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Stereoselective Aldol Additions of Achiral Ethyl Ketone-Derived Trichlorosilyl Enolates

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Methods for the preparation of geometrically defined enoxy(trichlorosilanes) derived from ethyl ketone enolates have been developed. The addition of enoxy(trichlorosilanes) (trichlorosilyl enolates) to aldehydes proceeds with good yields in the presence of catalytic amounts of chiral phosphoramides. The reaction of *Z*-trichlorosilyl enolates to aryl aldehydes affords aldol products with good to excellent diastereo- and enantioselectivities. Phosphoramide-catalyzed aldol additions lacked substrate generality providing modest selectivities with unsaturated and aliphatic aldehydes. In all cases, the phosphoramide-catalyzed aldol addition of *E*-trichlorosilyl enolates to aldehydes provided good yields with moderate to good stereoselectivities.

Introduction

The aldol addition is among one of the most important methods for the stereocontrolled construction of carbon−carbon bonds.[1] The utility and application of this transformation is illustrated by the vast number of reviews written on the subject over the past decade.[2] 1,3-Oxygenated carbon chains as afforded by the aldol reaction are common structural motifs observed in many natural products.[3] The formation of these carbon chains is typified by the addition of an enol or enolate to an aldehyde to form two new stereogenic centers in the case of substituted nucleophiles. Controlling the relative and absolute configuration of the new stereogenic centers has been the primary focus of most new developments in this field. The nonenzymatic methods that are currently utilized often provide the desired structural motifs with excellent stereocontrol. Unfortunately, these processes are typically restricted to the use of either stoichiometric amounts of the chiral modifying agent, limited substrate classes, or poor stereochemical correlation between the starting enolate donor and aldol product.[4] Stereoselective routes employing unactivated ketones have also been developed. Although this burgeoning field is highly promising, excessively long reaction times and narrow substrate classes currently prevent its broad application.[5]

Background

Recent reports from these laboratories have documented the utility of trichlorosilyl enol ethers as a new

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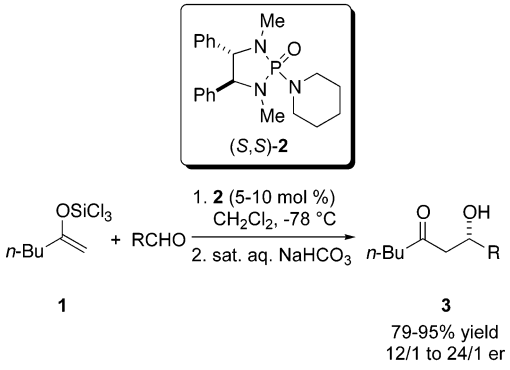
class of aldol reagents.[6] These species react spontaneously with aldehydes at or below ambient temperature to afford aldol adducts in good to high diastereoselectivity for substituted enolates. For unsubstituted enolates, e.g. methyl ketone enolate **1**, reaction with various aldehydes occurs cleanly at room temperature to afford aldol adducts in 86−93% yield in the absence of external agents.

Most importantly, however, these reactions are accelerated by the addition of catalytic quantities of Lewis bases, in particular chiral phosphoramides, Scheme 1.[7] By the use of these Lewis basic additives, excellent enantioselectivities can be achieved from a variety of methyl and cyclic ketone enolates with various aldehydes. A distinct advantage over the use of chiral Lewis acids is that the geometric configuration in conformationally-restricted, substituted enolates is transferred to the relative diastereoselectivity of the aldol products. Thus, reactions of trichlorosilyl enolates are believed to proceed through closed transition structures organized around silicon. This report details our current investigations regarding the stereoselective preparation of achiral trichlorosilyl enolates derived from ethyl ketones and their subsequent additions to achiral aldehyde acceptors.

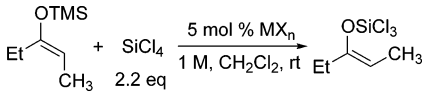
SCHEME 1



Results

A. Preparation of Enolates. The preparation of methyl and cyclic ketone trichlorosilyl enolates by metal-catalyzed trans-silylation has been described in detail.[8] In these foregoing studies the geometry of the resultant trichlorosilyl enolate either was fixed within a ring or was not an issue as in the case of methyl ketones. Thus, the effect of the reaction conditions in controlling the geometry of trichlorosilyl enol ethers had not been of concern. To begin this investigation, an exhaustive survey of metal salts and metal complexes for the trans-silylation of 3-pentanone-derived trimethylsilyl enol ether **4** to the corresponding trichlorosilyl enol ether was initiated. The metal catalysts were evaluated on the basis of their effectiveness in catalyzing the trans-silylation and if applicable the level of geometric control in the trichlorosilyl enol ethers. To more effectively evaluate the level of geometric control, it was desirable to begin with highly enriched *E*- or *Z*-trimethylsilyl enol ethers. Thus, **4** was prepared in a 30/1 *E*/*Z* mixture by using lithium tetramethylpiperidide following the method of Collum.[9] The *Z*-isomer was prepared without purification according to the method of Evans[10] through the formation of the boron enolate with dibutylboron triflate[11] and subsequent trapping with chlorotrimethylsilane (TMSCl). Although the TMS enol ether was generated with high *Z*-selectivity based upon ^{1}H NMR analysis, attempts to isolate and purify it proved unsuccessful. A survey of metal salts and metal complexes was therefore undertaken with the *E*-enolate. As a general protocol, TMS enol ether **4** (30/1, *E*/*Z*) was added dropwise to a mixture of $SiCl_4$ and metal catalyst in CH_2Cl_2 at room temperature, Table 1. The progress of the reaction was easily monitored by ^{1}H NMR by using the diagnostic signals at δ 0.2 (TMS-O) and 0.4 (TMS-Cl).

TABLE 1. Survey of Metal Salt Catalysts for the Trans-Silylation of 4 to 5



MX_n	time, h	result	(*E*/*Z*)[a]
$Hg(OAc)_2$	2	trans-silylation	**5**, 1/2
$Pd(OAc)_2$	2	trans-silylation	**5**, 1/6
$PdBr_2$	24	isomerization	**4**, 1/3
$Rh_2(OAc)_4$[b]	24	isomerization	**4**, 1/6
$NiCl_2$	24	isomerization	**4**, 1/5
$PtCl_2$	24	isomerization	**4**, 1/8
$(PhCN)_2PtCl_2$	24	isomerization	**4**, 1/4
$ZnCl_2$	24	isomerization	**4**, 5/1

[a] Determined by ^{1}H NMR analysis. [b] Used 2.5 mol % of the metal catalyst.

Interestingly, only the mercury and palladium acetate salts were able to affect trans-silylation and afforded predominantly the *Z*-trichlorosilyl enolate. It is important to note that isomerization of the trimethylsilyl enol ether was observed by ^{1}H NMR spectroscopy at early reaction times for both $Hg(OAc)_2$ and $Pd(OAc)_2$. Although this was an unexpected result, it provided an important insight into the mechanism of metal-catalyzed trans-silylation.

The remainder of the metal salts evaluated in this initial survey could only affect isomerization of the TMS enol ether to afford predominantly *Z*-TMS enol ether without participating in trans-silylation. Although previous attempts to selectively prepare pure samples of (*Z*)-**4** were unsuccessful, the results from the preliminary catalyst survey could be used advantageously to prepare the opposite geometric isomer. Thus, the 30/1, *E*/*Z*

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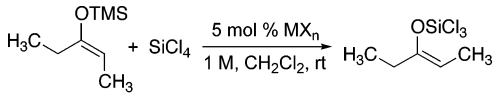
mixture of trimethylsilyl enol ethers was isomerized and purified to afford a 1/4, *E*/*Z* mixture with $PtCl_2$.

For the remainder of the survey, a 3/1, *E*/*Z* mixture of trimethylsilyl enol ethers, prepared with lithium diisopropylamide (LDA), was used due to the observed isomerization prior to trans-silylation. Summarized in Table 2 are the results for all successful trans-silylations attempted with various metal salts and metal complexes. With the exception of the trans-silylation with $Pd(OAc)_2$, all reactions were heterogeneous.

TABLE 2. Results from Successful Trans-Silylations



4 3/1 (*E*/*Z*) **5**

MX_n	time, h	yield, %[a]	**5**, *E*/*Z*[b]
$Hg(OAc)_2$	5	72	1/2
$Hg(TFA)_2$	5	60	1/2
$HgCl_2$	48[c]	31	1/2
$Pd(OAc)_2$	5	76	1/6
$Pd(TFA)_2$	15	70	1/7
$Tl(TFA)_3$	24[c]	20	1/3

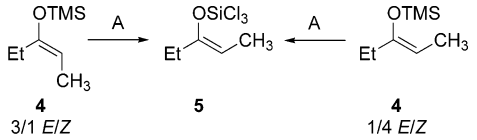
[a] Yield of distilled material. [b] Determined by ^1H NMR analysis. [c] Trans-silylations were incomplete.

Of the metal catalysts tried, only $Hg(OAc)_2$, $Hg(TFA)_2$, $Pd(OAc)_2$, and $Pd(TFA)_2$ affected complete trans-silylation. The use of $PdCl_2$, $Pd(dba)_2$, $Ru(COD)Cl_2$, Rh(COD)Cl, $CdBr_2$, $Zn(OAc)_2$, and CsCl, led only to isomerization of the trimethylsilyl enol ether. On the other hand, the use of $Pd(COD)Br_2$, $Ni(OAc)_2$, $(CH_3CN)_2PtCl_2$, AgOAc, AgTFA, CdI_2, $AlCl_3$, Ph_2GeCl_2, $LaCl_3{\cdot}7H_2O$, $SnCl_2$, $SnCl_4$, Me_2SnCl_2, Ph_2SnCl_2, and $Pb(OAc)_2$ resulted in hydrolytic protodesilylation of the trimethylsilyl enol ether to afford 3-pentanone (vide infra). Finally, $HgCl_2$, $Tl(TFA)_3$, $Pd(PPh_3)_4$, $TiCl_4$, and BCl_3 afforded small amounts of trichlorosilyl enol ether, but the rate of trans-silylation was extremely slow compared with that of the other metal salts.

Interestingly, starting with either a 30/1 or 4/1, *E*/*Z* mixture of trimethylsilyl enol ethers, trans-silylation afforded predominantly (*Z*)-**5** in a 1/2 or 1/6, *E*/*Z* mixture for mercury and palladium catalysts, respectively. This suggests that although an equilibration between the *E*/*Z* isomers exists, the final geometric selectivities for metal-catalyzed trans-silylations of this type are kinetically controlled with the ratio being dictated by the metal employed. Metatheses were complete within 5 h when 5 mol % of $Hg(OAc)_2$, $Hg(TFA)_2$, and $Pd(OAc)_2$ were used. However, $Pd(TFA)_2$ was less effective, requiring 15 h for complete conversion. It is notable to mention that certain batches of commercially available $Pd(TFA)_2$ were able to generate (*Z*)-**5** in as high as 1/16, *E*/*Z*. Attempts to clarify these results by either directly preparing $Pd(TFA)_2$ or recrystallizing commercial material were unsuccessful. Although these results were not the norm, they were applied to the selective preparation of (*Z*)-**5** used in subsequent sections.

When starting with a 1/4, *E*/*Z* mixture of **4**, metal-catalyzed trans-silylation afforded **5** with the same selectivity as when either a 30/1 or 3/1, *E*/*Z* mixture was used, Table 3. Taken together, these results indicate that

TABLE 3. Convergence of Geometric Selectivity



4 3/1 *E*/*Z* **5** **4** 1/4 *E*/*Z*

A: $SiCl_4$, 5 mol % MX_n, 1 M CH_2Cl_2, rt

MX_n	**4**, *E*/*Z*	yield, %[a]	**5**, *E*/*Z*[b]
$Hg(OAc)_2$	30/1	65	1/2
$Hg(OAc)_2$	3/1	72	1/2
$Hg(OAc)_2$	1/4	60	1/2
$Pd(OAc)_2$	30/1	62	1/6
$Pd(OAc)_2$	3/1	76	1/6
$Pd(OAc)_2$	1/4	69	1/6
$Pd(TFA)_2$	3/1	70	1/6
$Pd(TFA)_2$	1/4	43	1/6

[a] Yield of distilled material. [b] Determined by ^1H NMR analysis.

the final ratio of geometrical isomers is metal dependent and under kinetic control, but that there is also a preequilibrium that causes the starting materials to converge (vide infra).

Having completed a general survey of the trans-silylation of 3-pentanone TMS enol ether **4** to trichlorosilyl enolate **5**, the scope and efficiency of mercury- and palladium-catalyzed trans-silylation was then studied with use of various ethyl ketone-derived TMS enol ethers. To evaluate a variety of steric demands for the spectator group (the nonparticipating and nonenolized substituent from the corresponding ketone), butanone (methyl), 2-methyl-3-pentanone (isopropyl), 2,2-dimethyl-3-pentanone (*tert*-butyl), and propiophenone (phenyl) were subsequently studied. Additionally, propanal was included as a test substrate where the spectator group is simply hydrogen.

The trimethylsilyl enol ethers of propanal (**6**) and 2-butanone (**7**) were prepared by treatment of the carbonyl compounds with chlorotrimethylsilane and triethylamine in hot DMF as developed by House.[12] Unfortunately the products contained significant amounts of hexamethyldisiloxane that could not be removed by fractional distillation. The desired compounds were ultimately purified sacrificially with use of silica gel chromatography. Trimethylsilyl enol ether **8** was prepared by enolization with LDA followed by subsequent trapping of the lithium enolate with TMSCl. The bulkier substrates **9** and **10** were prepared by enolization and trapping with in-situ-generated iodotrimethylsilane in acetonitrile.

The various TMS enol ethers were each subjected to trans-silylation with 5 mol % of $Hg(OAc)_2$, $Pd(OAc)_2$, and $Pd(TFA)_2$, Table 4. Curiously, the rates of metathesis in all cases were slower than that of enol ether **4**. In fact, initial attempts to affect trans-silylation of **9** and **10** resulted in significant hydrolysis of the product during the long reaction times. However, it was determined that the levels of hydrolysis could be minimized by increasing the amounts of metal catalyst to 10 mol %.

The results in Table 4 show that the size of the spectator group has a profound influence on the geomet-

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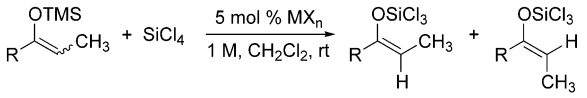
ric composition of the trichlorosilyl enolate. Relatively large substituents such as *tert*-butyl and phenyl afford the *Z* isomer almost exclusively, for all metals used, whereas smaller substituents such as methyl exert little to no bias on the stereochemical outcome. Interestingly, when the spectator group is H, the selectivities are improved relative to methyl regardless of the metal employed.

TABLE 4. Trans-Silylation of Various Ketone-Derived TMS Enol Ethers to Trichlorosilyl Enolates



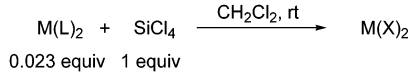
entry	enol ether	R	MX_n	enolate	time, h	yield, %[a]	*Z*/*E*[b]
1	**6**	H	$Hg(OAc)_2$	**11**	16	50	8/1
2	**6**	H	$Pd(OAc)_2$	**11**	16.5	25	8/1
3	**6**	H	$Pd(TFA)_2$[c]	**11**	36	35	4/1
4	**7**	Me	$Hg(OAc)_2$	**12**	16.5	58	2/1
5	**7**	Me	$Pd(OAc)_2$	**12**	16.5	73	3/1
6	**7**	Me	$Pd(TFA)_2$	**12**	24	53	8/1
7	**4**	Et	$Hg(OAc)_2$	**5**	5	72	2/1
8	**4**	Et	$Pd(OAc)_2$	**5**	5	76	6/1
9	**4**	Et	$Pd(TFA)_2$	**5**	15	70	7/1
10	**8**	*i*-Pr	$Hg(OAc)_2$	**13**	18	65	8/1
11	**8**	*i*-Pr	$Pd(OAc)_2$	**13**	18	58	9/1
12	**8**	*i*-Pr	$Pd(TFA)_2$[c]	**13**	20	54	17/1
13	**9**	*t*-Bu	$Hg(OAc)_2$	**14**	24	55	>20/1
14	**9**	*t*-Bu	$Pd(OAc)_2$[c]	**14**	29.5	50	>20/1
15	**9**	*t*-Bu	$Pd(TFA)_2$[c]	**14**	22	55	>20/1
16	**10**	Ph	$Hg(OAc)_2$[c]	**15**	18	66	99/1
17	**10**	Ph	$Pd(OAc)_2$[c]	**15**	23	65	99/1
18	**10**	Ph	$Pd(TFA)_2$[c]	**15**	22	55	99/1

[a] Yield of distilled material. [b] Ratio determined by ^1H NMR analysis. [c] Using 10 mol % of the metal salt.

To better understand the role of the counterion in the mercury- and palladium-catalyzed trans-silylation, the fate of the metal species during the course of the reaction needed to be determined. Thus, $Hg(OAc)_2$, $Pd(OAc)_2$, and $Pd(TFA)_2$ were independently treated with 20 equiv of $SiCl_4$ under standard reaction conditions to elucidate the nature of the catalytic species. After evaporation, the resulting residues were then isolated, washed with CH_2Cl_2, and dried for elemental analysis. In each case, analysis revealed little to no carbon and high levels of chloride, suggesting the catalytic species may be the corresponding metal chlorides. Interestingly, both $Hg(OAc)_2$ and $Pd(OAc)_2$ completely exchange to the chloride salts within 5 min of treatment with $SiCl_4$ as inferred by the low percentages of carbon and hydrogen observed in entries 1 and 2, Table 5. However, unlike $Pd(OAc)_2$, $Pd(TFA)_2$ required several hours to fully exchange to $PdCl_2$, compare entries 3 and 4. Even so, exchange to the chloride adduct is significantly faster than trans-silylation.

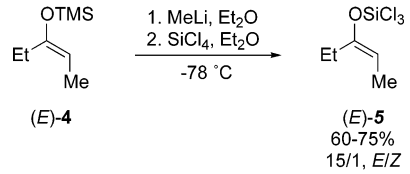
Although it was hoped that *E*-trichlorosilyl enolates could be prepared via a similar metal-catalyzed trans-silylation, the observation of stereoconvergence from both (*E*)- and (*Z*)-**4** deemed this unlikely. Alternatively, attempts at direct trichlorosilylation with either $SiCl_4$ or $SiCl_3OTf$ from lithium enolates generated with amide bases afforded intractable mixtures. To avoid the presence of basic compounds during trichlorosilylation, the lithium enolates were generated amine free via addition of MeLi to the corresponding TMS enol ether.[13] The rate of silyl cleavage can be monitored by NMR spectroscopy, noting the disappearance of the O-TMS peak at roughly δ 0.2 ppm. Gratifyingly, the substrate was not subject to isomerization during this procedure and could provide (*E*)-**5** in essentially the same geometric mixture as the corresponding *E*-TMS enol ether with typical yields between 60 and 75%, Scheme 2.

TABLE 5. Elemental Analysis of the Metal Residue Taken Following Treatment with $SiCl_4$



$M(L)_2$	time	results, % composition of $M(X)_2$
$Hg(OAc)_2$	5 min	C, 0.42; H, 0.21; Cl, 17.17; Hg, 64.09 theoretical for $HgCl_2$: C, 0.00; H, 0.00; Cl, 26.12; Hg, 73.88 theoretical for $Hg(OAc)_2$: C, 15.08; H, 1.90; Hg, 62.94
$Pd(OAc)_2$	5 min	C, 1.26; H, 0.52; Cl, 31.92; Pd, 51.07 theoretical for $PdCl_2$: C, 0.00; H, 0.00; Cl, 39.99; Pd, 60.01 theoretical for $Pd(OAc)_2$: C, 21.40; H, 2.69; Pd, 47.40
$Pd(TFA)_2$	5 min	C, 11.86; H, 0.81; Cl, 0.00; F, 16.03; Pd, 35.75 theoretical for $PdCl_2$: C, 0.00; H, 0.00; Cl, 39.99; Pd, 60.01 theoretical for $Pd(TFA)_2$: C, 14.45; H, 0.00; F, 34.29; Pd, 47.40
$Pd(TFA)_2$	12 h	C, 0.12; H, 0.14; Cl, 37.46; F, 0.21; Pd, 55.17 theoretical for $PdCl_2$: C, 0.00; H, 0.00; Cl, 39.99; Pd, 60.01 theoretical for $Pd(TFA)_2$: C, 14.45; H, 0.00; F, 34.29; Pd, 47.40

SCHEME 2

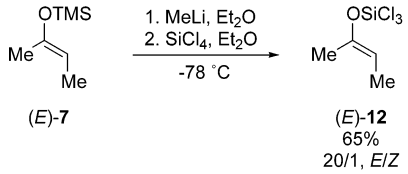


As with (*E*)-**5**, (*E*)-**12** was prepared by trapping of the configurationally defined lithium enolate generated from (*E*)-**7**. Initial attempts to obtain (*E*)-**7** by chromatographic separation of mixtures of (*E*)- and (*Z*)-**7** resulted in hydrolysis to the ketone. Following the method of Vedejs, (*E*)-**7** could be generated in as high as 22/1, *E*/*Z*.[14] Unfortunately, yields for this carbenoid rearrangement were typically poor, between 35 and 45%. Nonetheless, (*E*)-**7** could be prepared and was treated with MeLi to generate the amine-free lithium enolate in situ. Trapping with 10 equiv of $SiCl_4$ afforded a 65% yield of the corresponding trichlorosilyl enolate with a 20/1, *E*/*Z* ratio, Scheme 3.

B. Aldol Additions. Optimization studies of (*Z*)-**5** were conducted with benzaldehyde as the aldehyde acceptor. Additions were done at 10 and 15 mol % catalyst loadings at −78 °C in CH_2Cl_2, Table 6, entries 1 and 2.

(13) Denmark, S. E.; Ghosh, S. K. *Angew. Chem., Int. Ed.* **2001**, *40*, 4759.
(14) Vedejs, E.; Larsen, S. D. *J. Am. Chem. Soc.* **1984**, *106*, 3030.

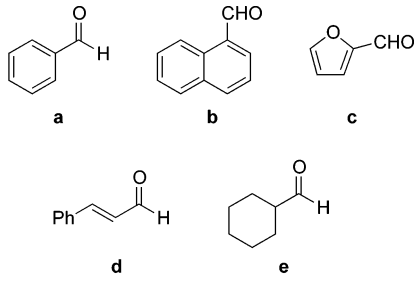
SCHEME 3



(*E*)-**7** (*E*)-**12**
65%
20/1, *E*/*Z*

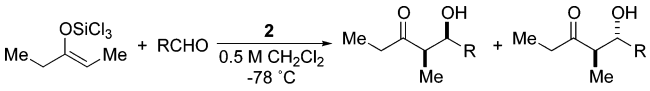
Although reactions with 10 mol % of the catalyst were equally stereoselective, the survey was performed with 15 mol % of the catalyst because benzaldehyde is often the most reactive electrophile. Indeed, the addition of **5** to *trans*-cinnamaldehyde was incomplete after 2 h. A brief investigation revealed that reactions with aldehydes other than benzaldehyde, Chart 1, required 8 h for complete conversion. This time scale would be used in all subsequent aldol additions.

CHART 1



To study the generality with respect to the aldehyde donor, trichlorosilyl enolate (*Z*)-**5** was combined with various aldehydes in the presence of 15 mol % of (*S*,*S*)-**2** and the reaction was quenched after 8 h. With the exception of cyclohexanecarboxaldehyde the yields in all cases were good. Unfortunately, both diastereoselectivities and enantioselectivities were greatly attenuated with respect to benzaldehyde, especially when employing nonaryl-based aldehydes such as *trans*-cinnamaldehyde and furfuraldehyde, Table 6.

TABLE 6. Survey of Various Aldehydes in the Stereoselective Aldol Addition of (*Z*)-5 Catalyzed by 2



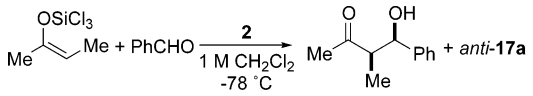
(*Z*)-**5** *syn* *anti*

entry	aldehyde	loading, mol %	product	dr, syn/anti[a]	er (syn)[b]	yield, %[c]
1	**a**	10	**16a**	16/1	19/1	85
2	**a**	15	**16a**	16/1	21/1	84
3	**b**	15	**16b**	8/1	9/1	80
4	**c**	15	**16c**	4/1	5/1	79
5	**d**	15	**16d**	5/1	3/1	85
6	**e**	15	**16e**	1/2	1/1	45

[a] Determined by ^{1}H NMR analysis. [b] Determined by CSP SFC analysis. [c] Yield of chromatographically homogeneous material containing a mixture of diastereomers.

To optimize the phosphoramide-catalyzed aldol additions with (*Z*)-**5** for substrates other than benzaldehyde, a loading study was performed with 2-furfuraldehyde, Table 7. Other than moderating the catalyst loadings, the reaction concentrations were increased to 1 M. The yields of isolated adducts were similar for all runs, though a slight improvement from 79 to 83% yield was observed for reactions run with 20 and 50 mol % of the catalyst as opposed to 5 mol % of the catalyst. Likewise, enantioselectivities were significantly improved from 5/1 to 8/1 er when the catalyst loadings were increased from 5 to 20 mol %. Curiously, the diastereoselectivities remained relatively constant at roughly 6/1, syn/anti throughout the loading study. In any case, no improvement was observed when increasing the amount of catalyst beyond 20 mol %.

TABLE 7. Aldol Addition of (*Z*)-12 to Benzaldehyde, Using Varying Amounts of Phosphoramide 2



(*Z*)-**12** *syn*-**17a**

loading, mol %	dr, syn/anti[a]	er (syn)[b]	yield, %[c]
2.5	4/1	1.2/1	53
5	5/1	1.2/1	75
10	5/1	1.2/1	79
15	10/1	1.5/1	65
20	7/1	1.7/1	86
50	16/1	28/1	82
100	15/1	21/1	85

[a] Determined by ^{1}H NMR analysis. [b] Determined by CSP SFC analysis. [c] Yield of chromatographically homogeneous material containing a mixture of diastereomers.

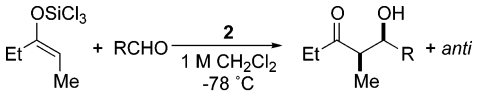
To evaluate the influence of the spectator group, aldol additions were carried out with 2-butanone enolate (*Z*)-**12**. A reaction with 10 mol % of the catalyst with benzaldehyde revealed that both diastereo- and enantioselectivities were attenuated compared to (*Z*)-**5**. Attempts to optimize this reaction with benzaldehyde further revealed a dramatic catalyst loading effect unobserved with the 3-pentanone-derived enolate. Although the reaction is responsive to the effects of the chiral catalyst, at least 50 mol % of the phosphoramide was required to provide good stereoselectivities. Certainly nonideal, this is, however, a dramatic improvement over reactions run at standard catalyst loadings with (*Z*)-**12**. Further attempts to improve stereoselectivities by modifying the chiral catalyst will be discussed later.

Aldol additions with *E*-enolates were performed in the same manner as the *Z*-enolates as described above. Beginning with (*E*)-**5**, a survey of aldehydes was conducted at 1 M concentration in CH_2Cl_2, using 15 mol % of catalyst, and were quenched after 8 h. The results are summarized in Table 8. Interestingly, the results for the aldol addition to benzaldehyde were much poorer when-compared to those with (*Z*)-**5**. Not only was the enantioselectivity attenuated, but the diastereoselectivity was among the lowest of the group. Considering the remaining unsaturated aldehydes, the results are similar to those obtained with (*Z*)-**5**, with aryl aldehydes affording higher selectivities, although now with the anti product being favored. Again with the exception of cyclohexanecarboxaldehyde, the yields in all cases were good.

In light of the results obtained for (*Z*)-**12**, a loading study was performed for (*E*)-**12**, using 25 and 50 mol % of catalyst, to determine if stereoselective aldol additions were viable under the current conditions. Benzaldehyde

was again selected as the representative substrate with reactions being conducted at 1 M concentration in CH_2Cl_2 and were quenched after 8 h. The yields were similar in both cases, ranging from 76 to 80% for 25 and 50 mol % loadings, respectively. Unfortunately, even with 50 mol % of the catalyst, the reactions only afforded an 8/1, syn/anti mixture of the undesired diastereomer in racemic form.

TABLE 8. Survey of Aldehyde Acceptors for the Addition of (*E*)-5 Catalyzed by 2



(*E*)-**5** *syn*

aldehyde	product	dr, syn/anti[a]	er (syn)[b]	yield, %[c]
a	**16a**	1/1	8/1	86
b	**16b**	1/8	12/1	82
c	**16c**	1/2	3/1	76
d	**16d**	1/5	3/1	82
e	**16e**	1/13	1/1	53

[a] Determined by ^{1}H NMR analysis. [b] Determined by CSP SFC analysis. [c] Yield of chromatographically homogeneous material containing a mixture of diastereomers.

The aldol additions with (*Z*)-**12** clearly showed an increase in enantioselectivity by increasing the loading of catalyst from 5 to 50 mol %. To further improve on this result and to reduce the amount of catalyst required, several dimeric catalysts based on **2** were prepared and their ability to catalyzed aldol additions was evaluated. The use of dimeric phosphoramides is predicated on the knowledge that two phosphoramides are required in the transition state to provide high levels of stereoselectivity.[15] It was envisioned that covalently tethered Lewis basic residues would enhance the relative concentration of the second coordinating species, allowing more facile formation of the two-phosphoramide complex. Although similar dimeric catalysts have been employed successfully in allylations with allyltrichlorosilanes,[16] aldehyde−aldehyde aldol additions,[13] and silyl ketene acetal additions to ketones,[17] no attempts have been made thus far to evaluate their efficacy in ketone−aldehyde aldol additions.

The dimeric catalysts were prepared as previously described, Scheme 4. Preparation of the chiral phosphoryl chloride followed by treatment with the lithiated dimethyl diamine linker afforded the tethered phosphoramides as stable white powders, Chart 2.

SCHEME 4

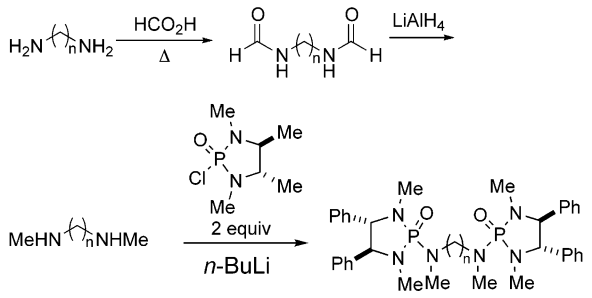
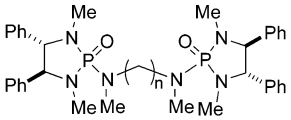
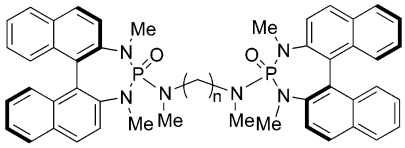


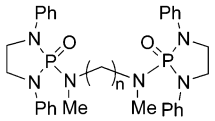
CHART 2



(*R*,*R*)-**18**, n = 4
(*R*,*R*)-**19**, n = 5
(*R*,*R*)-**20**, n = 6
(*R*,*R*)-**21**, n = 7
(*R*,*R*)-**22**, n = 8

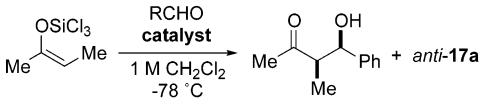


23, n = 5



24, n = 5

TABLE 9. Survey of Dimeric Phosphoramides in the Aldol Addition of (*Z*)-12 to Benzaldehyde



(*Z*)-**12** *syn*-**17a**

catalyst	dr, syn/anti[a]	er (syn)[b]	yield, %[c]
18	15/1	1.3/1	69
19	16/1	1.2/1	48
20	15/1	1.8/1	64
21[d]	8/1	2.8/1	78
22[d]	8/1	2.1/1	63
23[e]	2/1	1/1	85
24[e]	1/1	N/A	62

[a] Determined by ^{1}H NMR analysis. [b] Determined by CSP SFC analysis. [c] Yield of chromatographically homogeneous material containing a mixture of diastereomers. [d] Began with an 8/1, *Z*/*E* mixture. [e] 15 mol % of the catalyst used.

The effectiveness of the dimeric phosphoramides in aldol addition reactions was evaluated with (*Z*)-**12** and benzaldehyde. As before, reactions were run at 1 M concentration in CH_2Cl_2, using 5 mol % of the catalyst. The reactions were allowed to proceed for 8 h before being quenched with saturated, aqueous sodium bicarbonate solution and CH_2Cl_2. The results of the catalyst survey are summarized in Table 9. Although with only a single example, the dimers **18**−**22** were superior to the linked binaphthyldiamine-derived phosphoramide, **23**, which had been employed with great success in previous allylation and crossed-aldehyde aldol additions. Even though the enantioselectivities were extremely modest, the diastereoselectivities were essentially perfect for reactions run with the chiral stilbene-1,2-diamine-derived dimers

(15) (a) Denmark, S. E.; Pham, S. M. *Helv. Chim. Acta* **2000**, *53*, 1846. (b) Denmark, S. E.; Su, X.; Nishigaichi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 12990.

(16) (a) Denmark, S. E.; Fu, J. *Org. Lett.* **2002**, *4*, 1951. (b) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488. (c) Denmark, S. E.; Wynn, T. A. *J. Am. Chem. Soc.* **2001**, *123*, 6199.

(17) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233.

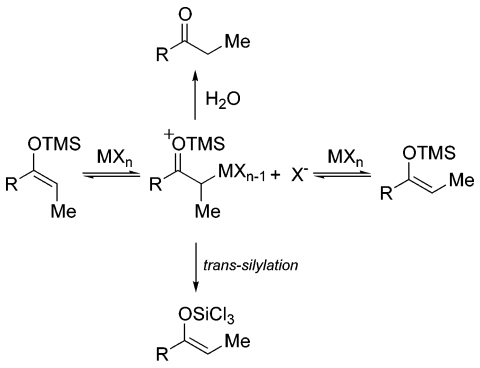
18−**22**. Interestingly, for this class of linked phosphoramides a tether length of seven methylene units appears to be optimal with respect to enantioselectivity. This differs from the allylations and aldehyde−aldehyde aldoladditions where a tether length of five methylene units was found to be optimal.

Although the pentanone-derived enolates did not display a selectivity enhancement with respect to catalyst loading, a survey of the dimeric phosphoramides was also performed with (*Z*)-**5** and 1-naphthaldehyde. Again, reactions were conducted at 1 M concentration in CH_2Cl_2 with 5 mol % of the catalyst for 8 h. Yields for reactions catalyzed by dimers **19**−**22** ranged from 68 to 71%. Unfortunately, reactions of (*Z*)-**5** in the presence of the dimeric phosphoramides demonstrated poor diastereoselectivities, 2.7/1 to 3.0/1 syn/anti, with little to no enantioselectivity, even with the optimal tether length.

Discussion

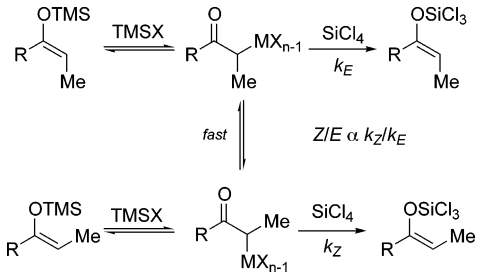
A. Metal-Catalyzed Trans-Silylation. A variety of ethyl ketone-derived trichlorosilyl enolates were prepared via mercury(II)- or palladium(II)-catalyzed trans-silylation beginning with the corresponding trimethylsilyl enol ethers. Although a diverse assortment of Lewis acidic metal salts and complexes was studied, only the acetate and trifluoroacetate salts of mercury and palladium gave consistently high levels of silicon metathesis. In a few cases, such as $PtCl_2$, $(PhCN)_2PtCl_2$, and $NiCl_2$, isomerization of the trimethylsilyl enol ether was observed without trans-silylation. The remaining metal salts provided significant levels of hydrolyzed product. Although it is possible that formation of the ketone could occur via protodesilylation of the silyl enol ether, it is more likely that adventitious water present in the salt interrupted the metathetical pathway by quenching the metal enolate, Scheme 5. Interestingly since $Pd(TFA)_2$ was the slowest acting metathesis catalyst, isomerization was observed well before significant amounts of trans-silylation had taken place (vide infra).

SCHEME 5



By the use of various mixtures of geometric isomers of **4**, it appeared that isomerization occurs prior to, or is concomitant with trans-silylation as alluded above. The use of a 30/1 or a 1/4, *E*/*Z*-mixture of (*E*/*Z*)-**4** afforded **5** with similar geometric ratios depending upon the choice of metal, but regardless of the initial geometric mixture. This result indicates that metal-catalyzed trans-silylation affords a mixture of both *E*- and *Z*-trichlorosilyl enolates with the final ratio being a function of the partitioning

SCHEME 6



between the rate of formation of the *Z*-isomer (k_Z) and the rate of formation of the *E*-isomer (k_E) as governed by the nature of the metal, Scheme 6.

Further studies with various ethyl ketone derived TMS enol ethers have shown that substitution on the spectator side has a profound influence on selectivity during trans-silylation. In fact, large substituents effectively diminish the difference in selectivities observed previously for the pentanone-derived silyl enol ether **4** when mercury and palladium are used. Likewise, there is little difference between mercury and palladium when substituents are smaller than ethyl as seen in the trans-silylation of **6** (R = H) and **7** (R = Me). For each case, the metatheses catalyzed by $Hg(OAc)_2$ and $Pd(OAc)_2$ gave virtually identical results. Interestingly, increasing steric bulk from methyl to phenyl increases the level of *Z*-selectivity for silicon metathesis, such that trimethylsilyl enol ether **10** (R = Ph) metathesizes to give only (*Z*)-**15**, regardless of the metal catalyst. These steric effects are likely manifested by the minimization of 1,2-eclipsing interactions between the spectator group and the methyl substituent of the metal enolate. As the spectator group increases in size, the equilibrium between the conformers shifts to avoid unnecessary steric interactions.

The increase in steric bulk of the spectator also reduces the rate of trans-silylation such that the metathesis of **10** required an increase in catalyst concentration even when $Hg(OAc)_2$ was used, the most effective trans-silylation catalyst. Curiously, a decrease in steric bulk from ethyl to hydrogen resulted in slower trans-silylations as well, possibly from a decrease in nucleophilicity of the aldehyde enolate. Thus, the metathesis of **6** and **7** required longer reactions times compared to **4** regardless of the catalyst. As of yet, the origin of the rate attenuation remains unclear. In all cases, longer reaction times resulted in lower yields of trichlorosilyl enol ethers. It is presumed that this is due to hydrolysis of the trichlorosilyl enolate as it remains in the reaction flask during long reaction times.

The results from these studies provided a key insight into the mechanism of trans-silylation. It may be postulated that Lewis acidic metals rapidly and reversibly combine with trimethylsilyl enol ethers to generate an organometallic species capable of allowing isomerization of the enol ether. The nature of this species has not been investigated, although it is possible to envision isomerization via a zwitterionic oxycarbenium adduct, Figure 1.

It is likely that complexation of the metal catalyst gives rise to organometallic species of type **I**. In fact, the formation of α-mercurioketones by this route is well

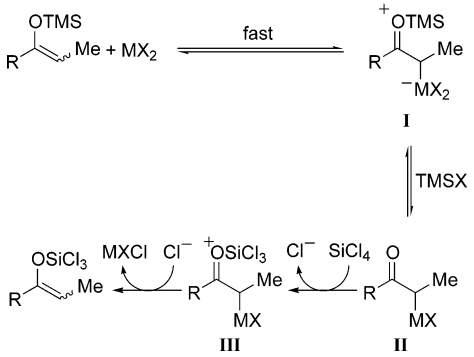


FIGURE 1. Proposed trans-silylation mechanism.

precedented in the work of both House[18] and Yamamoto.[19] In either case, the intermediacy of **I** allows for rapid isomerization of the trimethylsilyl enol ether.

The next step in this process is postulated to involve the loss of a metal counterion followed by removal of the TMS group to afford either an α-mercurioketone (vide supra) or an α-palladioketone. Complexation of the α-metalloketone by $SiCl_4$ with concomitant displacement of chloride generates a new trichlorosilyl oxycarbenium ion adduct, **III**. Attack of chloride on the metal affords the trichlorosilyl enolate and regenerates a form of the metal catalyst.

From the proposed mechanism, some of the metal chlorides are required to catalyze the trans-silylation after two turnover events regardless of the results for the exchange reactions. However, the exchange studies clearly demonstrate that counterion exchange is rapid compared to trans-silylation, suggesting that a metal(II) chloride is the active catalyst that is formed in situ. Thus, the effect of the counterion on the selectivity of trans-silylation would be minimal at best for both $Hg(OAc)_2$ and $Pd(OAc)_2$ because these exchange so rapidly. Conversely, it is conceivable that counterion exchange with $Pd(TFA)_2$ may be competitive with trans-silylation, although as stated previously, full exchange to the more reactive metal(II) chloride would be expected after two turnover events.

Nonetheless, the effect of the counterion on the rate of metathesis can be profound if $Pd(OAc)_2$ and $Pd(TFA)_2$ are compared. For the trans-silylation of enol ether **4**, $Pd(TFA)_2$ is nearly a factor of 8 slower than $Pd(OAc)_2$. The exchange studies also determined that $Pd(TFA)_2$ exchanges much more slowly than $Pd(OAc)_2$, supporting the hypothesis that $PdCl_2$ is the active catalyst. Therefore, when beginning with $Pd(TFA)_2$, trans-silylation does not occur until sufficient quantities of $PdCl_2$ are produced. It is likely that chloride is required to displace the TMS group as TFA may not be of sufficient nucleophilicity to affect this process. This is further evidenced by the presence of TMSCl during the early stages of reaction, although a rapid ligand exchange between TMSOTf and adventitious chloride cannot be completely overlooked. Interestingly, trans-silylations are extremely slow when beginning with either $HgCl_2$ or $PdCl_2$. This apparent contradiction was also observed by Saegusa et al. in their $Pd(OAc)_2$-catalyzed dehydrosilylations of silyl enol ethers to generate α,β-unsaturated ketones.[20] The authors mention that $PdCl_2$ was less effective than $Pd(OAc)_2$ due to its poor solubility in acetonitrile. Likewise for trans-silylations, the in-situ formation of metal chlorides may be advantageous due to its increased dispersity and higher solubility.

The striking observation that the metal can influence the stereoselectivity of trans-silylation warrants special comment. In both cases, the stereodetermining event is most likely the loss of metal chloride to produce the trichlorosilyl enolate. The conformation of the metallospecies prior to the loss of metal salt is crucial for determining the geometry of the resultant trichlorosilyl enol ether. From a stereoelectronic standpoint, the carbon−metal bond should be orthogonal to the atomic plane so as to maximize overlap with the carbonyl π-system.

It is well-established that Group 11 and 12 metal enolates such as mercury exist primarily in the carbon-bound form.[18,21] This gives two limiting conformations for the loss of metal salt, Figure 2. The more favorable conformation places the hydrogen substituent on the metal-bearing carbon synclinal to the spectator group, **IV**, resulting in minimal gauche interactions between these two substituents. Demetalation from this conformation affords the *Z*-trichlorosilyl enol ether. The less favorable conformation places the methyl substituent on the metal-bearing carbon synclinal to the spectator group, **V**, causing larger steric interactions. Subsequent demetalation from this conformation would afford the *E*-trichlorosilyl enol ether. This explanation would clearly explain the effect that bulkier substituents[22] have on the stereoselectivity of trans-silylation. Thus, substituents such as *tert*-butyl and phenyl provide large steric interactions such that demetalation provides virtually only the *Z*-isomer.

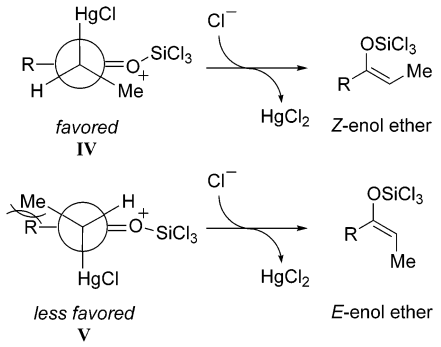


FIGURE 2. Proposed mechanism for mercury-catalyzed trans-silylation.

Interestingly, these steric arguments do not govern the stereoselectivity observed for the preparation of **6** (R = H). In fact, trans-silylation of **6** afforded the trichlorosilyl

(18) House, H. O.; Auerbach, R. A.; Gall, M.; Peet, N. P. *J. Org. Chem.* **1973**, *38*, 514.
(19) Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1982**, *104*, 2323.
(20) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(21) (a) Bluthe, N.; Malacria, M.; Gore, J. *Tetrahedron* **1984**, *40*, 3277. Drouin, J.; Boaventura, M.-A.; Conia, J.-M. *J. Am. Chem. Soc.* **1985**, *107*, 1726. (b) Drouin, J.; Boaventura, M.-A.; Conia, J.-M. *J. Am. Chem. Soc.* **1985**, *107*, 1726.
(22) For a discussion of steric effects in organic chemistry as well as a listing of Taft steric parameters, see: Newman, M. S., Ed. *Steric Effects in Organic Chemistry*; Wiley: New York, 1956.

enol ether with *greater Z*-selectivity than for the methyl derivative **7**. Although counterintuitive, the preference for silyl enol ethers of aldehydes to adopt a *Z*-configuration is well documented.[23] In the preparation of a variety of aldehyde enoxysilanes, Cazeau reported that the *Z*-isomer was the major product in each case.[23b] Although the author does not provide a rationalization for the observed stereoselectivity, he does comment that these enoxysilanes were prepared under thermodynamic control.

Unlike Group 11 and 12 metal enolates, Group 7 through 10 enolates have been proposed to exist dynamically as η^3-oxaallylmetallo enolates and 2-oxoalkylmetallo enolates.[20,24] Although the isolation and characterization of an oxo-π-allylpalladium complex has only recently been reported,[25] speculation of their existence has been proposed extensively in the literature.[26] Thus, revising the proposed mechanism for palladium catalysis to incorporate the η^3-oxaallylpalladium intermediate would prove insightful, Figure 3. For these intermediates an unfavorable conformation exhibits severe $A^{1,2}$ strain from the positioning of the methyl substituent on the metal-bearing carbon with the spectator group in a synplanar fashion, **VI**. Therefore, demetalation would occur preferentially through a structure similar to that of **VII** to position the methyl substituent antiperiplanar with respect to the spectator group. This would lead to the formation of *Z*-trichlorosilyl enol ethers. It follows that the magnitude of $A^{1,2}$ strain increases with larger spectator groups, such that trans-silylations of **9** (R = *t*-Bu) and **10** (R = Ph) are nearly completely selective for the *Z*-isomer. As was the case for mercury catalysis, explanations for the observed results with **6** (R = H) lie outside steric arguments alone. Thus it is conceivable that stereoelectronic factors play a large role in determining the stereochemical outcome of trans-silylations with aldehyde TMS enol ethers.

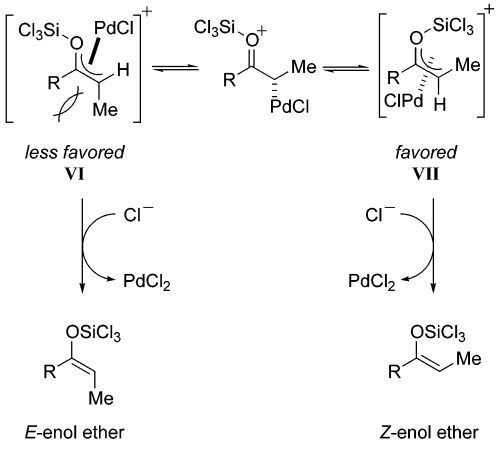


FIGURE 3. Proposed mechanism for palladium-catalyzed trans-silylation.

In summary, the difference in stereoselectivity exhibited by the various metal salts can be attributed mainly to the different manners in which enol ethers may complex. Complexation to mercury affords carbon-bound enolates. The level of stereoselection is directed by the magnitude of the gauche interactions between the methyl group and the spectator group for the two limiting conformations available for demetalation. On the other hand, complexation to palladium provides enolates that may be considered as an oxo-π-allylpalladium complex. In this case, the degree of stereoselection is directed by the magnitude of the $A^{1,2}$ strain between the methyl group and the spectator group during demetalation, allowing for greater levels of stereoselection in the case of some substrates.

B. Aldol Additions. Aldol additions of trichlorosilyl enolates to aldehydes catalyzed by phosphoramide **2** are believed to proceed through a two-phosphoramide mechanism characterized by chairlike transition structures. This affords diastereomeric products related to the starting enolate geometry as predicted by the Zimmerman−Traxler model.[27,28] For the addition of (*Z*)-**5** (R = Et) to benzaldehyde, essentially perfect diastereocontrol was achieved in that a 15/1, *Z*/*E* enolate mixture afforded aldol adduct **16a** in a 16/1, syn/anti ratio. The level of stereocontrol is further highlighted by the high enantioselectivity. Unfortunately, attenuated selectivities were observed when employing 1-naphthaldehyde as the electrophile. In this example, only an 8/1, syn/anti ratio was obtained suggesting a failure in the activated complex to sustain a chairlike transition structure, which may be manifested in either of two ways. First, the ability to achieve a 2:1 phosphoramide:enolate complex may be diminished when aldehydes other than benzaldehyde are used in reactions with **5**. This 1:1 complex would now have a propensity to react through a boatlike transition structure affording anti products.[15a] Second, the partitioning between chairlike and boatlike transition structures for the 2:1 complex of this enolate may allow the boat form to be competitive, Figure 4. Both scenarios are possible though it is unclear why 2:1 complexes would be less favorable for this class of trichlorosilyl enolate or why the 2:1 complex should be less selective for chairs.

The use of smaller electrophilic partners such as 2-furfuraldehyde and *trans*-cinnamaldehyde had little effect in improving stereoselectivities. Indeed, it is believed that phosphoramide-catalyzed aldol additions with trichlorosilyl enolates require relatively bulky aldehydes

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(27) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

(28) The configuration at silicon in the putatitve cationic two-phosphoramide transition structure depicted in Figure 4 is purely speculative, but based on the following rationale: (1) the observed cis-coordination of phosphoramides in $SnCl_4$ complexes (ref 29), (2) the preferred coordination of a complexed benzaldehyde molecule trans to a chlorine atom in a phosphoramide·$SnCl_4$ complex (ref 29), and (3) the expected activating effect of a stronly donating phosphoramide ligand trans to the enolate (ref 30).

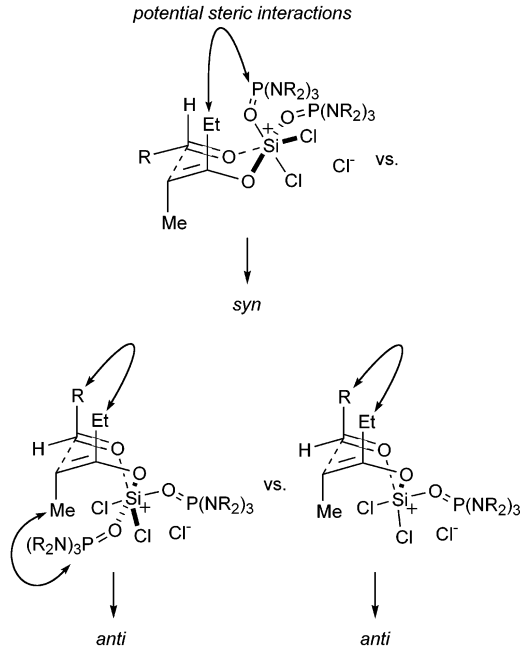


FIGURE 4. Competing transition structures which afford diastereomeric products.

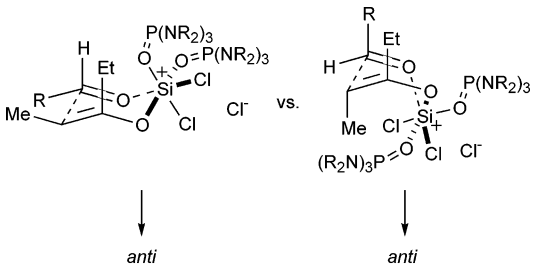
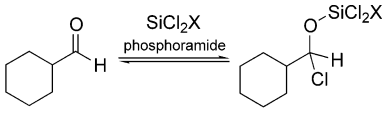


FIGURE 5. Competing chairlike and boatlike transition structures for the addition of (*E*)-**12** to aldehydes.

SCHEME 7



to enhance the energetic differences between the chair and boat transition structures. Not unexpectedly, the addition of (*Z*)-**5** to cyclohexanecarboxaldehyde was poor with regard to both stereoselectivity and yields. Although not typically problematic with unsaturated aldehydes, the reversible formation of chlorohydrins often leads to diminished yields with aliphatic aldehydes, Scheme 7. The lack of stereocontrol is evident by the formation of the undesired diastereomer in racemic fashion.

Surprisingly, use of (*E*)-**5** (R = Et) resulted in severely attenuated selectivities for additions to benzaldehyde. Unlike the near-perfect correlation of geometric information with (*Z*)-**5**, the *E*-counterpart afforded aldol adducts with no diastereoselectivity with benzaldehyde. A lack of chair−boat selectivity may further explain the reduced enantioselectivities in that addition of the minor geometric isomer through a boatlike transition structure should afford the desired diastereomer albeit with low enantioselectivity, Figure 5. The results for the remaining aldehydes reflect those observed for additions with (*Z*)-**12**. Again, 1-naphthaldehyde remained superior compared with additions to the smaller unsaturated aldehydes as well as cyclohexanecarboxyaldehyde.

Although competition between 2:1 and 1:1, phosphoramide:enolate pathways may sometimes be problematic, it is unlikely that such a competition may explain the less than ideal results observed for aldol additions with enolate **5**. The absence of a loading effect, albeit with modest diastereoselectivity for the addition of (*Z*)-**5** to 2-furfuraldehdye, suggests that 2:1 complexation is readily achieved. This further explains why no enhancement was obtained when attempting additions to 1-naphthaldehyde with the dimeric phosphoramides. Although the tethered catalyst certainly increases the relative concentration of the second phosphoramide, it is likely that the presence of the linker prevents ideal binding of the Lewis basic ends. Unfortunately in the monomeric phosphoramide **2**, the nature of the complex involving enolate **5** allows flexibility for the transition structure to rest in either a chair-form or boat-form resulting in diminished diastereoselectivities.

Interestingly, switching to a smaller spectator group in enolate **7** (R = Me) afforded dramatically different results. Severely diminished selectivities were observed for the addition of (*Z*)-**7** to benzaldehyde with typical catalyst loadings of 10−15 mol %. Unlike (*Z*)-**5**, (*Z*)-**7** was highly responsive to catalyst concentration, achieving excellent results when utilizing 50 mol % of phosphoramide **1**. This suggests that binding of the second phosphoramide with enolate **5** may be less facile compared to enolate **7**, allowing aldolization through a one-phosphoramide pathway to become competitive. Thus, increasing the relative concentration of the second phosphoramide through the use of dimeric catalysts afforded aldol products with essentially perfect correlation of enolate geometry to diastereoselectivity. Interestingly, the optimal tether length was seven methylene units, unlike previous examples where five methylene units proved to be superior, Figure 6. This suggests that the relative orientation around silicon is different for allylation reactions than for aldol additions, although this may not be entirely the case as the optimal lengths were determined with different catalyst structures. For the aldol additions, tether lengths of four and five methylene units afforded poor enantioselectivities. This may be the result of the methylene tether restricting coordination of the Lewis basic units to a nonoptimal orientation. Increasing the tether length to six and seven methylene units may allow added flexibility to achieve a more

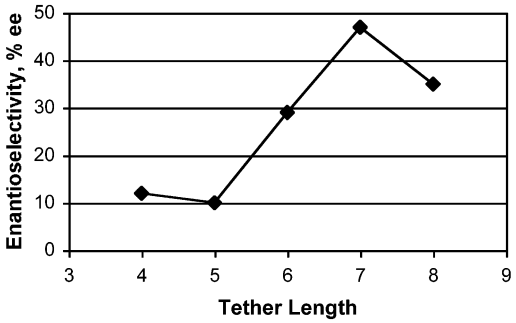


FIGURE 6. Correlation of enantioselectivity vs catalyst tether length.

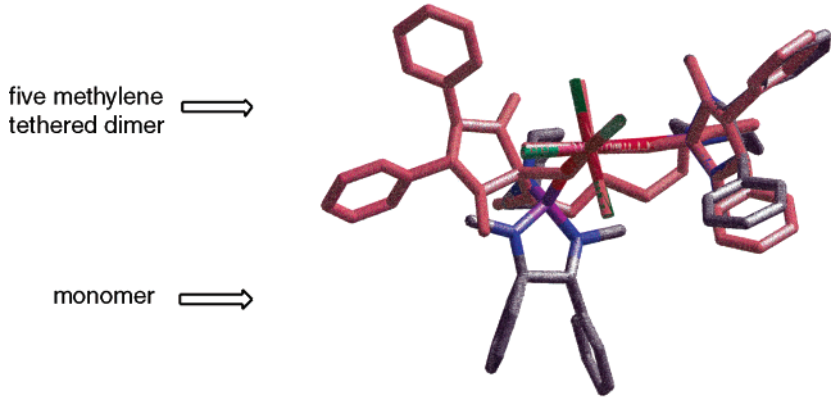


FIGURE 7. Overlay of the 2:1 monomer complex and five methylene tether phosphoramide complex.

desirable coordination geometry. A decrease in enantioselectivity at eight methylene units may imply an entropic consequence that disfavors chelation. Although improved enantioselectivities could not be achieved, enhancement of chair selectivity through the use of as little as 5 mol % of a dimeric phosphoramide clearly demonstrates the utility of linked catalysts for increasing the relative concentration of the second binder. Unfortunately, results with (*E*)-**7** were disappointing. Although only a small loading study was conducted, formation of the undesired diastereomer in racemic form was observed even when 50 mol % of the catalyst was used.

To better understand the nature of the activated complex, a computational modeling was done with X-ray crystal structures of the tin complexes for the monomeric phosphoramide **2** and the dimeric, five methylene tether phosphoramide **19** as templates.[29] The X-ray crystal structures of **2** and **19** with tin tetrachloride were viewed and manipulated with *Cerius*[2]. Initial observation of the tin complexes revealed that the orientation of the phosphoramides was distinctly different between the 2:1 monomeric complex and the 1:1 dimeric complex. By aligning the vertices of the octahedral complex, it is observed that there exists little overlap between the second phosphoramides of the two complexes, Figure 7. Analysis of the crystal structures shows a rotation of the second phosphoramide unit, in the dimeric complex, away from the preferred orientation established by the crystal structure of the 2:1 complex. It is likely that this was necessary to avoid bond distortion in the methylene tether.

Methylene units were then sequentially added and the resulting structure was minimized to evaluate the effect of increasing tether lengths on the orientation of the phosphoramides. Unfortunately this provided little insight as each of the minimized complexes adopted nearly the same phosphoramide conformation for five methylene up to eight methylene unit tethers. Attempts to access other minima by severely distorting the tether were also unsuccessful, observing that the complexes each relaxed back to their original conformation. Thus it appears that regardless of the length, the methylene tether distorts the dimer complexation geometry away from the presumed idealized geometry established with the 2:1 complex, using the monomeric phosphoramide.

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Conclusions

Z-Trichlorosilyl enolates can be prepared by mercury(II) and palladium(II) catalysis from the corresponding trimethylsilyl enol ethers. Although $Pd(TFA)_2$ could also catalyze the trans-silylation, its activity was attenuated by slow exchange to the chloride salt. From this process, good to excellent stereoselectivity was observed for large spectator groups (Ph, *t*-Bu); however, only moderate stereoselection was achieved for smaller groups (Me, Et).

The scope of aldol additions involving trichlorosilyl enolates has been expanded to include ethyl ketone enolates, with reactions proceeding in good to high yields for all reactions with the exception of aliphatic aldehydes. Excellent stereoselectivities were observed for the addition of (*Z*)-**5** and (*Z*)-**7** to benzaldehyde. Unfortunately, the reactions with these substituted enolates lack substrate generality with stereoselectivities becoming attenuated when electrophilic partners other than benzaldehyde are used. Efforts to improve the overall generality of aldol additions of substituted trichlorosilyl enolates to aldehydes by the design of second-generation dimeric phosphoramides and the development of alternate reaction manifolds are currently underway.

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Supporting Information Available: Detailed procedures for the preparation and aldol addition reactions of trichlorosilyl enolates along with spectroscopic characterization of the enolates and aldol products. This material is available free of charge via the Internet at http://pubs.acs.org.

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