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Mukaiyama-Michael Reaction of Cyclic Ketene Silyl Acetals and Enones. Importance of Ring Flexibility in Electron Transfer Process

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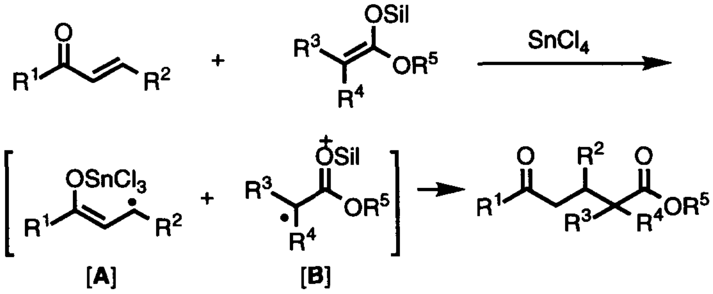
Abstract: Michael reaction of macrocyclic ketene silyl acetals or α-enones occurs smoothly under electron transfer conditions while the reaction of 6-membered analogs is more sluggish, indicating the importance of the ring flexibility to allow the α,β-carbon-carbon bonds of both reaction components to rotate when the radical species are generated. © 1997 Elsevier Science Ltd.

Previously, we disclosed that Mukaiyama-Michael reaction is initiated by electron transfer from ketene silyl acetal to Lewis acid when the ketene silyl acetals involve relatively small trialkylsilyl and/or alkoxy group(s) while the conventional nucleophilic mechanism operates with bulky ketene silyl acetals.[1-4] The electron transfer mechanism is depicted in Scheme 1 representatively with $SnCl_4$. This Lewis acid is reduced to the $SnCl_4$ anion radical which spontaneously decomposes to the $SnCl_3$ radical and Cl^-. The $SnCl_3$ radical adds to α-enone in a 1,4-fashion to give the stannyl enolate radical **A**. The ketene silyl acetal is converted to the cation radical **B** which couples with **A** to give the Michael adduct. On the basis of MO calculations and experimental results, rotation of the α,β-carbon-carbon bonds of the ketene silyl acetal and α-enone was suggested upon formation of these radical species. As a result, the spin densities in SOMO are localized mostly on the β-positions to promote the coupling between these reaction sites.

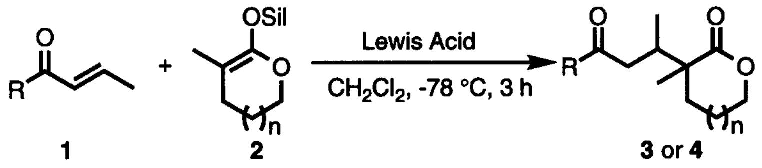
Scheme 1



It is well recognized that the 6-membered rings are conformationally rigid whereas the macrocycles are flexible.[5] If the generation of the radical species, **A** and **B**, is facilitated by the double bond rotation, the six-membered α-enones and ketene silyl acetals would be difficult to undergo the electron transfer. On the other hand, facile electron transfer reactions are expected with macrocyclic counterparts. In this letter, we report that this is indeed the case and, thus, the electron transfer process is highly plausible in Mukaiyama-Michael reaction.

We have chosen two reaction conditions: Sil = $^{t}BuMe_2Si$; Lewis acid = $TiCl_4$ for the nucleophilic reaction (NU) and Sil = Et_3Si; Lewis acid = $SnCl_4$ for the electron transfer reaction (ET).[2,4] Table 1 shows the results of Michael reaction of ketene silyl acetals derived from lactones under these conditions. Six-membered ketene silyl acetal **2a** (n = 1) smoothly reacts with enones **1** in the NU path (entries 1 and 3) but a little more sluggishly in the ET path (entries 2 and 4). By contrast, with 16-membered ketene silyl acetal **2b**(n = 11), both nucleophilic and electron-transfer reactions take place smoothly (entries 5-7).

Table 1. Michael Reaction of Ketene Silyl Acetals Derived from Lactones.



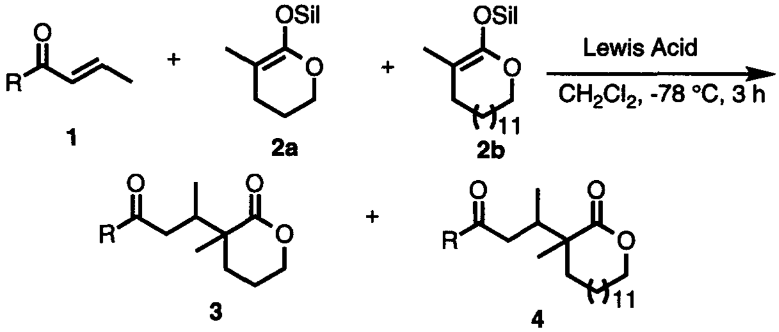
entry	n	Enone	Reaction Conditions[a]	Yield (%)[b]	
1	1	**1a** (R = ^{t}Bu)	NU	**3a**	75
2			ET		21
3		**1b** (R = Mesityl)	NU	**3b**	79
4			ET		40
5	11	**1a** (R = ^{t}Bu)	NU	**4a**	84
6			ET		93
7		**1b** (R = Mesityl)	ET	**4b**	74

[a] NU: Nucleophilic conditions (Sil = $^{t}BuMe_2Si$; Lewis acid = $TiCl_4$); **1**:**2**:$TiCl_4$ = 1.0:1.3:1.0. ET: Electron Transfer conditions (Sil = Et_3Si; Lewis acid = $SnCl_4$); **1**:**2**:$SnCl_4$ = 1.0:1.3:0.1. [b] Isolated yield.

The greater reactivity of **2b** than **2a** under the electron transfer conditions was exemplified by the competition reactions (Table 2). NU failed to differentiate **2a** and **2b** (entry 1 and 3) while the predominant or exclusive formation of Michael adduct **4** indicates that ET is facilitated with ketene silyl acetal derived from macrolide (entries 2 and 4).

More explicit differentiation was observed with cyclic α-enones. As seen from Table 3, when 3-methyl-2-cyclohexenone was exposed to ketene silyl acetal **5** under ET conditions, only a 31 % yield of the Michael adduct was obtained. In sharp contrast, 12- and 15-membered analogs[6] afforded the desired adducts in excellent yields under the same conditions.

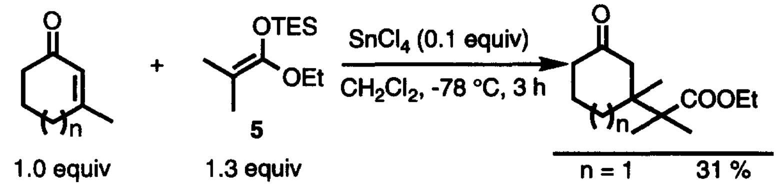
Table 2. Competition Reaction between Ketene Silyl Aetals Derived from Lactones of Different Ring Size.



entry	Enone	Reaction Conditions[a]	Yield (%)[b]		3:4
			3	4	
1	**1a** (R = ^{t}Bu)	NU	30	30	50:50
2		ET	8	35	19:81
3	**1b** (R = Mesityl)	Nu	34	36	49:51
4		ET	0	69	0:100

[a] **1**:**2a**:**2b**:$TiCl_4$ = 1:1:1:1. **1**:**2a**:**2b**:$SnCl_4$ = 1:1:1:0.1. [b] Isolated yield.

Table 3. Micheal Reaction of Cyclic Enones under Electron-Transfer Conditions.

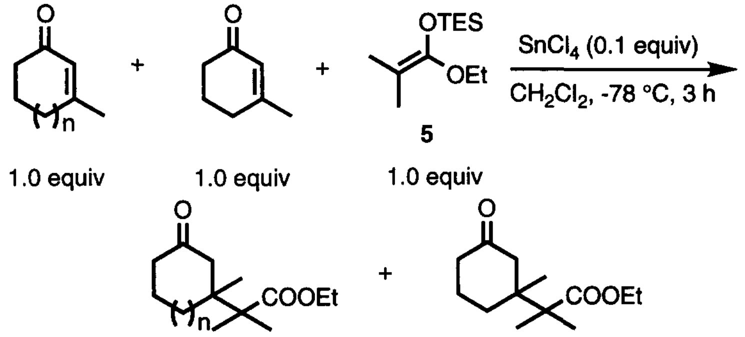


n = 1	31 %
= 7	90 %
= 10	89 %

(Isolated yields)

The preference of the macrocyclic α-enones in ET is highlighted by the competition reactions (Table 4). An equimolar mixture of a macrocyclic α-enone and 3-methyl-2-cyclohexenone was exposed to **5** in the presence of $SnCl_4$ (0.1 equiv). After 3 h, a quantitative yield of the Michael adduct derived from the former enone was obtained while no adduct from the latter was detected by GLC analysis. It has been proved again that the flexibility of the ring system is crucial for generating the metal enolate radical.

Table 4. Competition Reaction of Cyclic Enones of Different Ring Size under Electron-Transfer Conditions.



n = 7	98 %	0 %
= 10	96 %	0%

(Yields by GLC)

In summary, we have shown that ET occurs smoothly with macrocyclic ketene silyl acetals and α-enones. Apparently, the α,β-carbon-carbon bonds of these compounds rotate much more easily than those of the six-membered counterparts. These results not only provide useful mechanistic information but will find synthetic merits in carbon-carbon bond formation on the macrocyclic skeleton which is otherwise difficult to achieve.

References and Note

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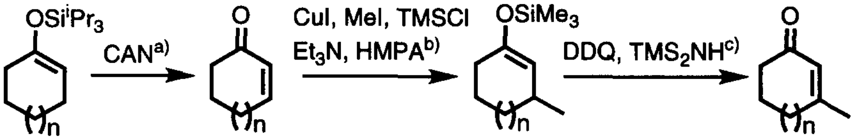
6. The macrocyclic enones were prepared according to the following method:



(a) Evans, D. A.; Longmire, J. M.; Modi, D. P. *Tetrahedron Lett.* **1995**, *36*, 3985. (b) Binkley, E. S.; Heathcock, C. H. *J. Org. Chem.* **1975**, *40*, 2156. (c) Ryu, I.; Hatayama, Y.; Sonoda, N. *Tetrahedron Lett.* **1978**, 3455. We obtained a single isomer but the geometry of the double bond was not assigned although the *E*-geometry is highly conceivable.

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