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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 chemistry[1]. 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 nucleophiles[2], solvent and temperature[3], steric bulk[4] and transition-metal additives[5]. 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 acids[6]. 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 $TiCl_4/Et_3N$, 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 $Ti(O^iPr)_4$ was added to activate the enone.

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Scheme 1

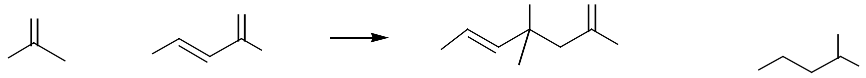
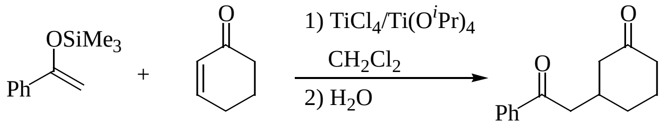


Table 1 Regioselective 1, 2 addition of Ti(IV) enolate to α, β–unsaturated carbonyl compounds[7]

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**	$Ti(O^iPr)_4$	**2a**	8	**3a**	82
3	**1a**	$Ti(O^iPr)_4$	**2b**	5.5	**3b**	90
4	**1b**	$Ti(O^iPr)_4$	**2a**	8	**3c**	89
5	**1b**	none	**2c**	9	**3d**	51
6	**1b**	$Ti(O^iPr)_4$	**2c**	9	**3d**	76
7	**1c**	$Ti(O^iPr)_4$	**2c**	9	**3e**	71
8	**1a**	$Ti(O^iPr)_4$	**2d**	7.5	**3f**	75

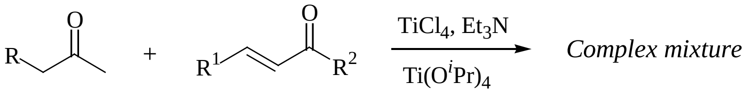
[a] Isolated yields.

Scheme 3



5 **2d** **6**

Scheme 4



7 R = H
8 $R = CH_3$

2a or **2c**

The mechanism of the $Ti(O^iPr)_4$-promoted reaction can be reasoned as follows. The $TiCl_4$-enolates derived from **1** and $TiCl_4$ 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 $Ti(O^iPr)_4$ coordination should promote 1,2 addition[6].

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

1. For a review, see: P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon Press, Oxford, **1992**.
2. a) E. M. Kaiser, C. L. Mao, C. F. Hauser, *J. Org. Chem.,* **1970**, *35*, 410. b) T. V. Rajan Babu, *J. Org. Chem.,* **1984**, *49*, 2083. c) D. A. Hunt, *Org. Prep. Proced. Int.,* **1989**, *21*, 707. d) W. C. Still, A. Mitra, *Tetrahedron Lett.,* **1978**, *30*, 2659.
3. a) T. Cohen, W. D. Abraham, M. Myers, *J. Am. Chem. Soc.,* **1987**, *109*, 7923. b) H. J. Reich, W. H. Sikorski, *J. Org. Chem.,* **1999**, *64*, 14. c) W. H. Sikorski, H. J. Reich, *J. Am. Chem. Soc.,* **2001**, *123*, 6527. d) A. G. Schultz, Y. K. Lee, *J. Org. Chem.,* **1976**, *41*, 4044. e) P. C. Ostrowski, V. V. Kane, *Tetrahedron Lett.,* **1977**, 3549. f) K. Ogura, M. Yamashita, G. I. Tsuchihashi, *Tetrahedron Lett.,* **1978**, 1303.
4. a) D. Seebach, R. Locher, *Angew. Chem. Int. Ed. Engl.,* **1979**, *18*, 957. b) K. Maruoka, M. Ito, H. Yamamoto, *J. Am. Chem. Soc.,* **1995**, *117*, 9091. c) J. Lucchetti, A. Krief, *J. Organomet. Chem.,* **1980**, *194*, C49.
5. For reviews, see: a) G. H. Posner, *Org. React.,* **1977**, *19*, 1. b) B. H. Lipshutz, S. Sengupta, *Org. React.,* **1992**, *41*, 135.
6. G. Deng, X. Tian, Z. Qu, J. Wang, *Angew. Chem. Int. Ed.,* **2002**, *41*, 2773.
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 CH_2Cl_2 (10 mL) at –78 °C was added dropwise $TiCl_4$ (209 mg, 1.1 mmol) and Et_3N (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 CH_2Cl_2 (2 mL). The reaction mixture was stirred for another 5.5 h at –78 °C and then quenched with saturated aqueous NH_4Cl (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/Et_3N) to afford only product **3b** (204 mg, 90 %).
8. a) T. Mukaiyama, K. Banno, K. Narasaka, *J. Am. Chem. Soc.,* **1974**, *96*, 7503. b) K. Saigo, M. Osaki, T. Mukaiyama, *Chem. Lett.,* **1976**, 163. c) K. Narasaka, K. Soai, Y. Aikawa, T. Mukaiyama, *Bull. Chem. Soc. Jpn.,* **1976**, *49*, 779.

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