Chemistry of Trichlorosilyl Enolates. 1. New Reagents for Catalytic, Asymmetric Aldol Additions

Scott E. Denmark,* Stephen B. D. Winter, Xiping Su, and Ken-Tsung Wong

Roger Adams Laboratory, Department of Chemistry University of Illinois, Urbana, Illinois 61801

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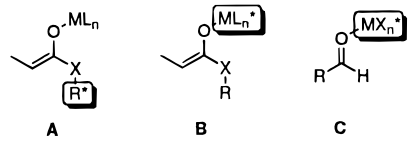
The asymmetric aldol addition is among the most powerful reactions in synthetic organic chemistry and has been extensively studied over the past 15 years.[1] The strategies for *reagent-controlled* asymmetric induction fall into three broadly defined classes (Chart 1): (1) asymmetric modification of the enolate with chiral acyl auxiliaries (**A**), (2) asymmetric modification of the enolate with chiral metalloid auxiliaries (**B**), and (3) asymmetric modification of the aldehyde with chiral Lewis acids (**C**). Each of these strategies has yielded spectacular success, and each has unique advantages and disadvantages. The chiral auxiliary approaches are extremely general and give high selectivities by virtue of the highly ordered nature of the transition structures (closed) which results from the structure of R*/L* and the organizational features of the metal M.[1a,c,2] Unfortunately, these reactions have yet to be made catalytic. The chiral Lewis acid approach takes advantage of the Mukaiyama aldol reaction[3] of enoxysilane derivatives and is demonstrably catalytic and often diastereo- and enantioselective. However, these reactions are less general and the selectivity is most likely dominated by van der Waals interactions which guide the matching of enantiotopic faces in open transition states.[3,4]

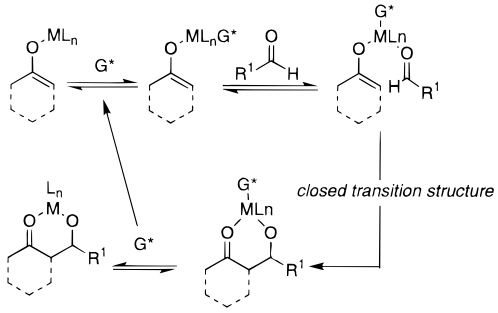
We set for ourselves the goal of inventing a new type of aldol addition reaction which involves the ordered preassembly of enolate, aldehyde and chiral agent for maximum asymmetric influence and which would be catalytic in the chiral reagent. The formulation of this concept, Scheme 1, requires a metal enolate moiety capable of expanding its valence by two and a chiral Lewis base G*. The basis of this proposal for ligand-promoted aldehyde additions finds precedent in our recently disclosed asymmetric allylations (crotylations) with allylic trichlorosilanes.[5] *We wish to report that the corresponding trichlorosilyl enolates are highly reactive agents for the aldol reaction and that their additions can be asymmetrically catalyzed by chiral phosphoramides*.

While substantial literature exists on the generation and reactions of trichlorostannyl[6] and trichlorotitanium[7] enolates, the chemistry of trichlorosilyl enolates[8] is embryonic by comparison.[9] For the initial studies, the use of isolated, purified trichlorosilyl enolates was deemed essential, and we followed the general procedure of Baukov and Lutsenko,[8a] Scheme 2. Thus, from methyl tributylstannylacetate (**1**)[10] we could obtain the trichlorosilyl ketene acetal **2**[8a] as a distillable liquid (bp 25 °C/5 mmHg),[11] which thermally isomerized to methyl

Chart 1



Scheme 1



Scheme 2

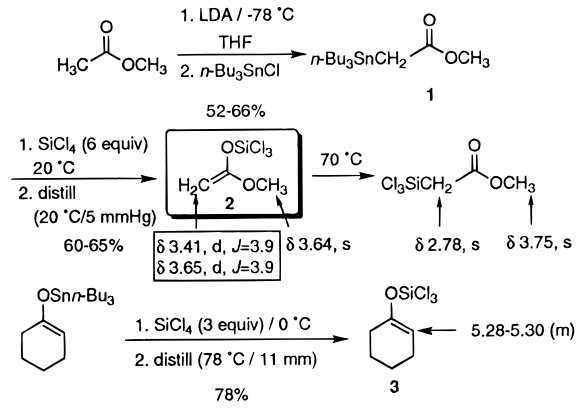


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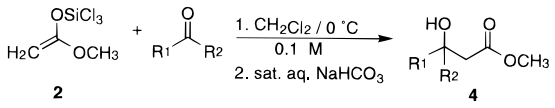
Table 1. Aldol Reactions of **2** with Pivalaldehyde: Solvent and Additive Effects[a]

entry	solvent	promoter, equiv	conversion/time,[b] %/min
1	toluene-d_8	none	18/120
2	CD_2Cl_2	none	50/120
3	THF-d_8	none	69/120
4	CD_2Cl_2	HMPA (0.1)	100/<3

[a] Reactions monitored by ^{1}H NMR (500 MHz) at −80 °C. [b] Percent consumption of pivalaldehyde.

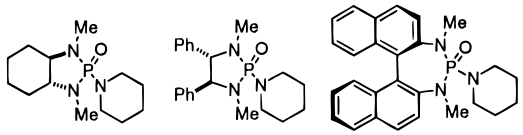
Table 2. Preparative Aldol Reactions of **2**[a]



R^1	R^2	product	yield,[b] %
phenyl	H	**4a**	98
benzyl	H	**4b**	94
(*E*)-cinnamyl	H	**4c**	89
2-phenethyl	H	**4d**	96
cyclohexyl	H	**4e**	96
tert-butyl	H	**4f**	99[c]
phenyl	methyl	**4g**	97[d]

[a] All reactions carried out at a 1.0 mmol scale. [b] Yields of analytically pure material. [c] Reaction run at 20 °C. [d] Reaction run at 20 °C/0.5 M with 10 mol % of HMPA.

Chart 2



trichlorosilylacetate.[8d] Similarly, 1-((tributylstannyl)oxy)cyclohexene[12] underwent clean metathesis to the trichlorosilyl enolate of cyclohexanone (**3**) (bp 76−78 °C/11 mmHg).[8e,11]

The ketene acetal **2** reacted spontaneously with a number of aldehydes at −80 °C (VT-NMR observation). Only pivalaldehyde reacted slowly enough to be followed spectroscopically. The results in Table 1 show a solvent effect on the rate of reaction at −80 °C. However, most exciting is the acceleration observed with a catalytic amount of HMPA (entries 2 and 4).

The preparative utility of the unpromoted reactions was demonstrated by the survey of aldehydes shown in Table 2. The aldol addition products **4** were obtained analytically pure in excellent yield. The range of substrates attests to the generality of the reaction and the compatibility of branched and highly enolizable aldehydes. No evidence of 1,4-type addition with cinnamaldehyde was observed. Remarkably, even acetophenone gave the acetate adduct (with HMPA at 20 °C).

The demonstration of catalysis by HMPA clearly presaged the use of chiral phosphoramides. The promoters[11] (**5**,[5a] **6,** and **7**) shown in Chart 2 were all surveyed with both benzaldehyde and pivalaldehyde, and the results are collected in Table 3.

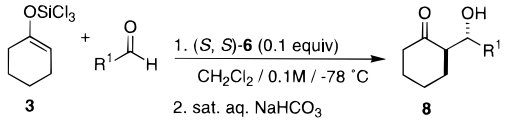
All promoted reactions of **2** were initially carried out at −78 °C in CH_2Cl_2 with 10 mol % of the promoter. The results with benzaldehyde were initially disappointing with enantioselectivities <40% ee. No improvement was observed with changes in solvent (THF, toluene) or temperature (−90, 0 °C). The enhanced selectivity (53% ee, entry 5) obtained with 1.0 equiv of **6** confirmed that the background reaction was competitive even at −80 °C.

Table 3. Catalytic Asymmetric Aldol Reactions of **2**: Survey of Promoters[a]

entry	aldehyde	promoter, equiv	product	ee[b] (yield[c]), %
1	PhCHO	**5** (0.1)	(*R*)-**4a**	20 (88)
2	PhCHO	**6** (0.1)	(*S*)-**4a**	33 (87)
3	PhCHO	**7** (0.1)	(*S*)-**4a**	23 (91)
4[d]	PhCHO	**6** (0.1)	(*S*)-**4a**	38 (94)
5	PhCHO	**6** (1.0)	(*S*)-**4a**	53 (84)
6	*t*-BuCHO	**5** (0.1)	(*R*)-**4f**	26 (76)
7	*t*-BuCHO	**6** (0.1)	(*S*)-**4f**	40 (78)
8	*t*-BuCHO	**7** (0.1)	(*S*)-**4f**	49 (75)
9[d]	*t*-BuCHO	**7** (0.1)	(*S*)-**4f**	50 (78)
10	*t*-BuCHO	**7** (1.0)	(*S*)-**4f**	62 (77)

[a] All reactions performed at −78 °C/0.1 M. [b] Determined by chiral HPLC. [c] Chromatographically homogeneous material. [d] Slow addition of aldehyde.

Scheme 3



R^1 = phenyl: 95% yield; anti/syn, 65/1; ee (*anti*-**8a**) 93%
R^1 = (*E*)-cinnamyl: 94% yield; anti/syn, >99/1; ee (*anti*-**8b**) 88%

The results with pivalaldehyde are also in accord with that hypothesis. For all of the promoters examined, the enantioselectivity was superior, although interestingly the best selectivity (50% ee) was obtained with **7**. The intervention of the nonpromoted pathway with pivaladehyde was suggested as well by the improved selectivity observed with 1.0 equiv of **7** (entry 10).

Preliminary results from the reaction of enoxychlorosilane **3** show that the chiral Lewis base promoted aldol addition has significant synthetic potential, Scheme 3. In combination with benzaldehyde and (*E*)-cinnamaldehyde, the *anti* aldol products **8** were obtained in excellent diastereoselectivity (65−99/1) and very good enantioselectivity (88−93% ee)[13] with catalytic amounts (10 mol %) of promoter **6**.

While it is not possible to construct rational transition state structures for the promoted aldol additions, our working hypothesis is a classic chairlike arrangement of reactive partners assembled around a hexacoordinate siliconate species. Methods for in situ generation of trichlorosilyl enolates, exploration of modulated chlorosilyl enolates, and optimization of promoter structure are currently under investigation.

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Supporting Information Available: Procedures for the preparation and full characterization of **1**, **2**, **3**, **4a**−**g**, (*S*)-**4a**, (*S*)-**4f**, **6**, **7** (−)-*anti*-**8a**, and (+)-*anti*-**8b** (25 pages). See any current masthead page for ordering and Internet access instructions.

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(13) The absolute configuration of (−)-*anti*-**8a** has been determined to be (2*R*,1′*S*) by X-ray analysis of the 4-bromobenzoate derivative. This will be described in a full account.