Product-catalyzed Mannich-type Reaction between Trimethylsilyl Enolates and *N*-Tosylaldimines

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Mannich-type reaction between trimethylsilyl enolates and *N*-tosylaldimines in the presence of a catalytic amount of the alkoxide anion proceeded smoothly to afford the corresponding Mannich-adducts in good to high yields. This result indicated that the initially-formed *N*-anion of Mannich-adduct behaved as an effective Lewis base in performing the product-catalyzed Mannich-type reaction.

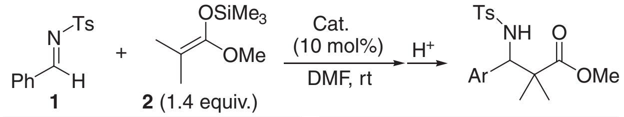
The product-catalyzed or -initiated autocatalytic reaction has been recognized as a new class of catalytic reaction and is of a growing intresting topic in organic chemistry. Soai's asymmetric autocatalytic reaction in asymmetric addition of dialkylzinc to aldehydes is among the well-known example and there are also several other examples of autocatalytic reactions using silyl reagents.[1]

In the course of our investigation[2] on the Lewis base-catalyzed aldol reaction between aldehydes and trimethylsilyl (TMS) enolates, it was observed that the produced aldolate anion activate the TMS enolate by forming hypervalent silicates to promote the product-catalyzed aldol reaction when alkoxide- or the corresponding aldolate anion was used as an activator.[3]

Now, we would like to describe the autocatalytic Mannich-type reaction between aldimine and silyl enolate which is one of the most important methods for the construction of β-amino carbonyl compounds. Recently, it was shown from our laboratory that the nitrogen and oxygen containing-anions generated from amides, imides, or carboxylic acids behaved as useful Lewis base catalysts in promoting the Mannich-type reaction between *N*-tosylaldimines and TMS enolates.[4]

In the above Lewis base catalyzed Mannich-type reaction, regeneration process of the catalyst is suggested as follows: the formed silylated Lewis base worked as a silylating reagent and the subsequent silyl group transfer from the silylated Lewis base to the *N*-lithiated Mannich-adduct **A** would lead to the formation of the corresponding *N*-silylated Mannich-adduct **B** along with simultaneous regeneration of the Lewis base to complete a catalytic cycle. When an alkoxide is used as an activator of this reaction, on the other hand, **A** is formed along with the generation of the corresponding TMS ether. Silyl group transfer from the silyl ether to **A** never took place because TMS ethers were stable under basic conditions.[3] In the above case, the autocatalytic cycle would be performed if *N*-anion of the produced Mannich-adduct **A** activated TMS enolate as a Lewis base. In this communication, we would like to report on an autocatalytic Mannich-type reaction of *N*-tosylaldimines and TMS enolates.

Table 1.

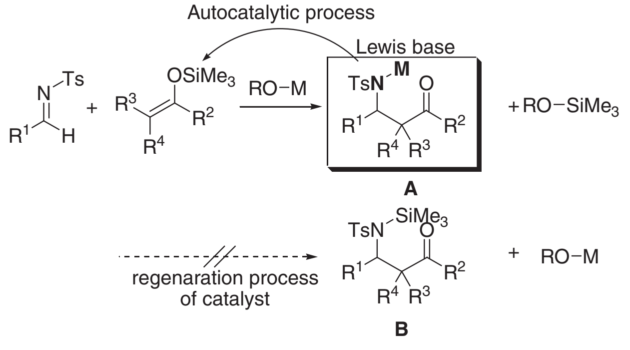


Entry	Cat.	Time /h	Yield[a] /%	Entry	Cat.	Time /h	Yield[a] /%
1	BnOLi	3	quant.	5	MeOLi	6	98
2	BnOLi	6	84[b]	6	EtONa	6	98
3	BnOLi	24	96[c]	7	*t*-BuOLi	6	90
4	BnOLi	24	trace[d]	8	*t*-BuOK	6	quant.

[a]Yield was determined by ^{1}H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]1 mol % of BnOLi was used. [c]The reaction was carried out at −45 °C. [d]THF was used instead of DMF.

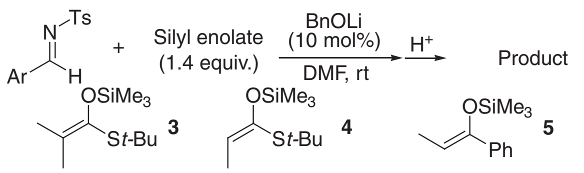
In the first place, Mannich-type reaction between *N*-tosylaldimine **1** and TMS enolate **2** was tried in the presence of 10 mol % of lithium benzylate at room temperature and the corresponding Mannich-adduct was obtained in quantitative yield (Table 1, Entry 1). This reaction proceeded smoothly to afford the Mannich-adduct in 84% yield even when 1 mol % of lithium benzylate was used (Entry 2). This indicates that the autocatalytic Mannich-type reaction proceeded in the presence of lithium benzylate, an initiator of the reaction. Then, conditions of alkoxide-initiated autocatalytic Mannich-type reaction were further screened. It was found that the reaction time should be longer at −45 °C to complete the reaction successfully. However, only a trace amount of the Mannich-adduct was detected when THF was used instead of DMF. In a similar fashion, various sodium and potassium alkoxides such as methoxide, ethoxide and tert-butoxide turned out to be effective initiators for the present Mannich-type reaction.

Next, alkoxide-initiated autocatalytic Mannich-type reaction was tried by using various aldimines and silyl enolates in DMF (Table 2). Aromatic aldimines reacted smoothly with **2** to afford the corresponding Mannich-adduct in high yields. Further, the corresponding Mannich-adducts were obtained in good



Scheme 1.

Table 2.



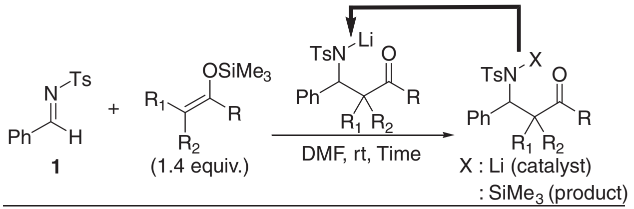
Entry	Ar	Silyl enolate	Time /h	Yield[a] /%
1	p-ClC_6H_4	**2**	6	81
2	p-CNC_6H_4	**2**	6	88
3	p-$O_2NC_6H_4$	**2**	6	70
4	p-MeC_6H_4	**2**	4	84
5	p-$MeOC_6H_4$	**2**	6	89
6	4-Pyridyl	**2**	6	84
7	p-$Me_2NC_6H_4$	**2**	24	84
8	**1**	**3**	6	79
9	**1**	**4**	6	quant.[b]
10	**1**	**5**	6	85[c]

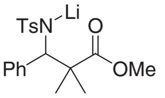
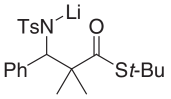
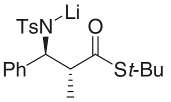
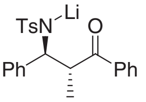
[a]Yield was determined by ^1H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard. [b]*anti*:*syn* = 3.3:1 [c]*anti*:*syn* = 1.6:1

to high yields even when the aromatic aldimines having a basic function were used (Entries 6, 7). When TMS enolates generated from thioester or ketone were employed, the corresponding Mannich-adducts were also obtained in good to high yields (Entries 8–10) with moderate *anti*-diastereoselectivity (Entries 9, 10).

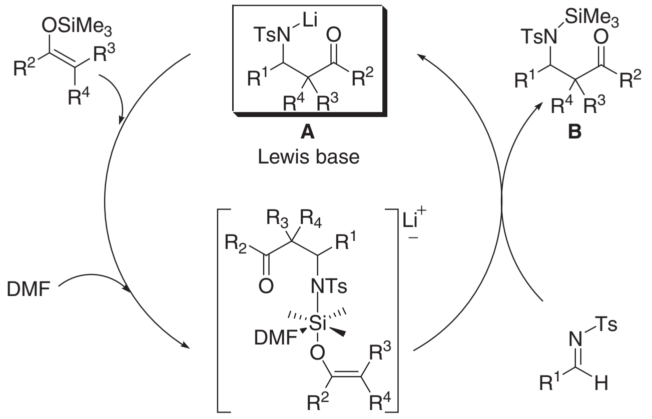
From environmental point of view, the corresponding product-catalyzed or -initiated reaction has great advantage because it is not necessary to discard the catalyst nor to separate it from the reaction mixture. Then, the product-initiated autocatalytic Mannich-type reaction was investigated by using the corresponding *N*-lithiated Mannich-adduct as a Lewis base catalyst (Table 3). It was found that the reactions also proceeded smoothly to afford the corresponding Mannich-adducts in high yields when other TMS enolates were used.

Table 3.



Entry	Silyl enolates	Cat. (10 mol %)	Time /h	Yield[a] /%
1	**2**		6	94
2	**3**		3	quant
3	**4**		6	91[b]
4	**5**		6	97[c]

[a]Yield was determined by ^1H NMR analysis (270 MHz) using 1,1,2,2-tetrachloroethane as an internal standard after desilylation. [b]*anti*:*syn* = 2.9:1 [c]*anti*:*syn* = 1.3:1



Scheme 2.

An assumed catalytic cycle of this reaction is illustrated in Scheme 2: namely, *N*-lithiated Mannich-adduct **A**, a Lewis base, firstly coordinates to the silicon atom of TMS enolate and further coordination of DMF to it would form a highly nucleophilic hexacordinated hypervalent silicate.[3] The reactivity of the enolate increased sufficiently to attack the *N*-tosylaldimine and formed a *N*-silylated **B** together with *N*-lithiated **A**. The intermediate **A** also effectively activated TMS enolate to complete an autocatalytic Mannich-type reaction.

Thus, the alkoxide or product-initiated autocatalytic Mannich-type reaction between TMS enolates and *N*-tosylaldimines was established. Further development of this reaction is now in progress.

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References

1 K. Soai, T. Shibata, and I. Sato, *Bull. Chem. Soc. Jpn.*, **77**, 1063 (2004); H. Hagiwara, S. Endou, M. Fukushima, T. Hoshi, and T. Suzuki, *Org. Lett.*, **6**, 1115 (2004); M. Hojo, A. Fujii, C. Murakami, and A. Hosomi, *Tetrahedron Lett.*, **36**, 571 (1995).

2 H. Fujisawa and T. Mukaiyama, *Chem. Lett.*, **2002**, 182; H. Fujisawa and T. Mukaiyama, *Chem. Lett.*, **2002**, 858; T. Mukaiyama, H. Fujisawa, and T. Nakagawa, *Helv. Chim. Acta*, **85**, 4518 (2002); T. Nakagawa, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, **32**, 462 (2003); T. Nakagawa, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, **32**, 696 (2003); T. Nakagawa, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, **33**, 92 (2004).

3 T. Mukaiyama, H. Fujisawa, and T. Nakagawa, *Adv. Synth. Catal.*, in press.

4 H. Fujisawa, E. Takahashi, and T. Mukaiyama, *Chem. Lett.*, **32**, 1036 (2003); E. Takahashi, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, **33**, 936 (2004).