On 1,4-Diastereoselectivity in the Aldol Condensation of Methyl Ketones

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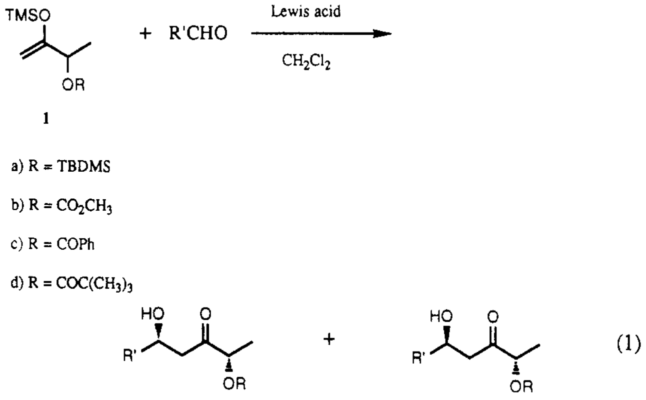
Summary: 2-(Trimethylsiloxy)-3-RO-1-butene serves as practical and simple chiral enolate equivalent of a methyl ketone for asymmetric aldol condensations.

The aldol condensation has become a major tool for stereocontrolled approach to acyclic systems.[1] A particularly important aspect for asymmetric induction utilizes chiral auxiliaries which require transmission of stereochemical information between distant centers. While such information transfer is quite successful for enolates of ethyl or higher alkyl ketones, this approach notably is much less successful with enolates of methyl ketones.[2-4] In the course of our studies of the bifunctional conjunctive reagents derived from 2-(trimethylsiloxy)-3-RO-1-butene,[5] we examined its role in the aldol condensation and discovered a remarkable dependence of remote diastereoselectivity on the choice of the RO group.

The acetoin derivatives were converted regioselectively into their corresponding terminal enol silyl ethers[6] using trimethylsilyl triflate and triethylamine (PhH, 0 °C to room temperature, 76–88%). Their participation in the aldol condensation was explored using aldehydes[7] and acetals[8] in the presence of Lewis acids and fluoride ion[9] according to eqs 1 and 2. Table I summarizes the results.

Fluoride ion initiated reactions were considerably poorer both in yield and diastereoselectivity than Lewis acid catalyzed reactions. Among the Lewis acids, titanium tetrachloride is marginally best. A dramatic effect arises by changing the oxygen substituent. The silyl[10] and methoxycarbonyl groups provide approximately 2:1 diastereomeric ratios (dr). On the other hand the benzoyl group shows a very good dr which further improves with the pivaloyl group. Condensations with the free aldehydes give higher dr than the acetal version.



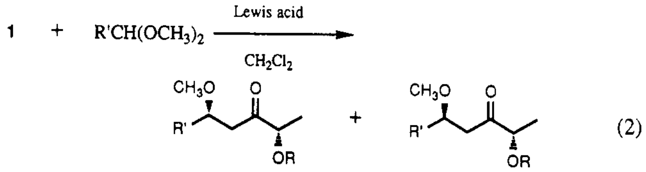
1

a) R = TBDMS

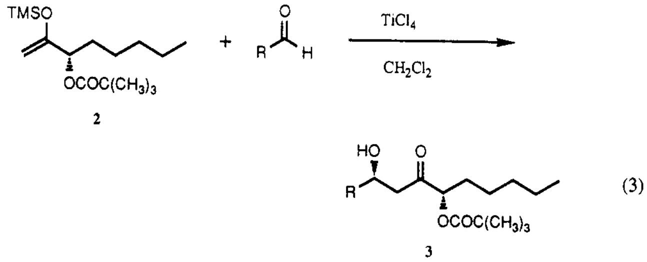
b) R = CO_2CH_3

c) R = COPh

d) R = $COC(CH_3)_3$



The reaction appears to be more general. For example, the higher homologue bifunctional reagent **2**[6] gives the corresponding aldol adducts in good yields (69–77%) and with excellent dr (**3a**, 92:8; **3b**, 97:3) (eq 3).



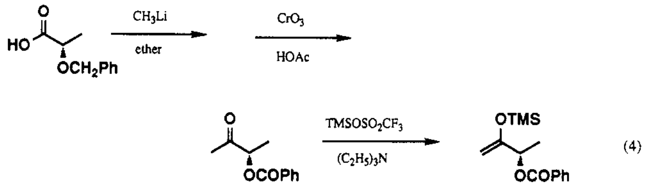
2

3

a) R = n-C_5H_{11}

b) R = i-C_3H_7

In order to establish the stereochemistry and to demonstrate the applicability for asymmetric synthesis, the *O*-benzyl ether of lactic acid was converted to the benzoate **1c** (*S*) of >98% ee [$[\alpha]_D^{26}$ + 32° (c = 1.0, $CHCl_3$)] according to eq 4.[11] To verify that enol silyl ether formation does



1c (*S*)

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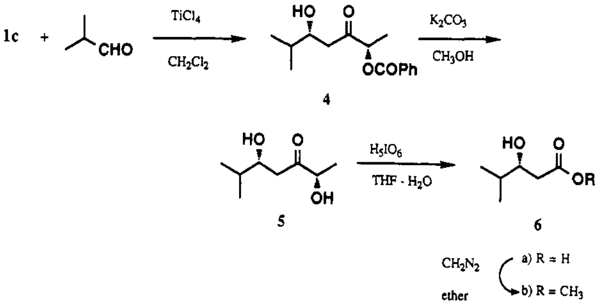
Table I. Diastereoselectivity of Aldol Condensation of 2-((Trimethylsilyl)oxy)-3-RO-1-butene[a]

entry	enol silyl ether	electrophile	catalyst	time, h	% yield[b]	dr[c]
1	**1a**	i-C_3H_7CHO	$TiCl_4$[d]	4	93 (66)[e]	67:33
2	**1b**	n-$C_5H_{11}CHO$	$TiCl_4$	1	75	63:37
3	**1b**	i-C_3H_7CHO	$TiCl_4$	1	64	75:25
4	**1b**	t-C_4H_9CHO	$TiCl_4$	3.5	36	66:34
5	**1b**	PhCHO	$TiCl_4$	1	nd	70:30
6	**1b**	PhCHO	TBAF[f]	4.5	10	60:40
7	**1b**	n-$C_5H_{11}CH(OCH_3)_2$	$TMSOSO_2CF_3$[h]	9	91	60:40
8	**1b**	i-$C_3H_7CH(OCH_3)_2$	$TMSOSO_2CF_3$	4	37	70:30
9	**1b**	i-$C_3H_7CH(OCH_3)_2$	$TiCl_4$	3.5	99	63:37
10	**1b**	t-$C_4H_9CH(OCH_3)_2$	$TMSOSO_2CF_3$	8	20	75:25
11	**1b**	$PhCH(OCH_3)_2$	$TMSOSO_2CF_3$	3	99	69:31
12	**1b**	$PhCH(OCH_3)_2$	$TiCl_4$	3.5	99	60:40
13	**1c**	i-C_3H_7CHO	$TiCl_4$	3.5	(88)[e]	92:8
14	**1d**	n-$C_5H_{11}CHO$	$TiCl_4$	3.5	94	89:11
15	**1d**	i-C_3H_7CHO	$TiCl_4$	3.5	99 (78)[e]	96:4
16	**1d**	i-C_3H_7CHO	BF_3 ether	3	30[i]	92:8[g]
17	**1d**	i-C_3H_7CHO	$C_2H_5AlCl_2$	3	92[i]	89:11[g]
18	**1d**	i-$C_3H_7CH(OCH_3)_2$	$TMSOSO_2CF_3$	9	67	83:17
19	**1d**	i-$C_3H_7CH(OCH_3)_2$	$TiCl_4$	3	99	81:19
20	**1d**	t-C_4H_9CHO	$TiCl_4$	3.5	(61)[e]	98:2

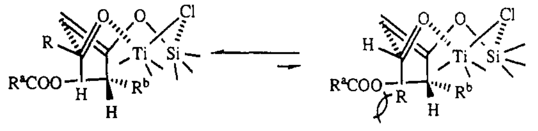
[a] All reactions were run in methylene chloride at −78 °C unless otherwise stated. [b] Yields determined by ^1H NMR using an internal standard. Isolated yields appear in parentheses. [c] Diastereomeric ratio (dr) determined by ^1H NMR before purification. [d] Cf. ref 7. [e] Purification does not affect dr. [f] This reaction performed in THF and produces the silyl ether, cf. ref 9. [g] Ratio obtained after desilylation with aqueous sulfuric acid in THF. [h] Cf. ref 8. [i] The product was a mixture of the alcohol and the silyl ether.

not cause racemization, aqueous sulfuric acid hydrolysis of the enol silyl ether returns the benzoate ester of acetoin of 98% ee. Aldol condensation with isobutyraldehyde with titanium tetrachloride in methylene chloride at −78 °C gives an 83% yield of the adduct 4 as a 92:8 ratio of diastereomers (eq 5, only major isomer depicted). Benzoate hydrolysis and periodate cleavage produces the known β-hydroxy acid **6a**[2a] whose esterification produces the known β-hydroxy ester **6b**.[12] The positive rotation of the acid indicates it to be *R*. (+)-Eu(hfc)$_3$-induced NMR shifts which provide excellent separation of the methyl ester signals [20 mol %, δ 4.13 (*S*)/4.31 (*R*); 40 mol %, δ 4.42 (*S*)/4.77 (*R*)] indicated a 91:9 ratio of *R* and *S* alcohols in excellent accord with the diastereomeric ratio of adduct **4**.



(5)

To account for the high selectivity observed, a cyclic transition state 7 involving titanium to activate the aldehyde and effect desilylation is proposed. Dipole–dipole interactions which should favor a conformation in which the α-oxygen substituent is anti are enhanced by using an electron-withdrawing oxygen substituent. Furthermore, increasing the steric bulk of R^a should amplify the effect. The combination of these two factors then accounts for the high diastereoselectivity without a substituent on the enol carbon which previously was required to help orient the reacting partners. The simplicity of these substrates, their accessibility in enantiomerically pure form, and the versatility of the substitution pattern created should make this approach useful for acyclic stereocontrol.[13]



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Acknowledgment. We thank the National Institutes of Health, General Medical Sciences, for their generous support of our programs.

Supplementary Material Available: Spectroscopic data for **1a–d**, **2**, **3a**, **3b**, and adducts of **1d** with isobutyraldehyde and pivaldehyde (2 pages). Ordering information given on any current masthead page.

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(11) For methyl ketone formation, see: Jorgenson, M. J. *Org. React.* **1970**, *18*, 58. For oxidation, see: Angyal, S. J.; James, K. *Carbohydr. Res.* **1970**, *12*, 147.

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(13) General procedure: A solution of 1.0 equiv of titanium tetrachloride in methylene chloride (1 M) was added to a solution of 1.0 equiv of the aldehyde in the same solvent (0.2 M) at −78 °C followed by 1.0 equiv of the enol silyl ether. After 3.5 h at −78 °C, the reaction was quenched with aqueous sodium bicarbonate at −78 °C, and the resultant mixture was extracted with ether. After the usual workup, flash chromatography (ether–hexane) gave the pure products.