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Diastereoselective Synthesis of β-Amino Esters by the Lewis Acid-Mediated Reaction of *N*-Tosyl Aldimines with Ketene Bis(trimethylsilyl) Acetals

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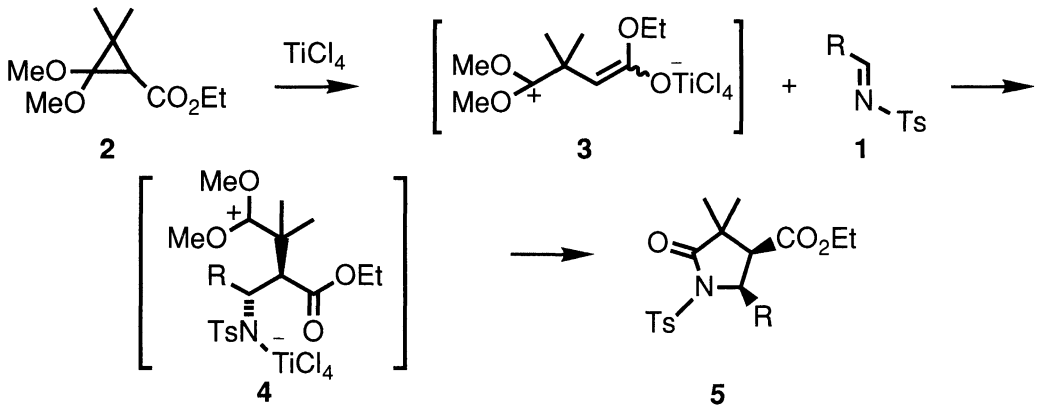
In the presence of titanium(IV) bromide, *N*-tosyl aldimines smoothly reacted with ketene bis(trimethylsilyl) acetals at low temperature, and upon esterification *anti*-β-amino esters were obtained selectively.

N-Sulfonyl imines have attracted increasing attention in organic synthesis because they are more reactive toward addition reactions than simple imines due to its electron-withdrawing sulfonyl group.[1,2] Recently, we have reported highly diastereoselective synthesis of γ-lactams by the titanium(IV) chloride-mediated reaction of *N*-tosyl aldimines **1** with ethyl 2,2-dimethoxy-3,3-dimethylcyclopropanecarboxylate (**2**).[3] In this reaction, among several types of imines examined, only *N*-tosylimines **1** exhibited high diastereoselectivity. As shown in Scheme 1, this reaction would involve ring-opened zwitterionic ester enolate **3**, which reacts with **1** to give *cis*-lactam **5** via *anti* β-amino ester intermediate **4**. On the basis of these results, we expected *anti*-β-amino ester would be selectively obtained by the Lewis acid-mediated reaction of *N*-tosyl aldimines **1** with ketene silyl acetals,[4,5] simpler ester enolate equivalents, and herein we wish to report the results.



Scheme 1.

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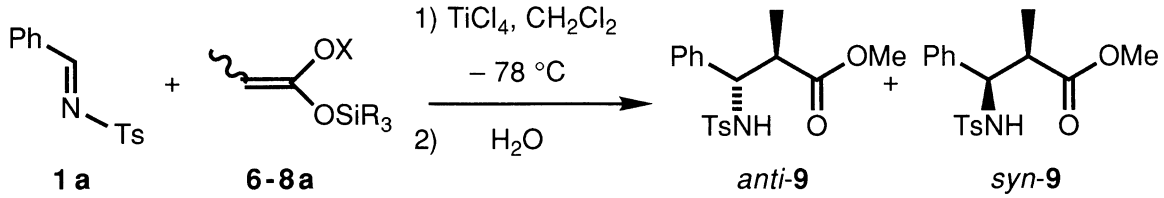


1a **6-8a** *anti*-**9** *syn*-**9**

Table 1. The Reaction of *N*-Tosyl Aldimine **1a** with Ketene Silyl Acetals **6-8a**

Entry	Ketene silyl acetal				Yield / % [a]	*Anti*: *Syn* [b]
		X	SiR_3	*E* : *Z*		
1	**6**	Me	$SiMe_3$	88 : 12	71	79 : 21
2				70 : 30	61	80 : 20
3				0 : 100	0	—
4	**7**	Me	Si^tBuMe_2	75 : 25	27	80 : 20
5 [c]	**8a**	$SiMe_3$	$SiMe_3$	—	89	91 : 9

a) Isolated yield. b) Determined by GLC. c) The initial product, β-amino carboxylic acid, was converted into methyl ester **9** by treatment with diazomethane. The yield and *anti* : *syn* ratio were determined as methyl ester **9**.

At first, we examined the reaction of benzylidene-*p*-toluenesulfonamide (**1a**) with three-types of propionic acid-derived ketene silyl acetals **6**, **7**, and **8a** (Table 1). Titanium(IV) chloride was used as an activator, and the reaction was performed at - 78 °C in dichloromethane. Ketene silyl acetal **6** gave *anti*-β-amino ester *anti*-**9** as a major product, as was expected (entry 1). The *E*:*Z* ratio of **6** did not affect the diastereoselectivity but the yield (entries 1-3). These results indicate that *Z*-**6** has no reactivity toward **1a** under these reaction conditions. *tert*-Butyldimethylsilyl acetal **7** was less reactive but gave almost the same *anti*:*syn* ratio of **9** (entry 4). The use of ketene bis(trimethylsilyl) acetal **8a**,[6,7] which has no *E*/*Z*-isomerism, improved not only the yield but also the selectivity (entry 5).[8] Next, we examined the effect of Lewis acid-activators. Titanium(IV) bromide exhibited slightly high selectivity (88% yield, *anti*:*syn* = 92 : 8), whereas trimethylsilyl trifluoromethanesulfonate was less selective (68% yield, *anti*:*syn* = 63 : 37), and tin(IV) chloride did not promote the reaction at all. The relative stereochemistry of **9** was determined by comparison of ^1H NMR data and GC retention time with those of authentic samples, which were individually synthesized from known β-lactams.[9]

On the basis of these results, we chose titanium(IV) bromide as an activator and tried the reaction of various *N*-tosyl aldimines **1** with ketene bis(trimethylsilyl) acetals **8**. The results are shown in Table 2. In all cases, *anti*-β-amino esters *anti*-**10** were selectively obtained.[10] The magnitude of selectivity depended on the substituent R^2 of **8**, and as the size of R^2 became larger the selectivity gradually decreased.[11] In the case of α,β-unsaturated imine (entry 5), 1,4-adduct **11** was also obtained.

A typical procedure is as follows: To a stirred solution of benzylidene-*p*-toluenesulfonamide **1a** (101 mg, 0.389 mmol) in dry dichloromethane (1 ml) was added drop by drop a solution of titanium(IV) bromide (0.42 mmol) in dichloromethane (0.45 ml) at room temperature. After the solution was cooled to -78 °C, ketene bis(trimethylsilyl) acetal **8a** (R^2=Me, 102 mg, 0.467 mmol) in dry dichloromethane (2 ml) was slowly added

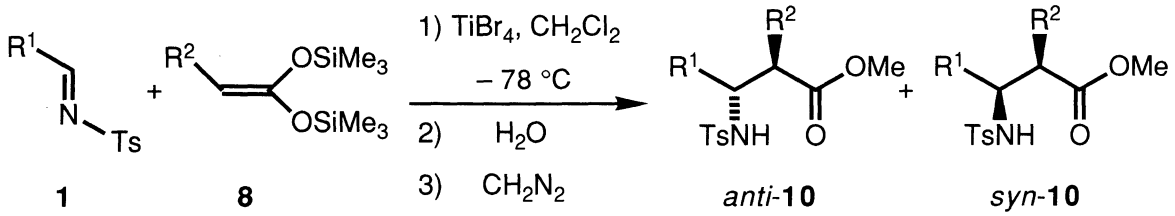
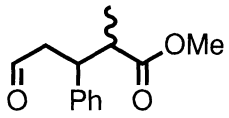


Table 2. The Reaction of *N*-Tosyl Aldimines **1** with Ketene Bis(trimethylsilyl) Acetals **8**

Entry	R^1	R^2	Yield / % [a]	*Anti*: *Syn*
1	Ph	Me	88	92 : 8 [b]
2	*p*-$MeOC_6H_4$		70	90 : 10 [c]
3	*p*-$NO_2C_6H_4$		85	91 : 9 [c]
4	2-Furyl		91	88 : 12 [b]
5 [e]	*trans*-PhCH=CH		22	87 : 13 [c]
6	Ph	Et	85	87 : 13 [b]
7		^{i}Pr	85	81 : 19 [d]
8		Ph	53	75 : 25 [c]

a) Isolated yield.
b) Determined by GLC.
c) Determined by ^1H NMR.
d) Determined by weight.
e) 1,4-Adduct **11** was also obtained in 34% yield.



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drop by drop (10 min). The reaction mixture was stirred for 2 h at -78 °C and quenched by adding water (1 ml) under vigorous stirring. The stirring was continued for 30 min, and then the mixture was allowed to warm to room temperature. To this mixture were added water (8 ml) and dichloromethane (15 ml), and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 8 ml). The combined organic layers were dried with anhydrous sodium sulfate. After filtration and evaporation, the crude β-amino carboxylic acid was dissolved in tetrahydrofuran (5 ml). To this solution was added a solution of diazomethane in ether until the yellow color of diazomethane became not to disappear. The excess of diazomethane was destroyed by adding an aqueous solution of acetic acid. After evaporation, the crude product was purified by TLC (eluent: hexane/CH_2Cl_2/ EtOAc = 5/5/1) to give an *anti*/*syn* mixture of β-amino ester **9** (120 mg, 88% yield based on the imine, *anti*: *syn*= 92 : 8).

N-Tosyl-protected β-amino carboxylic acids, the initial products of the reaction of **1** and **8**, can be easily converted into β-lactams by the method of Tanner and Somfai,[12] and the protection can be removed by treatment with sodium naphthalenide.[12] This reaction is considered to be useful for the synthesis of *N*-tosyl-protected β-amino carboxylic acid derivatives, valuable synthetic intermediates.

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References

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4) A recent review of Lewis acid-mediated reaction of ketene silyl acetals with imines: D. J. Hart and D.-C. Ha, *Chem. Rev.*, **89**, 1447 (1989).

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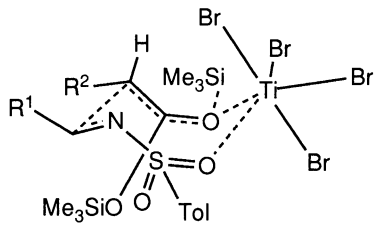
7) An example of the reaction of ketene bis(trimethylsilyl) acetals **8** with imines: J.-E. Dubois and G. Axiotis, *Tetrahedron Lett.*, **25**, 2143 (1984).

8) The mechanism of this reaction is not clear. But, diastereoselectivity of this reaction may be explained by assuming that the reaction proceeds through an eight-membered ring transition state like **12**. Transition state **12** seems to be more preferable than considerable transition states **13** and **14**.



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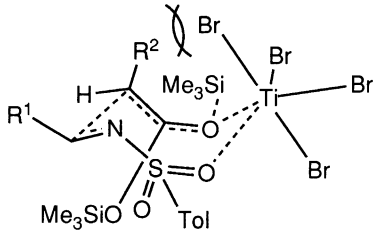

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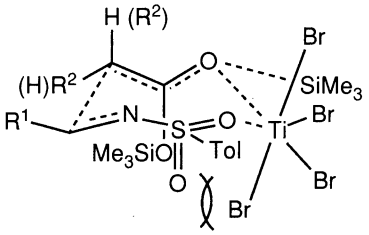

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9) *Anti*-**9** was synthesized from *trans*-3-methyl-4-phenyl-2-azetizinone[13] by methanolysis (HCl / MeOH) and tosylation (TsCl / pyridine). *Syn*-**9** was also synthesized from *cis*-isomer.[13]

10) The stereochemistry of other β-amino esters have not been determined unambiguously. But, in all cases except one case (Table 2 entry 8, in this case, the boiling point of the products are too high to perform GC analysis), the GC retention time of major isomer is shorter than that of the corresponding minor isomer. On the basis of these results, it is reasonable to consider that the major products are *anti*-isomers.

11) The tendency of stereoselectivity resembles that in the reaction of ketene bis(trimethylsilyl) acetals **8** with aldehydes: J.-E. Dubois, G. Axiotis, and E. Bertounesque, *Tetrahedron Lett.*, **25**, 4655 (1984).

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13) D.-C. Ha, D. J. Hart, and T.-K. Yang, *J. Am. Chem. Soc.*, **106**, 4819 (1984).

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