction mixture was subsequently allowed to warm to room temperature. After being stirred for 1 h at this temperature, H_2O (0.21 mL) and NaF (0.3 g) were added. The resulting mixture was filtered through a pad of Celite and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (Wako C-200, hexane / AcOEt, 50 / 1) to give the pure main isomer **4** (40 mg, 75% yield) and a mixture of **4** and its diastereomer (9.4 mg, 18% yield).
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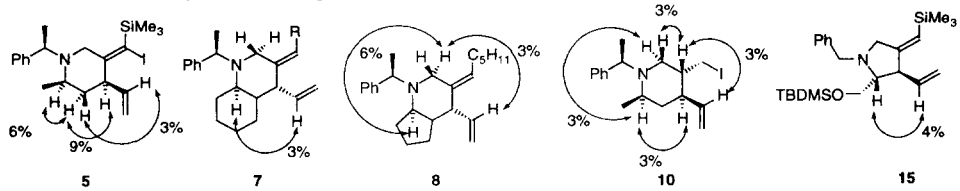
9. The stereochemistry of the main product was determined by NOE-difference experiments.



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