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New Possibilities in the Michael Reaction by the Use of Tin(II) Enolates

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The Michael addition reaction of tin(II) enolates with α,β-unsaturated ketones proceeds smoothly by the use of chlorotrimethylsilane as an activator to give the corresponding addition products in good yields.

The Michael addition reaction is a basic carbon-carbon bond forming reaction which is widely employed in organic synthesis.[1] The reactions in which metal enolates are employed as nucleophiles are of particular interest with great potentiality as a versatile method for the stereoselective synthesis of acyclic systems. However, in the reaction between metal enolates and α,β-unsaturated ketones, in most cases the problems of competitive 1,2-addition along with some polymerization of enones limit the application of metal enolate nucleophiles to the Michael addition.[2]

In connection with the results in previous papers[3] where we demonstrated diastereoselective and enantioselective aldol reactions by the efficient use of tin(II) enolates, in this communication, we wish to report the utilization of tin(II) enolates in the Michael addition reactions.

First, we examined the reaction between cyclohexenone and the tin(II) enolate generated from 3-propionyl-2-oxazolidone. No reaction was observed when cyclohexenone was added to the tin(II) enolate at -78 °C. Therefore, the addition of several activators to this reaction was studied in order to enhance the reactivity of the enone. (Table 1)

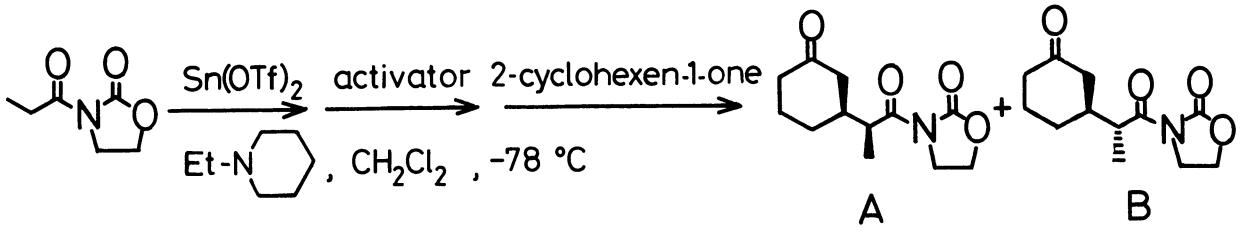


Table 1.

	Activator[a]	Yield/%	A : B[4]
1)	none	0	———
2)	$SnCl_4$	0	———
3)	Me_3SnCl	0	———

4)	$BF_3 \cdot OEt_2$	28	69:31
5)	Ph_2BCl	17	53:47
6)	TMSCl	84	62:38

a) Molar ratio of $Sn(OTf)_2$:N-ethylpiperidine:3-acyl-2-oxazolidone:activator:2-cyclohexen-1-one = 1.0:1.2:0.8:1.2-1.5:0.6.

As shown in Table 1, the addition of Lewis acids such as $BF_3 \cdot OEt_2$ and Ph_2BCl, did indeed promote the reaction. Moreover, in the presence of chlorotrimethylsilane (TMSCl), the reaction was promoted dramatically to give the desired Michael addition product in 84% yield.[7] The reaction was also effectively activated by other silyl compounds, such as chlorodimethylsilane, dichlorodimethylsilane and trimethylsilyl triflate.

The results of the reaction of tin(II) enolates with various enones are shown in Table 2. In all cases the reaction is effectively promoted by the silyl compound and the desired Michael addition product is obtained in moderate to good yields. Furthermore, it is noted that the diastereomer ratio of the products obtained was dependent on the activator employed and in some cases either diastereomer could be obtained predominantly by choosing either TMSCl or chlorodimethylsilane as activator. It is also noted that various enolates derived from ordinary ketones could be successfully employed in the present reaction.

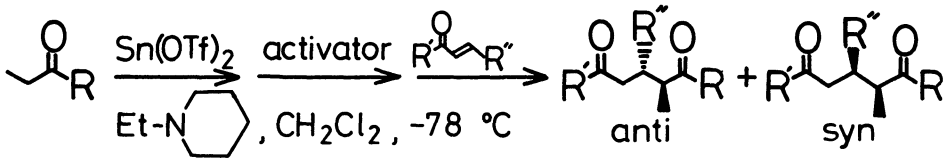
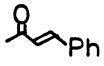
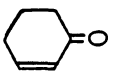
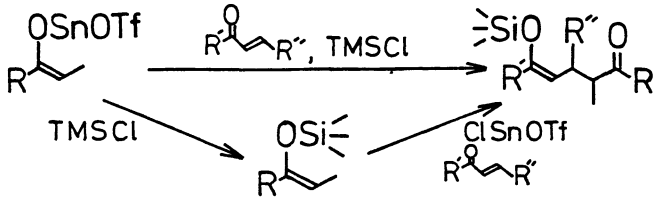


Table 2.

	R	Acceptor	Yield/%[c]	anti:syn[4]	Activator[a]
1			77	8:92	A
2	"	"	78	71:29	B
3	"		56	95: 5	A
4	"	"	56	71:29	B
5	"		85	75:25	A
6	"		84	62:38	B
7	-Et		72	____[b]	A

a) Activator A; chlorodimethylsilane, B; chlorotrimethylsilane.
b) Diastereomer ratio not determined.
c) In all cases, no 1,2-addition product was observed.

Regarding the mechanism of this reaction, the following two pathways are feasible. In one possible pathway, the nucleophilic species is the tin(II) enolate, with the activation of the acceptor by TMSCl. The other possibility is that the nucleophile is the silyl enol ether, formed by silylation of the tin(II) enolate by TMSCl, and the enone is activated by the tin(II) species. (Scheme 1)



Scheme 1.

Although, at present, the latter pathway cannot be completely eliminated, the following experimental results suggest that the nucleophilic species is in fact the tin(II) enolate and not the silyl enol ether.

The reaction between the silyl enol ether of propiophenone and phenylpropenylketone did not proceed in the presence of tin(II) triflate-chiral diamine. On the other hand, the addition of chiral diamine to the tin(II) enolate of propiophenone, followed by the addition of phenylpropenylketone and trimethylsilyl triflate gave an optically active Michael addition product. These results indicate that, in the presence of a diamine, tin(II) triflate is not strong enough as a Lewis acid to promote the Michael reaction between silyl enol ether and α,β-unsaturated ketone, and the reaction proceeds predominantly via the tin(II) enolate. Although the presence of diamine renders an exact comparison impossible, these facts imply that the tin(II) enolate is the active nucleophile in the present reaction.

Also, the special ability of silyl compounds to effectively promote this reaction should be noted. We believe this exemplifies the specific interaction between tin(II) and silyl compounds reported in a previous communication.[8)]

A typical procedure is described for the reaction of 3-propionyl-2-oxazolidone with phenylpropenylketone: To a suspension of $Sn(OTf)_2$ (343 mg, 0.82 mmol) and N-ethylpiperidine (116 mg, 1.03 mmol) in 2 ml of dichloromethane was added 3-propionyl-2-oxazolidone (97 mg, 0.67 mmol) in 1.5 ml of dichloromethane at -78 °C under argon with stirring. After stirring for 1 h, phenylpropenylketone (77 mg, 0.53 mmol) and TMSCl (107 mg, 0.99 mmol) were added successively to the reaction mixture. The reaction was further stirred for 2 h at -78 °C, then quenched with 10% citric acid solution, and the organic materials were extracted with dichloromethane three times. To completely hydrolyze the trimethylsilyl ether product, the crude Michael adduct obtained after evaporation of the solvent was dissolved in methanol and to this solution was added citric acid. After stirring for 1 h the reaction was quenched with pH 7 phosphate buffer. The organic layer was extracted three times with dichloromethane and the combined extracts were dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product was purified by preparative thin layer chromatography to afford the desired product (120 mg, 79%).

Thus, the Michael addition reaction of tin(II) enolates and α,β-unsaturated

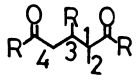
ketones proceeds smoothly by the use of TMSCl as activator to give the corresponding addition products in good yields. Further studies directed towards clarification of mechanism as well as further applications of this reaction are currently in progress in our laboratory.

References

1) E. D. Bergmann, D. Ginsburg, and R. Pappo, Org. React., 10, 179 (1959).

2) For examples of Michael additions of metal enolates to α,β-unsaturated ketones see: a) D. A. Oare and C. H. Heathcock, Tetrahedron Lett., 27, 6169 (1986); b) C. H. Heathcock, M. A. Henderson, D. A. Oare, and M. A. Sanner, J. Org. Chem., 50, 3019 (1985); c) C. H. Heathcock and D. A. Oare, ibid., 50, 3022 (1985); d) K. Kpegba, P. Metzner, and R. Rakotonirina, Tetrahedron Lett., 27, 1505 (1986); e) M. E. Krafft, R. M. Kennedy, and R. A. Holton, ibid., 27, 2087 (1986); f) W. Oppolzer, R. Pitteloud, G. Bernardinelli, and K. Baettig, ibid., 24, 4975 (1983); g) J. Mulzer, G. Hartz, U. Kühl, and G. Brüntrup, ibid., 19, 2949 (1978); h) J. Bertrand, L. Gorrichon, and P. Maroni, Tetrahedron, 40, 4127 (1984); i) G. H. Posner and S. B. Lu, J. Am. Chem. Soc., 107, 1424 (1985); j) G. H. Posner, S. B. Lu, and E. Asirvatham, Tetrahedron Lett., 27, 659 (1986); k) G. H. Posner and E. Asirvatham, ibid., 27, 663 (1986).

3) T. Mukaiyama, N. Iwasawa, R. W. Stevens, and T. Haga, Tetrahedron, 40, 1381 (1984), and references therein.

4) Assignment of stereostructure to the products. 
The relative stereochemistry of the products was assigned by the following methods. The product of entries 3,4 (Table 2) was converted to the methyl ester by treatment with sodium methoxide in methanol, and then compared with an authentic sample of known stereochemistry.[2d] Stereostructures of the products of entries 1,2,5 (Table 2) were tentatively assigned by ^{13}C NMR, based on the characteristic chemical shift of the primary carbon 2.[5] Stereochemistry of the product of entry 6 (Table 2) was assigned by analogy of ^{13}C NMR spectra to a similar compound, the structure of which has already been rigorously determined.[6]

5) For the ^{13}C NMR spectra of various similar Michael addition products, see C. H. Heathcock, M. H. Norman, and D. E. Uehling, J. Am. Chem. Soc., 107, 2797 (1985), supplementary material. It is noted that the chemical shift of carbon 2 of the anti isomer is 2-3 ppms larger than that of the syn isomer, and thus we assigned the stereochemistry of the products accordingly.

6) T. Mukaiyama, M. Tamura, and S. Kobayashi, Chem. Lett., 1986, 1017.

7) For examples of Michael type reactions enhanced by TMSCl, see; C. Chuit, J. P. Foulon, J. F. Normant, Tetrahedron, 36, 2305 (1980); E. J. Corey and N. W. Boaz, Tetrahedron Lett., 26, 6015 (1985); E. J. Corey and N. W. Boaz, ibid., 26, 6019 (1985); A. Alexakis, J. Berlan, and Y. Besace, ibid., 27, 1047 (1986); E. Nakamura, S. Matsuzawa, Y. Horiguchi, and I. Kuwajima, ibid., 27, 4029 (1986); Y. Horiguchi, S. Matsuzawa, E. Nakamura, and I. Kuwajima, ibid., 27, 4025 (1986); see also H. Oshino, E. Nakamura, and I. Kuwajima, J. Org. Chem., 50, 2802 (1985); and references therein.

8) N. Iwasawa and T. Mukaiyama, Chem. Lett., 1987, 463.

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