Diastereo- and Regio-selective Aldol Condensation by Trapping Dienolates with Tin

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Although the reaction of dienolate (**1**) with aldehydes is frequently lacking in regio- and diastereo-selectivity, the γ-tin substituted derivatives (**5**), easily obtainable from (**1**), give (**3**) and (**4**) diastereoselectively by controlling the reaction conditions.

Despite rapid progress in aldol chemistry during the past decade,[1] the problem of diastereo- and regio-selectivity in the reaction of the dienolate (**1**) with aldehydes remains unsolved. The reaction of (**1**) with aldehydes at higher temperatures under thermodynamically controlled conditions leads to the γ-adduct (**2**), and in turn (**2′**).[2] At lower temperatures under kinetically controlled conditions, α-regioselective carbon–carbon bond formation is realized. Unfortunately, however, the diastereoselectivity is low and frequently a mixture of (**3**) and (**4**) is produced (Scheme 1).[2] In this communication we report a method of trapping dienolates with tin to provide a solution to some of these problems.

The reaction of (**1**) with R_3SnCl gave (**5**) in an essentially quantitative yield (Scheme 1). The tin intermediate was stable enough to isolate through Kugelrohr distillation. Compound (**5**) (*Z*-isomer) was always contaminated with small amounts of the (*E*)-isomer. The results of the reactions of (**5**) with representative aldehydes under the influence of Lewis acids or Bu_4NF are summarized in Table 1.

The BF_3- and $ZnBr_2$-mediated reactions of (**5a**—**c**) with aldehydes at −78 °C produced the *anti* adduct (**4**) either exclusively or predominantly (entries 1, 4—8, and 10). Use of $TiCl_4$ gave a mixture of (**3**), (**4**), and the γ-products (entry 2). Although the F^- mediated reactions of (**5b**—**d**) at −78 °C afforded again (**4**) either exclusively or predominantly (entries 9, 12, and 14), the same reaction of (**5a**) gave (**3**) preferentially (entry 3). Further, (**5c**) and (**5d**) reacted with benzaldehyde at room temperature without Lewis acids or Bu_4NF assistance (entries 11 and 13), presumably owing to the increased Lewis acidity of these tin chlorides.[3]†

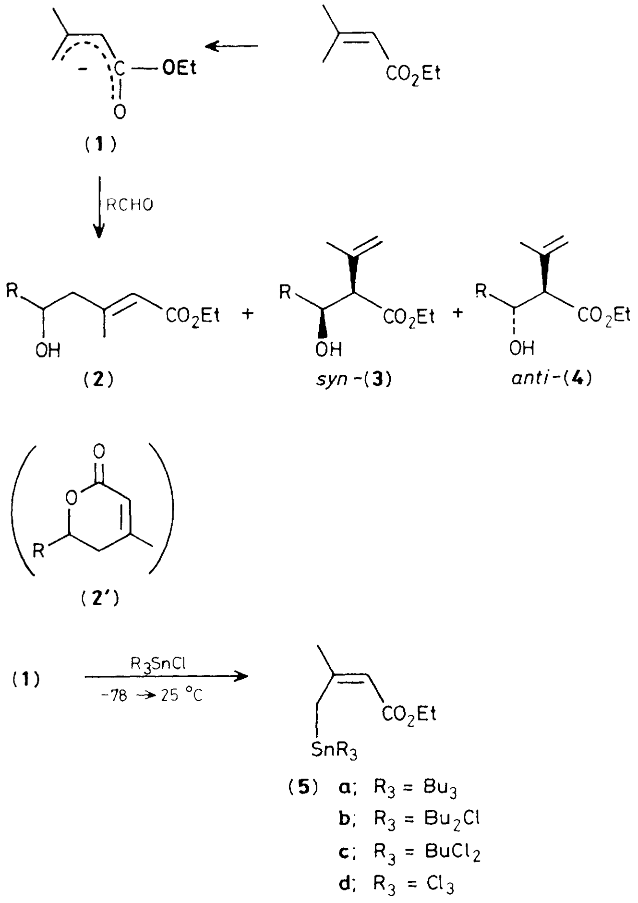
The above observations on diastereoselectivity are different from the recent results on γ-silylated α,β-unsaturated amides reported by Snieckus and coworkers.[4] The $TiCl_4$-mediated reaction of the silylated analogue produces the corresponding *syn* derivatives, while the F^- mediated reaction does not produce good diastereoselectivity.[4] The present diastereoselectivity can be explained as shown in Scheme 2.

The Lewis acid mediated reaction proceeds through the acyclic transition state (**6**), as proposed previously,[5] to produce the *anti* alcohol [*anti*-(**4**)] regardless of the geometry of the double bond. Without Lewis acids (entries 11 and 13), the (*Z*)-allylic stannanes (**5c,d**) again produce (**4**) *via* a six-membered cyclic transition state. The reaction of Bu_4NF

Table 1. Regio- and diastero-selective reaction of (**5**) with aldehydes.[a]

Entry	Tin	Aldehyde	Additive	Product ratio[b] (3)	(4)	(2)	Total yield[b,c] /%
1	(**5a**)	PhCHO	$BF_3 \cdot OEt_2$	—	100	—	100
2	(**5a**)	PhCHO	$TiCl_4$	22	34	44	100
3	(**5a**)	PhCHO	Bu_4NF	72	28	—	65
4	(**5a**)	EtCHO	$BF_3 \cdot OEt_2$	—	100	—	34
5	(**5a**)	$(Et)_2CHCHO$	$BF_3 \cdot OEt_2$	—	100	—	40
6	(**5a**)	PhCH=CHCHO	$BF_3 \cdot OEt_2$	16	84	—	69
7	(**5b**)	PhCHO	$BF_3 \cdot OEt_2$	—	100	—	33
8	(**5b**)	PhCHO	$ZnBr_2$	—	100	—	52
9	(**5b**)	PhCHO	Bu_4NF	—	100	—	65
10	(**5c**)	PhCHO	$BF_3 \cdot OEt_2$	—	100	—	30
11	(**5c**)	PhCHO	None	—	100	—	70
12	(**5c**)	PhCHO	Bu_4NF	—	100	—	30
13	(**5d**)	PhCHO	None	16	48	37	100
14	(**5d**)	PhCHO	Bu_4NF	22	78	—	100

[a] All reactions were carried out on 1 mmol scale at −78 °C, except entries 11 and 13 where the reactions were carried out at room temperature. CH_2Cl_2 (entries 1,2, 4—8, 10,11, and 13) or tetrahydrofuran (entries 3,9,12, and 14) solvent was used. [b] Determined by ^1H n.m.r. analysis. [c] When the yield was low, the self-condensation of (**5**) took place and the aldehyde was recovered.



Scheme 1

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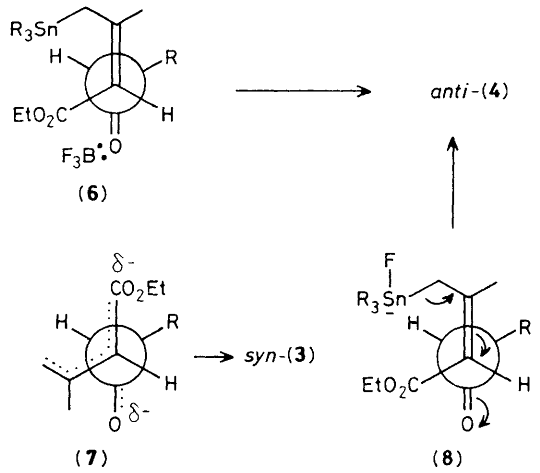
† The structures of (**2**)—(**4**) were unambiguously determined by comparison with authentic materials (ref. 2a).



Scheme 2

with (**5a**) may give the naked dienolate, in which the negative charge will be localized at the ester function. Accordingly, the reaction proceeds through (**7**) which is the most stable intermediate from both steric and electronic points of view, resulting in the predominant formation of (**3**). The reaction of Bu_4NF with (**5b—d**) may afford the ate complex owing to the strong electron withdrawing effect of the Cl atom. Thus, (**8**) must be the most stabilized transition state, leading to (**4**). In conclusion, this work provides not only a regio- and diastereoselective aldol methodology for dienolates, but also opens up the argument whether a naked anion is involved in F^- mediated reactions.

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