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Double nucleophilic addition reaction to α,β-unsaturated aldimines promoted by aluminum chloride and a limited amount of water

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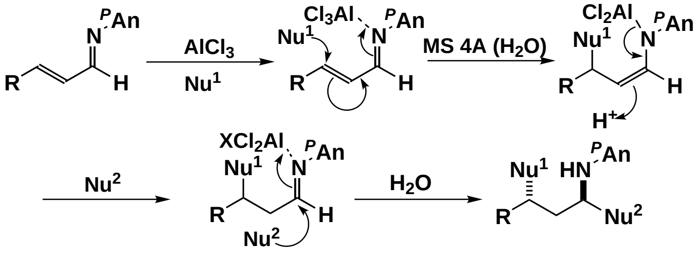
Abstract—In the presence of $AlCl_3$ and MS 4 A containing H_2O, ketene silyl acetals underwent 1,4- and then 1,2-addition with α,β-unsaturated imines to give doubly alkylated products in good yields with high diastereomeric excesses. © 2001 Elsevier Science Ltd. All rights reserved.

α,β-Unsaturated aldimines[1] are readily accessible from the parent aldehydes via simple condensation with amines. Although α,β-unsaturated imines potentially possess two electrophilic centers, use of both the carbons for carbon to carbon bond forming reactions in a stereocontrolled fashion has been a difficult task. Tandem alkylation reaction[2] to α,β-unsaturated imines appears to eliminate several drawbacks, and therefore, it is highly desirable to develop an operationally simple procedure for the addition reaction of two nucleophiles to α,β-unsaturated imines in a single-step. Since one of the most intriguing and unexplored fields of nucleophilic addition reactions involves a conjugate addition to α,β-unsaturated imino compounds,[3] we have already embarked on a project using such imino compounds as acceptors of two electrophiles, and reported that in the presence of 0.5 equiv. of titanium tetrahalide, ketene silyl acetals underwent 1,4- and subsequently 1,2-addition to α,β-unsaturated aldimines to give doubly alkylated products in good yields.[4] In the present study, we found that in the presence of molecular sieves 4 A containing water and 1.0 equiv. of aluminum chloride, reaction of ketene silyl acetals with α,β-unsaturated aldimines gave 1,4- and 1,2-doubly alkylated products in good yields with excellent diastereomeric excesses. Moreover, under the newly developed reaction conditions using $AlCl_3$-MS 4 A (H_2O),[5] tetra-, tri-, and di-substituted ketene silyl acetals and/or thioacetals gave 1,4-1,2-addition products in good yields, in terms of generality and stereoselectivity making a strong contrast to the examples previously reported where titanium tetrahalides were employed (Scheme 1).

When a mixture of imine **1** (R = Ph), $TiCl_4$ (25 mol%), $TiBr_4$ (25 mol%) and MS 4 A containing 1 equiv. of H_2O was treated with ketene silyl acetal **2** (3.0 equiv.) in CH_2Cl_2 at −78°C room temperature for 14 h, 1,4-1,2-adduct **3** was obtained in 11% yield along with 1,2-addition product **4** in 68% yield. After screening Lewis acids, a better yield of **3** was obtained using 3.0 equiv. of **2** in presence of 1.0 equiv. of $AlCl_3$ and MS 4



Scheme 1. Double nucleophilic addition.

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A (1 equiv. H_2O). The results are summarized in Table 1.[6]

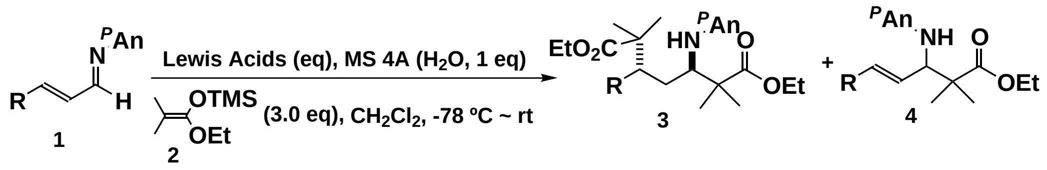
As shown in Table 1, the reaction using cinnamyliden *p*-anisyl imine **1** (R = Ph) in the presence of 25 mol% of $TiCl_4$ and 75 mol% of $TiBr_4$ and MS 4 A (1 equiv. H_2O) gave 1,4-1,2-adduct **3** in 73% yield (entry 2), whereas 1,4-1,2-adduct **3** was obtained in much better yield with excellent diastereomeric excess using 1.0 equiv. of $AlCl_3$ and MS 4 A (1 equiv. H_2O) (entry 4). The use of $SnCl_4$ was also effective, giving the desired double addition product **3** in 73% yield (entry 7). In the presence of $AlCl_3$, the reaction of imines derived from crotonaldehyde and *trans*-2-hexenal with ketene silyl acetal **2** gave 1,4-1,2-adduct **3** in 84 and 67% yields, respectively (entries 9 and 10). The relative stereochemistry of the 1,4-1,2-adduct **3** was determined by transformation into a lactam on treatment with phenylmagnesium bromide,[7] where the formation of the *anti*-adduct was confirmed.

The intermediary metalloenamine and/or α-metalloimine were successfully trapped by a TMS group, when the reaction was carried out in the absence of MS 4 A (H_2O). The results from the reaction in the absence of MS 4 A (H_2O) are summarized in Table 2.

In every case the formation of the silylated derivative **5**[8] was observed, indicating that the use of MS 4 A in the cases in Table 1 was very effective as a convenient carrier of a limited amount of water which protonated the intermediary metallated species.

We next examined various ketene silyl acetals as nucleophiles under the optimum reaction conditions using $AlCl_3$-MS 4 A (H_2O), and the results are summarized in Table 3.

Table 1. Reaction of ketene silyl acetal **2** with imine **1**

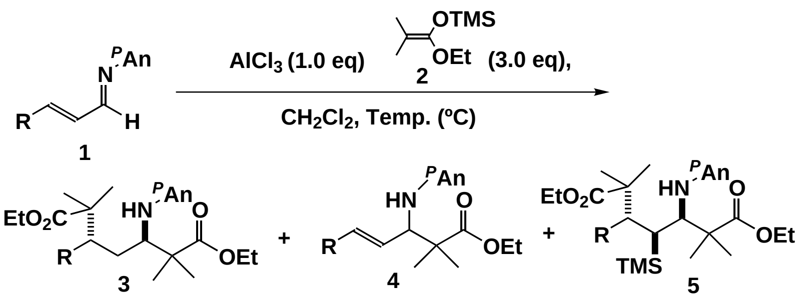


Entry	Lewis acids (equiv.)	R	Time (h)	**3** (%)[a]	*syn*:*anti*[b]	**4** (%)[a]
1	$TiCl_4$ (0.25) $TiBr_4$ (0.25)	Ph	14.0	11	1:>99	68
2	$TiCl_4$ (0.25) $TiBr_4$ (0.75)	Ph	18.0	73	1:>99	9
3	$AlCl_3$ (0.5)	Ph	18.0	14	1:>99	66
4	$AlCl_3$ (1.0)	Ph	15.7	81	1:>99	2
5	$AlBr_3$ (1.0)	Ph	15.9	29	1:>99	62
6	AlI_3 (1.0)	Ph	16.4	37	1:>99	45
7	$SnCl_4$ (1.0)	Ph	17.2	73	1:>99	13
8	$MgBr_2$ (1.0)	Ph	16.3	4	1:>99	80
9	$AlCl_3$ (1.0)	Me	17.0	84	1:>99	1
10	$AlCl_3$ (1.0)	*n*-Pr	17.0	67	1:>99	11

[a] Isolated yields.

[b] Determined by NMR or HPLC.

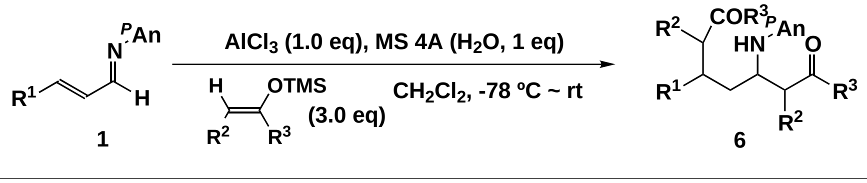
Table 2. Reaction of **2** with **1** in the absence of MS 4 A (H_2O)



Entry	R	Temp. (°C)	Time (h)	**3** (%)[a]	**4** (%)[a]	**5** (%)[a]
1	Ph	−78 ~ rt	16.0	54	Trace	25
2	Me	−78 ~ −20	2.8	42	4	41
3	*n*-Pr	−78 ~ −10	4.3	41	10	10

[a] Isolated yields.

Table 3. Reaction using various ketene silyl (thio)acetals



Entry	R^1	R^2	R^3	Time (h)	**6** (%)[a]
1	Ph	Me	OEt	17.7	3[b]
2	Ph	Me	SEt	17.0	69[c]
3	Ph	Me	S^{n}Pr	16.0	75[d]
4	Ph	Me	S^{i}Pr	16.7	53[e]
5	Ph	Me	S^{t}Bu	15.6	32[f]
6	Me	Me	SEt	17.1	63[g]
7	Ph	H	OEt	16.0	0[h]
8	Ph	H	S^{t}Bu	16.0	50[i]

[a] Isolated yields.

[b] 1,2-Addtion product was obtained in 54% yield.

[c] A 10:22:46:4:2:10:4:2 mixture of diastereomers was obtained.

[d] A 43:14:4:7:3:2:19: 8 mixture of diastereomers was obtained.

[e] A 8:3:13:17:40:19 mixture of diastereomers was obtained.

[f] A 7:6:4:14:54:15 mixture of diastereomers was obtained.

[g] A 13:83:4 mixture of diastereomers was obtained.

[h] 1,2-Addtion product was obtained in 77% yield.

[i] A 57:43 mixture of diastereomers was obtained.

The reaction of the ketene silyl acetals derived from ethyl propionate was carried out to give the doubly alkylated product **6** in low yield along with the 1,2-adduct as a major product (entry 1). The formation of the undesired 1,2-adduct was suppressed by using ketene silyl thioacetals in place of the corresponding oxygen analogues. The best result was obtained when the reaction was carried out with $AlCl_3$ in the presence of MS 4 A (1 equiv. H_2O) using the ketene silyl thioacetal derived from *n*-propyl thiopropionate, and the desired double alkylation product **6** was formed in 75% yield as a mixture of diastereomers (entry 3). As the ester parts (R^3) of the ketene silyl thioacetals became bulkier, the yields of the double alkylation products **6** decreased (entries 4 and 5). In strong contrast to the case with the ketene silyl acetal derived from ethyl acetate, the use of the ketene silyl thioacetal gave 1,4- and 1,2-double addition product in 50% yield (entries 7 and 8). This may be due to the enhanced ability of ketene silyl thioacetal to participate in better HOMO–LUMO interaction with the α,β-unsaturated imines.[9]

In conclusion, we have found that molecular sieves 4 A is an excellent carrier of a limited amount of water to protonate an intermediate to produce a neutral species which can undergo a subsequent reaction with a nucleophile. In the presence of MS 4 A (H_2O), Lewis acids such as TiX_4, SnX_4, MgX_2, and AlX_3 can be used without noticeable hydrolysis, offering a good opportunity to be employed as Lewis acids even in protic circumstances. The present success of the 1,4-1,2-double nucleophilic addition of nucleophiles to α,β-unsaturated aldimines is highly dependent on the use of a limited amount of water present in the Lewis acid mediated reactions.

Acknowledgements

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5. Molecular sieves 4 A containing H_2O were prepared as follows: Commercially available molecular sieves 4 A were heated under irradiation of microwave in an oven and dried in vacuo. The rigorously dried molecular sieves 4 A were placed in a flask saturated with moisture for several hours. The water content of the molecular sieves was calculated based on the increase in the weight.
6. A typical procedure for the addition reaction: To a solution of $AlCl_3$ (27.2 mg, 0.20 mmol) and MS 4 A (32.9 mg, 10.9 wt% H_2O) in CH_2Cl_2 (2.0 ml) was added a solution of *N*-*p*-anisylcinnamylidenimine **1** (47.5 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL) at −78°C, and the mixture was stirred at −78°C for 10 min. A mixture of 1-ethoxy-1-trimethylsiloxy-2-methylpropene **2** (113.1 mg, 0.60 mmol) in CH_2Cl_2 (2.0 mL) was added to the resulting mixture during 10 min at −78°C, and the mixture was gradually warmed to room temperature during 15.7 h. Saturated aqueous $NaHCO_3$ (8.0 mL) was added to the mixture, which was filtered through a Celite pad with the aid of ethyl acetate. The filtrate was extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to give a crude oil. Purification on silica gel TLC (toluene: ethyle acetate = 30:1 as eluent) gave *anti*-1,4-1,2-adduct *anti*-**3** (76.5 mg, 81%), 1,2-adduct **4** (1.2 mg, 2%).
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