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The Catalytic Asymmetric Aldol Reaction of Aldehydes with Unsubstituted and Monosubstituted Silyl Ketene Acetals: Formation of *Anti*-β-Hydroxy-α-Methyl Esters

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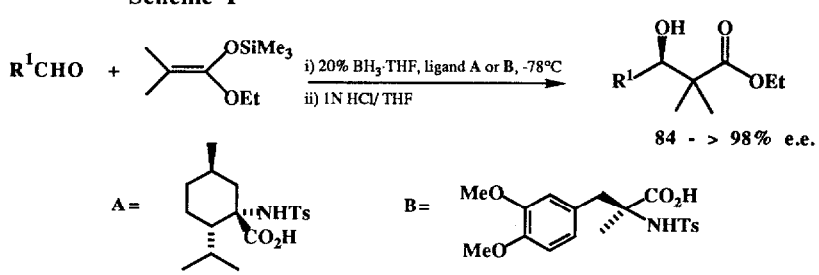
Abstract: The title reaction with unsubstituted and monosubstituted silyl ketene acetals proceeds with high enantioselectivity, and in the latter case good diastereoselectivity favoring the anti-β-hydroxy-α-methyl esters in all reported cases.

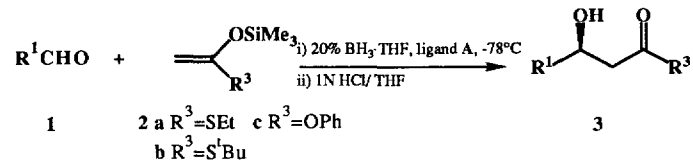
The Lewis Acid-catalyzed asymmetric aldol reaction between an achiral aldehyde and a silyl ketene acetal has recently attracted the interest of synthetic organic chemists,[1,2] notably Mukaiyama[3] and Yamamoto.[4] Our investigation in this area has led to the finding that excellent enantioselectivities can be achieved on addition of aldehydes to 1-trimethylsilyloxy-1-ethoxy-2-methyl-1-propene (dimethyl silyl ketene acetal) in the presence of a catalytic (10-20%) amount of the chiral borane complexes of α,α-disubstituted glycine arenesulfonamides **A** or **B**, as shown in Scheme I.[5] Described herein is an extension of this work to include unsubstituted and monosubstituted ketene acetals, both of which react with high enantioselectivity and in the latter case good diastereoselectivity favoring the *anti*-β-hydroxy-α-methyl esters in all reported cases. This stereochemical outcome contrasts sharply with that previously described for similar reactions.[3,4]

Scheme I

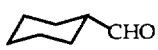
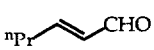
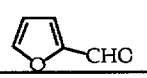


The aldol reactions were carried out by slow addition of a solution of the aldehyde to a -78°C mixture of the ketene acetal (1.2 eq.) and borane complex (0.2 eq., formed by addition of 1M BH_3·THF to a solution of the ligand in propionitrile). Stirring was then continued at that temperature until complete consumption of the starting materials was observed by t.l.c. analysis (1-48h). Quenching the reaction (pH 7 buffer) and extractive work up led to the isolation of the silyl ether as the major product, accompanied by a small proportion of the β-hydroxy ester. Desilylation of the mixture directly, using dilute hydrochloric acid or 1M $^{n}Bu_4NF$ in THF, yielded the desired aldol products **3** or **5/6** after chromatography.

Table 1: Catalytic Aldol Reactions of Silyl Ketene Acetals[a] **2a-c** with Aldehydes Mediated by Borane Complex of Ligand **A**.



1 2 a R^3=SEt c R^3=OPh 3
b R^3=S^{t}Bu

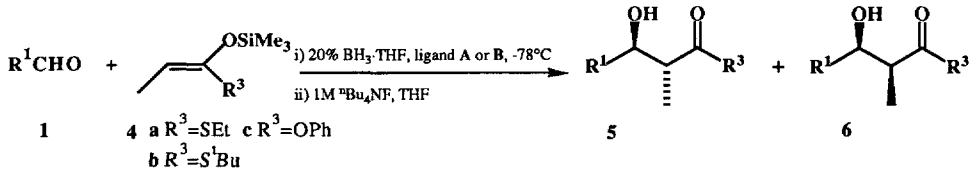
Entry	Aldehyde	R^3	Yield %	e.e %[b] (config)[c]
1	PhCHO	S^{t}Bu	86	87 (S)
2	PhCHO	SEt	89	89 (S)
3	PhCHO	OPh	77	93 (S)
4	$PhCH_2CH_2CHO$	S^{t}Bu	77	91 (R)
5	$PhCH_2CH_2CHO$	SEt	82	89 (R)
6	$PhCH_2CH_2CHO$	OPh	78	85 (R)
7	$CH_3CH_2CH_2CHO$	S^{t}Bu	91	92 (R)
8		S^{t}Bu	75	81 (S)
9		OPh	87	84 (S)
10		S^{t}Bu	91	82
11		S^{t}Bu	98	85

[a] Colvin, E. W. *Silicon Reagents in Organic Synthesis*; Acad. Press: London, 1988, pp. 99-102. [b]Determined by chiral Daicel OD or OJ HPLC column, or ^1H(300 MHz) and ^{19}F NMR analysis of the MTPA esters derived from **3**. [c] Absolute configurations determined by comparison of optical rotations of the corresponding 1,3-diols with those of newly or previously prepared diols; Masamune, S.; Sato, T.; Kim, B.M.; Wollmann, T.A. *J. Am. Chem. Soc.* **1986**, *108*, 8279, (See also Kim, B. M. M.I.T. Ph.D. thesis, 1987).

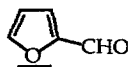
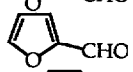
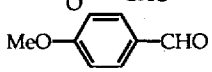
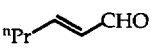
Results obtained with unsubstituted ketene acetals **2a-c** derived from thiol esters and phenyl acetate are summarized in Table 1. Ligand **A**, derived from (-)-menthone, provided superior selectivities, and hence, was used to form the chiral catalyst in every case. The reaction was tested using a variety of aldehydes and proceeded in high chemical yield and, pleasingly, with high enantioselection as well (81- 93% e.e.). Note that in all cases determined, products have the absolute configuration indicated by stereostructure **3**. Other alkyl esters - OBn, O^{t}Bu, OC_6H_{11} - gave reduced reactivity and selectivity.[6]

Next, the effect of a methyl substituent at the β-carbon was investigated. Ketene acetals **4a-c**, prepared from *S-ethyl* and *S-tert-butyl propanethioates and phenyl propionate respectively, were again*

Table 2: Catalytic Aldol Reactions of Silyl Ketene Acetals[a] **4a-c** with Aldehydes Mediated by Borane Complexes of Ligands **A** and **B**.



1 4 a R^3=SEt c R^3=OPh b R^3=S^{t}Bu 5 6

Entry	Aldehyde	R^3	Ligand (A or B)	Yield of 5/6 %	5(*anti*)/6(*syn*)[b]	e.e. %[c] (config) [d]
1	PhCHO	SEt	A	89	87/13	80 (R,S) /94 (S,S)
2	PhCHO	S^{t}Bu	A	78	94/6	82 (R,S) /66
3	PhCHO	OPh	A	77	77/23	87 (R,S) />98
4	PhCHO	SEt [Z(O)]	A	84	45/55	64 (R,S)/>98 (S,S)
5		SEt	A	94	66/33	89/90
6		S^{t}Bu	A	54	88/12	79/55
7		SEt	A	78	89/11	75/>98
8		SEt	A	80	80/20	60/73
9	$PhCH_2CH_2CHO$	SEt	B	85	91/9	82/81
10	$PhCH_2CH_2CHO$	OPh	B	72	90/10	75/>98
11	$CH_3CH_2CH_2CHO$	SEt	B	81	88/12	70 (R,R)/81

[a] Isomeric purity > 85/15 in all cases. See reference a in Table 1 and also Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. [b] Determined by comparison of ^{1}H NMR data with reported values for β-hydroxy esters **5/6** or the corresponding diols; i) ref. 2a. ii) Burgess, K.; Ohlmeyer, M. J. *Tetrahedron Lett.* **1989**, *30*, 395. [c] Determined by chiral Daicel OD or OJ HPLC column, or ^{1}H(300 MHz) and ^{19}F NMR analysis of the MTPA esters derived from **5/6**. [d] Absolute configurations determined by comparison of optical rotations with literature values for β-hydroxy esters **5/6** and the corresponding diols; i) Masamune, S.; Sato, T.; Kim, B.M.; Wollmann, T.A. *J. Am. Chem. Soc.* **1986**, *108*, 8279, (See also Kim, B. M. M.I.T. Ph.D. thesis, 1987). ii) Masamune, S.; Choy, W.; Kerdesky, F.A.J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566, ref. 11 and supplementary material. iii) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2797.

found to react under similar conditions with a number of aldehydes to yield a mixture of *anti* and *syn* products, as summarized in Table 2. In the reaction between benzaldehyde and the *E*(O)-isomers,[7] using catalyst derived from ligand **A** , the *anti* products were favored with good selectivity (entries 1-3). The enantiomeric excesses of both isomers were high, the minor isomer especially being formed in excellent

optical purity, except for entry 2. Other aromatic and α,β-unsaturated aldehydes behaved in a similar manner (entries 5-8).

The aldol reaction of propionate-derived ketene acetals with primary aldehydes was preferentially catalyzed by the borane complex of ligand **B**, to also give predominantly the *anti* products in high yield and enantioselectivity (entries 9-11). The use of ligand **A** in these reactions led to significantly diminished diastereoselectivities. Reaction of the Z(O)-isomer of ketene acetal **4a** with benzaldehyde (entry 4) resulted in lower reactivity and a complete loss of diastereoselection when either ligand **A** or **B** was used to form the catalyst, as was also observed by Mukaiyama with this Z(O)-isomer.[2a]

Our catalytic, enantioselective aldol process has been shown to proceed satisfactorily (although not perfectly) with all of the unsubstituted, methyl-substituted, and dimethyl-substituted[5] ketene acetals investigated. It should be pointed out that the transition state of the reaction appears to be similar for all cases in terms of both the conformation of the catalyst-aldehyde complex, and the enantioface selection of this complex in the reaction with ketene acetals. Futhermore, the predominant formation of *anti*-β-hydroxy-α-methyl esters with *E*(O)-2-methyl ketene acetals was somewhat unexpected for this type of aldol reaction and this Note presents the first examples of this preference for the catalytic asymmetric process. We reserve further discussions on this stereochemical aspect for a future publication.[8]

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6 The superiority of phenyl esters is precedented: (a) Gennari, C.; Colombo, L.; Bertolini, G.; Schimperna, G. *J. Org. Chem.* **1987**, *52*, 2754. (b) Reetz, M.T.; Kunisch, F.; Heitmann, P. *Tetrahedron Lett.* **1986**, *27*, 4721. (c) See ref. 4b.

7 For the *E*(O) and *Z*(O) descriptors, see Masamune, S.; Kaiho, T.; Garvey, D.S. *J. Am. Chem. Soc.* **1982**, *104*, 5521, footnote 1.

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