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Double nucleophilic addition to α,β-unsaturated aldimines induced by titanium tetrahalides

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Abstract

In the presence of 0.5 equiv. of TiX_4, ketene silyl acetals underwent 1,4- and then 1,2-addition with α,β-unsaturated imine to give doubly alkylated products in good yields. Moreover, a 1:1 mixture of ketene silyl acetal and allyltributylstannane reacted with α,β-unsaturated imine, where the ketene silyl acetal specifically underwent 1,4-addition reaction to give an enamine derivative, which in turn isomerized into an imine. Allyltributylstannane then reacted with the resulting imine to give the doubly alkylated product in good yield.

Keywords: titanium tetrahalide; α,β-unsaturated imine; double nucleophilic addition.

Titanium tetrahalide-promoted reactions are valuable tools in organic synthesis.[1] In particular, the Mukaiyama aldol reaction enables the stereocontrolled construction of β-hydroxy carbonyl compounds,[2] and its asymmetric reactions realize the power of titanium halides in promoting C–C bond formation in an enantiocontrolled manner.[3] For the synthesis of nitrogen analogues, an imino version of the Mukaiyama reaction also offers a convenient entry into a very versatile and biologically important class of compounds.[4] In connection with this class of compounds, one of the most intriguing and unexplored fields of nucleophilic addition reactions involves a conjugate addition to α,β-unsaturated imino compounds,[5] although the carbonyl versions have been well examined.[6] We have been interested in diastereoface–discrimination reactions using a variety of titanium tetrahalides, and have found that differences in the reactivities of tetrahalides can enable distinct reaction pathways through selection of an appropriate tetrahalide derivative to promote the reaction.[7] In the present study, we found that in the presence of a titanium tetrahalide, ketene silyl acetals undergo 1,4- and subsequently 1,2-addition to α,β-unsaturated aldimines to give doubly alkylated products in good yields (Scheme 1). Furthermore, the reaction of a mixture of a ketene silyl acetal and an allyltributylstannane with α,β-unsaturated aldimine gave regio- and chemoselectively 1,4- and 1,2-doubly alkylated products, in which the ketene silyl acetal underwent 1,4-addition while the allyltributylstannane underwent 1,2-addition.

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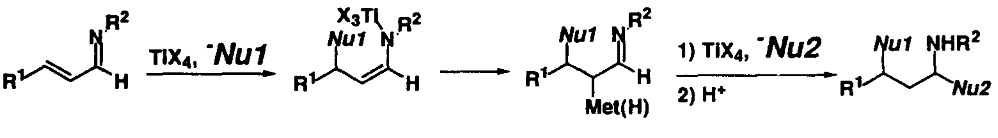
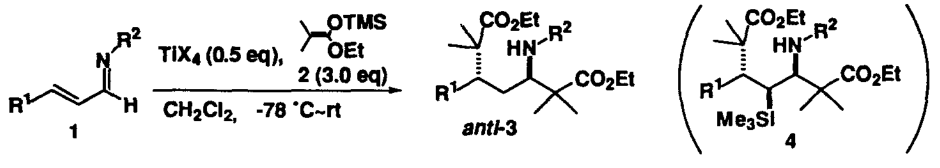


Scheme 1.

Table 1
Reaction of ketene silyl acetal **2** with imine **1** in the presence of TiX_4[a]



Entry	R1	R2	TiX4	3 (%)[b]	*syn* : *anti*[c]
1	Ph	Allyl	TiF_4	0	- : -
2	Ph	Allyl	$TiCl_4$	29	17 : 83
3	Ph	Allyl	$TiBr_4$	61	8 : 92
4	Ph	Allyl	TiI_4	51	25 : 75
5	Ph	Bn	$TiBr_4$	33	1 : 99
6	Ph	*p*-An	$TiCl_4$	35	1 : 99
7	Ph	*p*-An	$TiCl_4$	72[d]	15 : 85
8	Ph	*p*-An	$TiBr_4$	54[d] (7)[e]	1 : 99
9	Ph	*p*-An	TiI_4	50[d] (16)[e]	1 : 99
10	CH_3	*p*-An	$TiCl_4$	58[d]	2 : 98
11	*n*-C_3H_7	*p*-An	$TiCl_4$	31[d]	5 : 95

[a] The reaction was carried out with **1** : **2** : TiX_4 = 1.0 : 3.0 : 0.5 at -78 °C ~ rt. [b] Isolated yields. [c] Determined by HPLC. [d] In the presence of 4A molecular sieves. [e] Yield of **4** in the parentheses.

The initial examination of the reaction of a ketene silyl acetal with an imine promoted by titanium tetrahalide was carried out as outlined below using imine **1** and ketene silyl acetal **2**. When a mixture of imine **1** (R^1=Ph, R^2=allyl) and TiI_4 (10 mol%) was treated with ketene silyl acetal **2** (2.0 equiv.) in CH_2Cl_2 at −78°C–room temperature for 24 h, 1,4-1,2-double alkylation product **3** was obtained in 15% yield along with the 1,2-addition product in 29% yield. After screening the amounts of **2** and TiX_4, better yields of **3** were obtained using 3.0 equiv. of **2** in the presence of 50 mol% of TiX_4. The results are summarized in Table 1.

As shown in Table 1, the reaction using the cinnamylidene allyl imine **1** (R^1=Ph, R^2=allyl) in the presence of titanium tetrachloride gave 1,4-1,2-adduct **3** in 29% yield, whereas 1,4-1,2-adduct **3** was obtained in much better yields using the iodo and bromo analogues. The *N*-substituent is also important. The *p*-anisyl and benzyl imines showed the formation of doubly alkylated product in moderate yield, whereas a better result was obtained using the allyl derivative. The relative stereochemistry of the 1,4-1,2-adduct **3** was determined by transformation into a lactam by treatment with phenylmagnesium bromide.[8] In every case, the formation of the *anti*-adduct predominated. Regarding the reaction pathways, the second nucleophilic attack needs the imino functionality, as in **B**, which may be generated via isomerization of the initially formed metal imine **A** (Scheme 2). For this purpose, proton sources were added to the reaction media. In particular, the best result was obtained when the reaction was carried out in the presence of 4 Å molecular sieves using the anisyl derivative, and the desired double alkylation product **3** was formed in 72% yield (entry 7). Moreover, the addition reaction carried out with $TiBr_4$ or TiI_4 in the presence of 4 Å molecular sieves gave **3** with excellent diastereoselectivity along with the trimethylsilylated adduct **4** (entries 8 and 9). The reaction conducted in a manner similar to that of entry 7 but in the presence of deuterated molecular sieves (pretreated with D_2O and dried) gave the deuterated product **3′** in 47% yield with 43% deuterium incorporation. These results suggest the involvement of α-metalloimino species **B**.

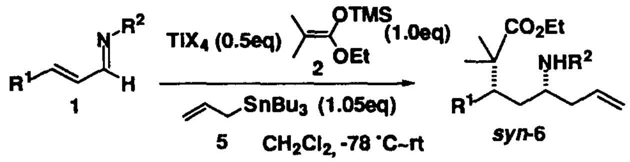
Scheme 2.

To clarify the reaction mechanisms and to extend this kind of double alkylation reaction, the use of a mixture of two kinds of nucleophiles was tested in the present reaction media. A 1:1.05 mixture of ketene silyl acetal **2** and allyltributylstannane **5** was added to a mixture of imine **1** and $TiCl_4$ in CH_2Cl_2 at −78°C. We obtained doubly alkylated product **6** in good yield, where the ketene silyl acetal underwent 1,4-addition and the allylstannane underwent 1,2-addition. The results are summarized in Table 2.[9]

The substituent at the nitrogen moiety is important. In contrast to the addition of ketene silyl acetal, allyl and benzyl imino derivatives did not give the 1,4- and 1,2-double addition product at all, whereas the anisyl counterpart provided good to excellent results, giving the tandem–double addition products in good yields. The ligand of the titanium tetrahalide is also crucial. $TiCl_4$ gave the best result, whereas the bromine and iodine counterparts gave the 1,4- and 1,2-double addition product in moderate yield. In this case, the order of addition is important. The best result was obtained when the reaction first involved the

Table 2

Double alkylation of α,β-unsaturated imine **1** with ketene silyl acetal **2** and allyltributylstannane **5** promoted by TiX_4[a]



Entry	R1	R2	TiX4	6 (%)[b]	*syn* : *anti*[c]
1	Ph	*p*-An	$TiCl_4$	70	93 : 7
2	Ph	*p*-An	$TiBr_4$	67	82 : 18
3	Ph	*p*-An	TiI_4	45	78 : 22
4	CH_3	*p*-An	$TiCl_4$	79	76 : 24
5	CH_3	*p*-An	$TiBr_4$	47	62 : 38
6	CH_3	*p*-An	TiI_4	24	67 : 33
7	*n*-C_3H_7	*p*-An	$TiCl_4$	60	77 : 23

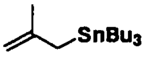
[a] The reaction was carried out with **1** : **2** : **5** : TiX_4 = 1.0 : 1.0 : 1.05 : 0.5 at -78 °C ~ rt. [b] Isolated yields. [c] Determined after separation on silica gel TLC. The relative stereochemistry of the 1,4-1,2-adduct **6** was determined by transformation into a lactam by treatment with phenylmagnesium bromide.

complexation of the imine with $TiCl_4$ followed by the addition of a mixture of ketene silyl acetal and allyltributylstannane to the complex.

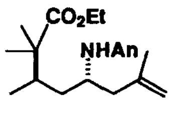
Regarding the metalloenamine **A**–imine **B** isomerization, in contrast to the cases using a single nucleophile, those using ketene silyl acetal and allyltributylstannane indicated that the presence of a proton source, e.g., 4 Å molecular sieves, completely altered the reaction pathway. The desired 1,4-1,2-hetero double nucleophilic attack was not observed. Instead, the homo double nucleophilic attack of the ketene silyl acetal was observed, and gave the double addition product **3** and 1,2-addition products in yields of 41 and 33%, respectively. This result suggests that isomerization of the enamine **A** to imine **B** using two kinds of nucleophiles may involve a metallated species such as **B**.

The imino functionality of the α,β-unsaturated imine is important. As indicated above, the coordination ability of the titanium tetrahalide to the imino moiety is greatly influenced by the substituent at the nitrogen. The best result was obtained using the anisyl derivative. This may be due to the size of the lone pair of the imino nitrogen atom. Calculation using the CAChe® extended Hückel application[10] clearly indicates that the anisyl derivative possesses the smallest lone pair among the derivatives examined (*p*-anisyl, allyl, and benzyl), which suggests that the relatively weak coordination ability of the imino nitrogen appears to be suitable for the present reaction.

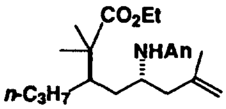
Other ketene silyl acetals and allylstannanes besides **2** and **5** were examined. However, the ketene silyl acetals derived from acetates, propionates and thioesters only gave 1,2-addition products in moderate yields, whereas methallylstannane derivative **7** also participated in the present reaction to give double alkylation products **8** and **9** in good yields, where the formation of *anti*-products predominated.



7



8: 59%
anti : *syn* = 88 : 12



9: 53%
anti : *syn* = 84 : 16

In conclusion, the double alkylation reaction studied here provides a new mode of reaction using α,β-unsaturated aldimine as a good acceptor of two kinds of nucleophiles. Since discrimination between two kinds of nucleophiles upon addition to α,β-unsaturated aldimine is highly controlled, this approach offers a new method for single-step double nucleophilic addition, an otherwise multi-step and rather tedious procedure.

Acknowledgements

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8. The adduct **3** or **6** was transformed into 5-pentanelactam, and analyzed by ^{1}H NMR. For cyclization into lactam. See, for example: (a) Shono, T.; Tsubata, K.; Okinaga, N. *J. Org. Chem.* **1984**, *49*, 1056. (b) Hattori, K.; Yamamoto, H. *Synlett* **1993**, 239.
9. A typical procedure for the addition reaction: To a solution of *N*-*p*-anisylcinnamylidenamine **1** (47.5 mg, 0.20 mmol) in CH_2Cl_2 (4.0 mL) was added $TiCl_4$ (0.10 mL, 0.10 mmol, 1.0 M in CH_2Cl_2) at −78°C, and the mixture was stirred at −78°C for 15 min. A mixture of 1-ethoxy-1-trimethylsiloxy-2-methylpropene **2** (113.0 mg, 0.60 mmol) and allyltributylstannane (69.5 mg, 0.21 mmol) in CH_2Cl_2 (2.0 mL) was added to the resulting mixture during 20 min at −78°C, and the mixture was gradually warmed to room temperature during 16.5 h. Saturated aqueous $NaHCO_3$ (8.0 mL) was added to the mixture, which was extracted with ethyl acetate (10 mL×3). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give a crude oil. Purification on silica gel TLC (*n*-hexane:ethyl acetate=20:1 as eluent) gave *syn*-1,4-1,2-adduct *syn*-**6** (52.6 mg, 65%) and *anti*-**6** (4.0 mg, 5%).
10. The AM1 and MNDO calculations were performed using MOPAC on CAChe®. Optimized structures were further characterized by the Hückel application.