

Regioselective 1, 2-Addition of Ti(IV)-enolate to α , β -Unsaturated Compounds

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Abstract: The nucleophilic addition of Ti(IV) enolate derived from methyl aryl ketones to α , β -unsaturated compounds was found to be highly selective to give 1, 2 addition products.

Keywords: Ti(IV) enolates, nucleophilic addition, regioselectivity, enones, Lewis acid.

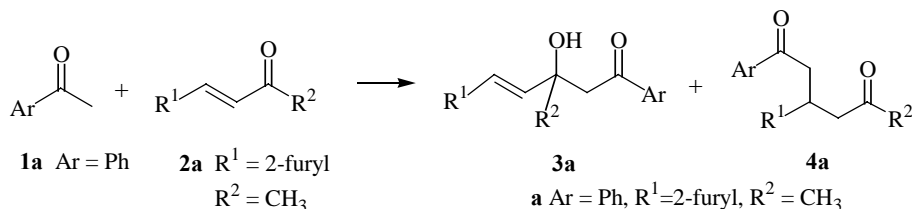
The nucleophilic addition to α , β -unsaturated carbonyl compounds is a fundamental C-C bond forming reaction in organic chemistry¹. Since there are two reaction sites in the α , β -unsaturated carbonyl group, the regioselectivity of the nucleophilic addition (1, 2 vs. 1, 4 addition) is of primary importance when applying this type of reaction in organic synthesis. Factors that control the regioselectivity include the softness and hardness of the attacking nucleophiles², solvent and temperature³, steric bulk⁴ and transition-metal additives⁵. Recently, we reported the selectivity for either 1, 2- or 1, 4-addition of Ti(IV) enolate to α , β -unsaturated carbonyl compounds could be controlled by choosing appropriate Lewis acids⁶. In this paper, we report the regioselective 1, 2-addition of the Ti(IV) enolate derived from methyl aryl ketone to α , β -unsaturated ketones.

Initially, we studied the nucleophilic addition of lithium enolate to enone **2a** (Scheme 1). When lithium diisopropylamide (LDA) was used as the base for the deprotonation of acetophenone **1a**, the reaction with enone **2a** gave a complex mixture, from which 1, 2- and 1, 4-addition products were isolated in 25 % yield with a ratio of **3a** : **4a** = 60 : 40. We could also isolate a mixture of other products, which were due to the further deprotonation of the addition product and the subsequent reaction with enone substrate. Similar results were obtained when lithium hexamethyldisilazide (LiHMDS) was used as base. When the acetophenone was deprotonated under the condition of TiCl₄/Et₃N, the reaction with enone **2a** gave 1, 2-addition product **3a** in 56 % isolated yield. In this case, 1, 4-addition product **4a** was not detected from ¹H NMR of the crude product.

The yield of **3a** could be further improved to 82 % when 1 equivalent of Ti(O^{*i*}Pr)₄ was added to activate the enone.

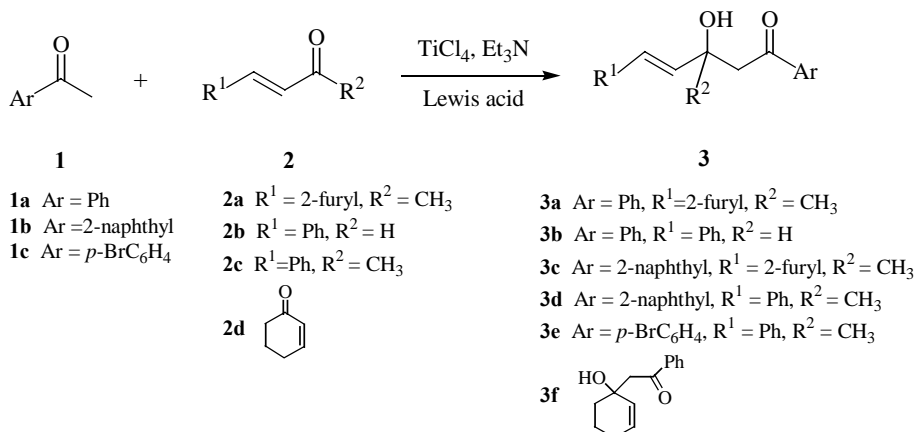
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Scheme 1



Reaction condition	Ratio 3a : 4a	Yield (3a + 4a)
LDA, THF, -78 °C, 9 h	60 : 40	25 %
LiHMDS, THF, -78 °C, 9 h	61 : 39	28 %
TiCl ₄ /NEt ₃ , CH ₂ Cl ₂ , -78 °C, 9 h	100 : 0	56 %
TiCl ₄ /Et ₃ N, Ti(O ^{<i>i</i>} Pr) ₄ , CH ₂ Cl ₂ , -78 °C, 8 h	100 : 0	82 %

Scheme 2

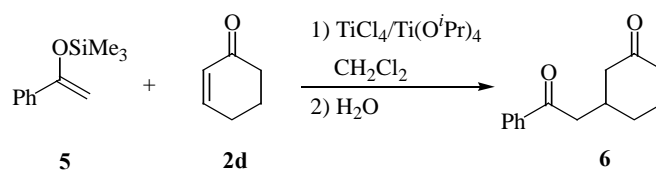
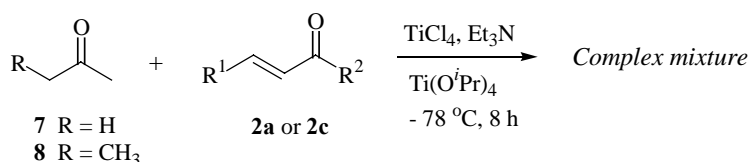


The generality of the selective 1, 2-addition reaction with Ti(IV) enolate derived from methyl aryl ketones was demonstrated by the examples shown in **Scheme 2** and **Table 1**⁷. The reaction of Ti(IV) enolate to enone or enal gave selectively 1, 2-addition product in good yields. The activation with Ti(O^{*i*}Pr)₄ generally increase the yields and slightly shorten the reaction time. The products **3a-f** were stable enough to be isolated by flash silica gel chromatography.

The exclusive formation of 1, 2-adducts in these reactions is in contrast to the reaction of silyl enol ethers with α,β -unsaturated ketones promoted by TiCl₄, in which cases 1, 4-addition products are formed predominantly. For example, Mukaiyama *et al.* reported that α -trimethylsiloxy styrene **5** reacted with 2-cyclohexen-1-one in the presence of TiCl₄ and Ti(O^{*i*}Pr)₄ at -78 °C to give 1,4-addition product **6** in 70 % yield (**Scheme 3**)⁸.

Table 1 Regioselective 1, 2 addition of Ti(IV) enolate to α , β -unsaturated carbonyl compounds⁷

Entry	Methyl aryl ketone 1	Lewis acid	α , β -Unsaturated carbonyl compound 2	Reaction time (h)	Product 3	Yield ^a (%)
1	1a	none	2a	9	3a	56
2	1a	Ti(O ^{<i>i</i>} Pr) ₄	2a	8	3a	82
3	1a	Ti(O ^{<i>i</i>} Pr) ₄	2b	5.5	3b	90
4	1b	Ti(O ^{<i>i</i>} Pr) ₄	2a	8	3c	89
5	1b	none	2c	9	3d	51
6	1b	Ti(O ^{<i>i</i>} Pr) ₄	2c	9	3d	76
7	1c	Ti(O ^{<i>i</i>} Pr) ₄	2c	9	3e	71
8	1a	Ti(O ^{<i>i</i>} Pr) ₄	2d	7.5	3f	75

^aIsolated yields.**Scheme 3****Scheme 4**

The mechanism of the Ti(O^{*i*}Pr)₄-promoted reaction can be reasoned as follows. The TiCl₄-enolates derived from **1** and TiCl₄ is considered as a soft nucleophile, and hence the reaction is likely to be frontier orbital controlled. It is known that the complexation of the Lewis acid with the oxygen of an α , β -unsaturated carbonyl compound increases its carbonyl coefficient of LUMO relative to that of the remote β -carbon, and hence Ti(O^{*i*}Pr)₄ coordination should promote 1,2 addition⁶.

Since selective 1, 2-addition may also find application in organic synthesis, we considered extending the scope of the reaction with general ketones. However, when the same reaction condition was applied to acetone **7** or methyl ethyl ketone **8**, a complex mixture was formed (**Scheme 4**). Therefore, the regioselective 1, 2-addition is only limited to the Ti(IV) enolate derived from methyl aryl ketones.

Acknowledgments

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References and Notes

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7. General procedure for the reaction of Ti(IV) enolates derived from methyl aryl ketones **1a-c** with α , β -unsaturated carbonyl compounds **2a-d** in one equivalent of Ti(O^{*i*}Pr)₄. To a solution of **1a** (120 mg, 1 mmol) in anhydrous CH₂Cl₂ (10 mL) at -78 °C was added dropwise TiCl₄ (209 mg, 1.1 mmol) and Et₃N (111 mg, 1.1 mmol). The resulting dark mixture was stirred at -78 °C for 1 h. To the above reaction mixture was added a solution of Ti(O^{*i*}Pr)₄ (284 mg, 1 mmol) and enal **2b** (119 mg, 0.9 mmol) in anhydrous CH₂Cl₂ (2 mL). The reaction mixture was stirred for another 5.5 h at -78 °C and then quenched with saturated aqueous NH₄Cl (5 mL). ¹H NMR (200 MHz) spectra of the crude product shown that there was no 1,4-addition product. The crude product was purified by short silica gel column (eluent 10:1:0.5 petroleum ether/EtOAc/Et₃N) to afford only product **3b** (204 mg, 90 %).
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