Reversal of Chemoselectivity in Organotin Lewis Acid-Catalyzed Reaction of Ketene Silyl Acetal with Aldehyde and α-Enal

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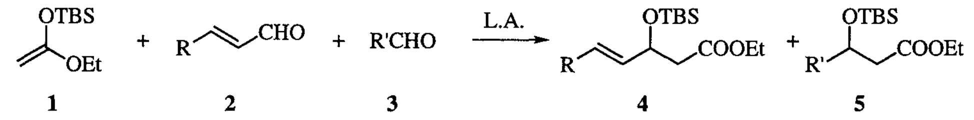
Abstract: The organotin Lewis acid-catalyzed reaction of ketene silyl acetal with aldehydes results in reversal of chemoselectivity: α-enals react preferentially or exclusively in competition with an alkanal or even aromatic aldehydes.

Addition of nucleophiles to carbonyls is one of the most important reactions in organic synthesis. In this context, differentiation between different carbonyl functions is highly desired.[1] In general, incorporation of electron-donating group on carbonyl decreases the electrophilicity of the carbonyl carbon. An α,β-unsaturated group also reduces the reactivity of the carbonyl group through the delocalization of π-electrons[2,3] and, hence, α-enones and -enals are less reactive than the corresponding alkanones and alkanals. Reversal of the reactivity between these carbonyl groups is of great synthetic interest but rather difficult to achieve. Reetz disclosed that $CH_3Ti(O^iPr)_3$ reacted with α-enone and -enal faster than the corresponding aliphatic ketone and aldehyde.[2] He explained this selectivity in terms of the more increased steric hindrance of aliphatic carbonyls. Recently, Markó et al. reported the analogous selectivity for the addition of thallium ate complexes to a mixture of enone and ketone; α-enones and acetophenones reacted preferentially over aliphatic ketones (selectivity 5:1 ~ >75:1).[3] In this case, the initial electron transfer from the ate complex to the carbonyls was put forth. It seems that such differentiation is more difficult between aldehyde pairs because of their higher reactivities. Herein, we report, for the first time, the high preference for α-enals over aldehydes in the reaction with ketene silyl acetals.

We have disclosed that organotin Lewis acids are so mild that various types of carbonyl functions could be discriminated.[4] The continuing study has led us to find that tributyltin perchlorate (TBTP) and dibutyltin bis(triflate) (DBTT) effectively catalyze the addition of ketene silyl acetal to aldehyde, in which α-enals are predominantly or exclusively consumed in competition with simple aldehydes.

A solution of 1-ethoxy-1-(*tert*-butyldimethylsiloxy)ethene (**1**), α-enal **2**, and aldehyde **3** (1 mmol each) in dichloromethane (10 mL) was stirred in the presence of TBTP or DBTT (0.1 mmol) at -78 °C for 2 h. Aqueous workup followed by evaporation afforded a crude product that was analyzed by GLC. The results are summarized in Table 1. In the reactions with a mixture of cinnamaldehyde and octanal, the former reacted exclusively (entries 1 and 2). The competition with benzaldehyde exhibited slightly decreased selectivities (entries 3 and 4). Basically, the same trend was observed in the reactions of crotonaldehyde (entries 9-12). Noteworthy are the effects of the *para*-

Table 1. Reversal of Reactivity between Aldehyde and α-Enal[a]



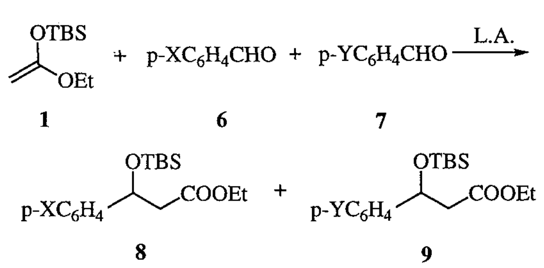
Entry	2	3	L.A.	yield/%[b] 4	5	4:5
1	PhCH=CHCHO	n-$C_7H_{15}CHO$	TBTP	81	0	100:0
2			DBTT	71	0	100:0
3		PhCHO	TBTP	77	7	92:8
4			DBTT	79	2	97:3
5		4-NCC_6H_4CHO	TBTP	78	0	100:0
6			DBTT	72	0	100:0
7		4-$MeOC_6H_4CHO$	TBTP	33	52	39:61
8			DBTT	21	57	27:73
9	$CH_3CH=CHCHO$	n-$C_7H_{15}CHO$	TBTP	69(4)[c]	0	100:0
10			DBTT	61(5)[c]	0	100:0
11		PhCHO	TBTP	62(4)[c]	16	80:20
12			DBTT	64(5)[c]	4	94:6

[a] Reaction conditions: **1**:**2**:**3**:L.A. = 1:1:1:0.1; CH_2Cl_2; -78 °C; 2 h. [b] Determined by GLC.

[c] Yield of 1,4-addition product in parentheses.

substituents on benzaldehyde (entries 5-8). An electron-withdrawing group suppressed the reactivity, thus increasing the preference for cinnamaldehyde while the selectivity was reversed by the electron-donating group. These results obviously oppose the conventionally accepted order of reactivity. To get further insight into this aspect, we conducted competitions between *p*-substituted benzaldehyde derivatives. As shown in Table 2, the same electronic effects were observed: the reactivity was enhanced by *p*-methoxy group while reduced by *p*-cyano group.[5] Note that the reaction of thallium ate complexes with *p*-substituted acetophenones gave the normal selectivities: deceleration by *p*-methoxy group and acceleration by *p*-cyano group.[2] Apparently, the reactivity of carbonyl in the presence of Lewis acid is different from that of free carbonyl. The reactivity becomes greater with increasing the coordinating ability of carbonyl.[5] The use of 2 equivalent amount of TBTP did not alter the selectivity (entry 6). Presumably, the preferential coordination with, and hence exclusive activation of, anisaldehyde occurred while the interaction with *p*-cyanobenzaldehyde was not effective. By contrast, the stoichiometric use of $TiCl_4$ failed to bias the selectivity (entry 8). In this case, the strongly acidic $TiCl_4$ would coordinate indiscriminately with both aldehydes.[6,7]

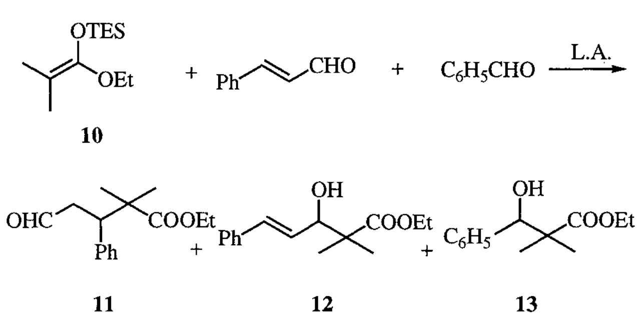
Table 2. Electronic Effects on Competition between Aldehydes[a]



Entry	X	Y	L.A.	yield/%[b] 8	9	8:9
1	H	MeO	TBTP	5	80	6:94
2			DBTT	0	83	0:100
3	H	CN	TBTP	71	4	95:5
4			DBTT	54	0	100:0
5	MeO	CN	TBTP	88	0	100:0
6			TBTP[c]	84	0	100:0
7			DBTT	81	0	100:0
8			$TiCl_4$[d]	34[e]	23[e]	60:40

[a] Reaction conditions: **1**:**6**:**7**:L.A. = 1:1:1:0.1; CH_2Cl_2; -78 °C; 2 h. [b] Determined by GLC. c) **1**:**6**:**7**:TBTP = 1:1:1:2. [d] **1**:**6**:**7**:$TiCl_4$ = 1:1:1:2. [e] Not the silyl ether but the alcohol.

Finally, the similar reactions employing dimethyl ketene silyl acetal **10** were studied (Scheme 1). Treatment of **10** with cinnamaldehyde afforded a mixture of 1,2- and 1,4-addition products. Nevertheless, the competition reaction employing an equimolar mixture of cinnamaldehyde and benzaldehyde also led to the high preference for the former.



L.A.	Yield/% 11	12	13	(11 + 12):13
TBTP	64	12	3	96:4
DBTT	42	20	3	95:5

Scheme 1

In conclusion, the preferential reaction of α-enal over aldehyde has been achieved by use of organotin Lewis acids. Mildness of the Lewis acids and their catalytic use are crucial for attaining the high selectivity. The catalyst should be acidic enough to trigger the reaction but not too much acidic to detect the delicate difference of carbonyl functions. The organotin Lewis acids meet well these requirements.

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References and Notes

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(7) More detailed discussion on this issue will be given by Nakai's group: Hanuyda, K.; Hirai, K.-i.; Nakai, T *Synlett* **1997**, 31.