Highly trans-Selective Synthesis of β-Lactams by Tandem Phenoxide Anion-catalyzed Mannich-type Addition and Cyclization

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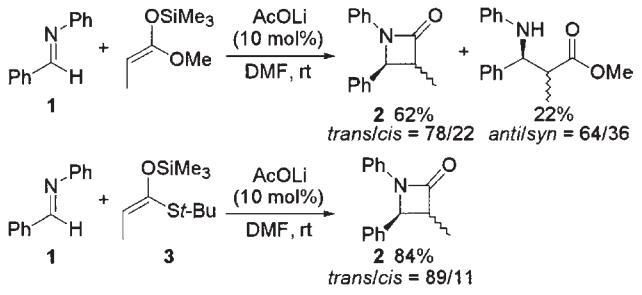
Highly trans-selective synthesis of β-lactams by tandem Lewis base-catalyzed Mannich-type addition and cyclization was established; that is, reaction of benzylideneanilines and trimethylsilyl enolates derived from *S*-ethyl thioates proceeded smoothly to afford the corresponding β-lactams in good to high yields with high trans-selectivity by using Lewis base catalyst such as lithium phenoxide or tetrabutyl ammonium phenoxide in DMF at −45 °C or THF at −78 °C, respectively.

β-Lactams are important compounds for their biological activities and there are various methods developed for their syntheses. Of those methods, one-pot synthesis of β-lactams between aldimine and silyl enolate attracted much attention because of their utilities and several useful methods have thus been reported:[1] i.e. Ojima et al. reported one-pot synthsis of β-lactams between silyl ketene acetals with aldimines by using a stoichiometric amounts of a Lewis acid such as $TiCl_4$.[1a,1b] Annunziata et al. reported the first catalytic one-pot synthsis of β-lactam from aldimines and silyl ketene thioacetals derived from 2-pyridyl thioesters by using a Lewis acid such as $Yb(OTf)_3$.[1c] Recently, Matsukawa et al. introduced an useful reaction by using highly nucleophilic tris(2,4,6-trimethoxyphenyl)phosphine as a catalyst.[1d]

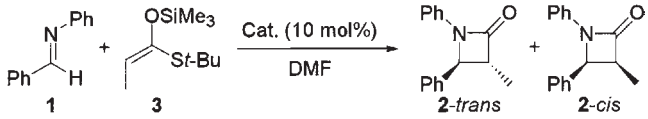
In the course of our investigation on the activation of trimethylsilyl (TMS) enolates by a Lewis base catalyst,[2–4] one-pot syntheses of β-lactams by tandem Lewis base-catalyzed Mannich-type addition and cyclization were recently found.[5] Since the diastereoselection of this reaction was moderete, a highly diastereoselective synthesis of β-lactam was studied in order to increase its utility. In this communication, we would like to describe highly trans-selective one-pot syntheses of β-lactams by tandem Lewis base-catalyzed Mannich-type addition and cyclization.

In our previous communication, it was shown that reaction between benzylideneaniline **1** and TMS enolate derived from methyl propionate afforded the corresponding β-lactam **2** in moderate trans-selectivity together with β-amino ester, a co-product, at room temperature. Further, the use of silyl ketene thioacetal **3** derived from *S-tert*-butyl thiopropionate gave the β-lactam **2** dominantly in good yield with moderate trans-selectivity.



Scheme 1.

Table 1. Screening of Lewis base catalyst

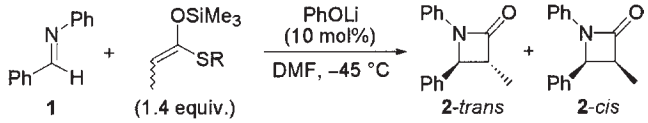


Entry	Cat.	Temp/°C	Time/h	Yield[a]/%	trans:cis
1	—	rt	12	n.d.[b]	—
2	AcOLi	−45	24	trace	—
3	$PhCO_2NBu_4$	−45	24	trace[c]	—
4	PhOLi	rt	8	96	88:12
5	PhOLi	−45	12	32	98:2
6	PhOLi	−60	12	12	99:1

[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]n.d.; not detected. [c]Solvent; THF.

Taking these results into consideration, trans-selective tandem Lewis base-catalyzed Mannich-type addition and cyclization was then attempted by using silyl ketene thioacetal **3** (Table 1). It was considered that the selectivity of the reaction could be controlled if the reaction was carried out at lower temperature. In the first place, therefore, reaction of **1** with **3** was tried at −45 °C by using 10 mol % of AcOLi in DMF or $PhCO_2NBu_4$ in THF, but only a trace amount of β-lactam was formed (Entries 2 and 3). Then, Lewis base catalysts were screened and the corresponding β-lactam was found to afford in 32% yield. However, the ratio of trans:cis was successfully increased up to 98:2 when 10 mol % of PhOLi was used at −45 °C.

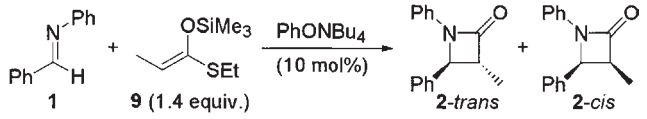
Table 2. Screening of silyl ketene thioacetal



Entry	Silyl enolate	R		Time/h	Yield[a]/%	trans:cis
1		SPh	**4**	12	3	99:1
2	OSiMe3	S-*c*-hex	**5**	12	trace	—
3	SR	S-*i*-Pr	**6**	12	19	99:1
4		S-*n*-Bu	**7**	6	85	98:2
5		SEt	**8**	6	91	95:5
6	OSiMe3 SEt		**9**	6	98	97:3

[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.

Table 3. Tandem $PhONBu_4$-catalyzed Mannich-type addition and cyclization of imine **1** and silyl keten thioacetal **9**



Entry	Temp/°C	Solv.	Time/h	Yield[a]/%	trans:cis
1	−45	DMF	6	96	97:3
2	−45	THF	12	quant.	97:3
3	−78	THF	6	87	99:1
4	−78	THF	12	95	99:1

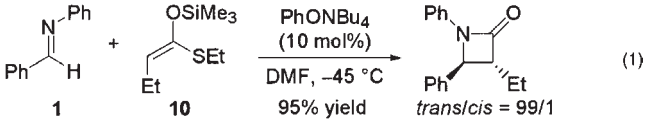
[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard.

In order to improve the efficiency of this reaction, silyl ketene thioacetals were screened by using PhOLi at −45 °C in DMF (Table 2). It was found that the yields depended on the nature of silyl ketene thioacetals employed. When the reaction was tried by using silyl ketene thioacetals such as **4** or **5**, only a trace amount of β-lactam **2** was formed. On the other hand, the yield increased when silyl enolate **7** or **8** was used. Further, both high yield and trans-selectivity were attained when silyl ketene thioacetal **9** was used. This concluded that silyl ketene thioacetal **9** was an appropriate donor of this reaction.

The optimization of the reaction conditions was further tried by taking tandem phenoxide anion-catalyzed Mannich-type addition of imine **1** with silyl ketene thioacetal **9** and cyclization of the resulted adduct, as a model (Table 3). Then, high yield and excellent trans-selectively (trans:cis = 99:1) were eventually attained when the reaction was carried out by using 10 mol % of tetrabutylammonium phenoxide ($PhONBu_4$) in THF at −78 °C (Entry 4).

The scope of acceptor aldimines in tandem $PhONBu_4$-catalyzed Mannich-type addition and cyclization was investigated by using silyl ketene thioacetal **9** (Table 4). Then it was found that the aromatic aldimines smoothly reacted with **9** and afforded the corresponding β-lactams in high yields with excellent trans-selectivities. The reaction also proceeded smoothly even in the case of using aldimines having a basic function (Entries 6 and 7).

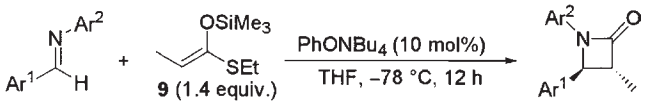
This reaction was further tried by using silyl ketene thioacetal **10** (Eq 1). The reaction also proceeded smoothly to afford the corresponding β-lactam in good yield with excellent trans-selectivity.



(1)

Thus, highly trans-selective tandem Lewis base-catalyzed Mannich-type addition and cyclization of forming β-lactam was developed by the combined use of silyl ketene thioacetals derived from *S*-ethyl thioates and Lewis base catalyst such as PhOLi or $PhONBu_4$. This method is quite practical and is applicable to the syntheses of various β-lactams in one-pot process. Further development of this reaction is now in progress.

Table 4. Tandem $PhONBu_4$-catalyzed Mannich-type addition and cyclization of various imines and silyl keten thioacetal **9**



Entry	Ar^1	Ar^2	Yield[a]/%	trans:cis
1	4-ClC_6H_4	Ph	quant.[b]	>99:1
2	4-BrC_6H_4	Ph	97[b]	>99:1
3	4-$CF_3C_6H_4$	Ph	91	>99:1
4	4-$MeOC_6H_4$	Ph	77[c]	99:1
5	2-Naphthyl	Ph	74	98:2
6	4-$Me_2NC_6H_4$	Ph	51[c,d]	98:2
7	3-Pyridyl	Ph	94[b]	>99:1
8	Ph	4-ClC_6H_4	92[b]	97:3
9	Ph	4-$MeOC_6H_4$	81[c]	98:2

[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]Isolated yield. [c]20 mol % of catalyst and 2 equiv. of silyl enolate were used at −45 °C. [d]DMF was used instead of THF.

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