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## Stereocontrolled Intramolecular Michael-Aldol Reaction Mediated with Bu<sub>2</sub>BOTf and (TMS)<sub>2</sub>NH

Masataka Ihara, Takahiko Taniguchi, Masami Yamada, Yuji Tokunaga and Keiichiro Fukumoto\*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-77, Japan

Abstract: Treatment of keto-esters 1-5 with Bu<sub>2</sub>BOTf and (TMS)<sub>2</sub>NH caused a tandem Michael-aldol reaction to give polycyclic cyclobutanes 6-10 with high stereoselection. It was proved that the reaction was accelerated by the addition of Bu<sub>4</sub>NI.

We have recently developed a new methodology for the construction of polycyclic ring systems fused to cyclobutane by a tandem intramolecular Michael-aldol reaction. The cyclization reaction was carried out under two complementary conditions: TBDMSOTf-Et<sub>3</sub>N<sup>1</sup> and TMSI-(TMS)<sub>2</sub>NH.<sup>2</sup> It must be crucial for the tandem reaction to trap the aldol intermediate as a stable form. Keeping this in mind, we further examined various reaction conditions consisting of both Lewis acid and base. In this letter, we report the third method using a novel combination with Bu<sub>2</sub>BOTf<sup>3</sup>-(TMS)<sub>2</sub>NH to achieve a highly stereoselective assembly of polycyclic cyclobutanes.

Results of the intramolecular Michael-aldol reaction of keto  $\alpha,\beta$ -unsaturated esters 1–5 are summarized in Table 1. When 1 was treated for 18 h at rt with Bu<sub>2</sub>BOTf-(TMS)<sub>2</sub>NH in dichloroethane, 6 was obtained in 42% yield (62% yield based on the recovered substrate) as a single stereoisomer (entry 1). The reaction was accelerated with Bu<sub>4</sub>NI. The yield of 6 increased to 64% by addition of Bu<sub>4</sub>NI and, after the reaction, the starting material was almost consumed (entry 2). Reaction of 1 with TMSI-(TMS)<sub>2</sub>NH gave a 2 : 1 mixture of bicyclic compound 6 and its stereoisomer (entry 3).<sup>2</sup> The bicyclo[4.2.0]octane 7 was synthesized in 15% (33% yield based on the recovered substrate) from 2<sup>4</sup> with Bu<sub>2</sub>BOTf-(TMS)<sub>2</sub>NH (entry 4) and in 54% yield with Bu<sub>2</sub>BOTf-(TMS)<sub>2</sub>NH-Bu<sub>4</sub>NI (entry 5). Treatment of 2 with TMSI-(TMS)<sub>2</sub>NH provided 7 in only 25% yield (entry 6). By the same treatments carried out under three different conditions, 3<sup>5</sup> was converted into the corresponding bicyclic compound 8 in 21% yield (33% yield based on the recovered

entry	substrate	conditions <sup>a</sup>	product	yield (%) <sup>b</sup>
1		A		42 (62)
2	CO <sub>2</sub> Me	В	H CO <sub>2</sub> Me	64
3	1	С	6	91 <sup>c, d</sup>
4	$ \land \downarrow $	A <sup>e</sup>	H	15 (33)
5	CO <sub>2</sub> Me	B <sup>e</sup>	H, COoMe	54
6	2	С	7	25
7		A	NOE	21 (33)
8	CO <sub>2</sub> Me	В		17
9	3	С	8	9
10	MeO <sub>2</sub> C O	A		50
11		В	Hundred Com	53
12	4	С	9	70 <sup>c</sup>
13		۵	07549	31 (78)
13	$\bigwedge$	D	H H H	AC
14	O CO <sub>2</sub> Me	Б		40
15	3	С	10	57 °

Table 1 Intramolecular Michael-Aldol Reaction of Keto-Esters

a Conditions A =  $Bu_2BOTf$  (3.0 eq), (TMS)<sub>2</sub>NH (4.0 eq), ClCH<sub>2</sub>CH<sub>2</sub>Cl for 18 h at rt; conditions B =  $Bu_2BOTf$  (3.0 eq), (TMS)<sub>2</sub>NH (3.5 eq), Bu<sub>4</sub>NI (3.5 eq), CHCl<sub>2</sub>CH<sub>2</sub>Cl for 18 h at rt; conditions C = TMSI (1.2 eq), (TMS)<sub>2</sub>NH (1.5 eq), ClCH<sub>2</sub>Cl for 18 h at 0 °C - rt.

b Yield (in parenthesis) based on the consumed starting material.

c Ref. 2a.

d A 2: 1 diastereoisomeric mixture.

e Reaction was carried out for 2 h.

substrate) (entry 7), 17% yield (entry 8) and 9% yield (entry 9). Stereostructures of 7 and 8, which were obtained as a single stereoisomer, respectively, were determined by NOE experiments.<sup>6</sup>

Tricyclic compound  $9^{2a}$  and  $10^{2a}$  were obtained in medium yields from 4 and 5, respectively (entries 10-15).

The active species in the reaction using  $Bu_2BOTf$  and  $(TMS)_2NH$  would be 11 as Simchen and coworkers<sup>7</sup> considered a similar complex formation from TMSOTf and Et<sub>3</sub>N. Although the exact reason is obscure, a more hindered hydrogen is selectively abstracted to afford a thermodynamically stable enol ether 12 (Scheme 1). In fact, formation of the silyl enol ether was detected on TLC during the above reactions.<sup>8</sup>

Scheme 1



Usefulness of the above system was further demonstrated in the intramolecular Michael reaction. Namely, treatment of 13 with Bu<sub>2</sub>BOTf and (TMS)<sub>2</sub>NH in dichloroethane produced  $14^{2b}$  as a 1.3 : 1 diastereoisomeric mixture in 70% yield. No four membered compound was obtained by the reaction.

Scheme 2



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## **References and Notes**

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- 3. Inoue, T.; Mukaiyama, T. Bull. Chem. Soc. Jpn. 1980, 53, 174-178.
- 4. The substrate 2 was prepared as follows.



5. The substrate 3 was prepared as follows.



6. MMX energies calculated using PCMODEL<sup>9</sup> indicated that the streroisomes A were most stable one among four possible *cis*-fused bicyclic isomers A-D.



8. Productions of silyl enol ethers 15 and 16 were established by <sup>1</sup>H NMR spectroscopy after their isolation using preparative TLC.



9. PCMODEL (Version 4.0), Serena Software, P. O. Box 3076, Bloomington, IN.

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