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Enantioselective Ring Opening of Epoxides with Silicon Tetrachloride in the Presence of a Chiral Lewis Base: Mechanism Studies

Scott E. Denmark,[a,*] Paul A. Barsanti,[a] Gregory L. Beutner,[a] and Tyler W. Wilson[a]

[a] 245 Roger Adams Laboratory, Box 18, Department of Chemistry, University of Illinois, 600 S. Mathews Ave., Urbana, IL 61801, USA
Fax: (+1)-217-333-3984; phone: (+1)-217-333-0066; e-mail: denmark@scs.uiuc.edu

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This paper is dedicated to Professor Masakatsu Shibasaki in recognition of his pioneering and creative contributions to the field of asymmetric catalysis.

Abstract: The enantioselective ring opening of *meso*-epoxides (from both cyclic and acyclic olefins) with silicon tetrachloride under catalysis by chiral phosphoramides affords enantiomerically enriched chlorohydrins in excellent yields. Experiments designed to elucidate the mechanistic foundation and origins of enantioselectivity are described. From studies on the loading and stoichiometry of the reagent ($SiCl_4$) and the catalyst [(*R*)-**1**] it was established that only one chloride per $SiCl_4$ is delivered and that the nature of reactive species does not change over the course of the reaction. Kinetic studies together with asymmetric amplification experiments have suggested that more than one catalyst molecule may be bound to $SiCl_4$ in the stereochemistry-determining transition structure.

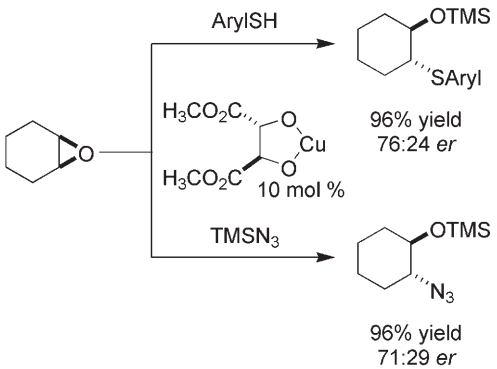
Keywords: asymmetric catalysis; C–C bond formation; cross-coupling; enzyme catalysis; homogeneous catalysis

Introduction

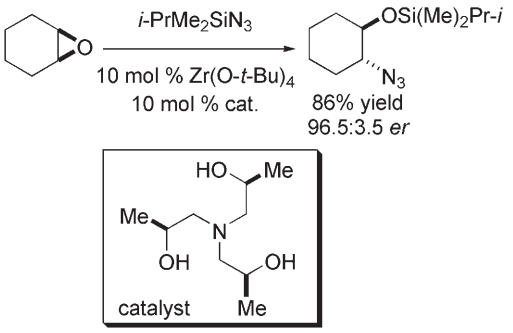
The desymmetrization of *meso*-compounds is an intriguing strategy for asymmetric synthesis.[1] Whereas asymmetric transformations often involve enantiotopic face selection with compounds that contain no stereogenic centers, these reactions involve enantiotopic group selection with C_s symmetric compounds that may contain a number of stereogenic centers. Therefore, in a maneuver termed by Fischli the "*meso*-trick", a number of stereogenic centers can be unveiled at once by a single transformation with high diastereo- and enantioselectivity.[2] Epoxides are a readily available class of *meso*-compounds that have been the focus of continuing interest.[3] The myriad ring opening reactions of epoxides with many different nucleophiles makes them extremely versatile synthetic intermediates for organic synthesis.[4] Therefore it is not surprising that the enantioselective syntheses[5] and transformations[6] of epoxides remain active research endeavors.

Background

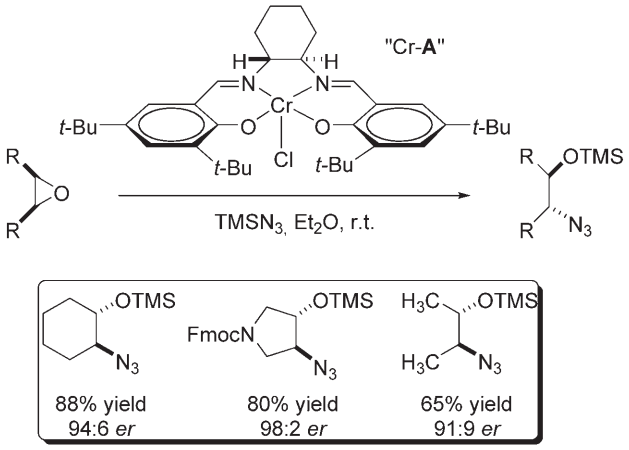
Despite extensive studies on site and stereochemical selectivity in epoxide opening reactions,[4] an enantioselective variant did not appear until Yamashita's seminal report on the first asymmetric ring opening of a *meso*-epoxide in 1985 (Scheme 1).[7] In the presence of either zinc or copper tartrate complexes, $TMSN_3$ reacted with a variety of epoxides in good yields but



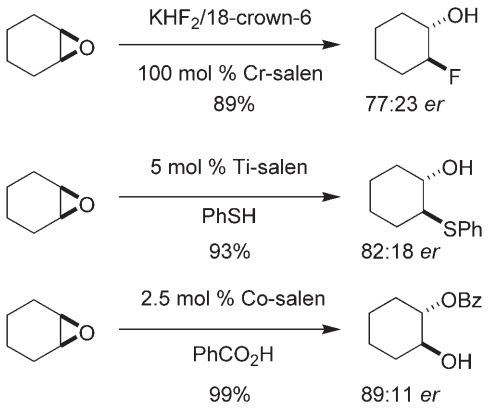
Scheme 1.



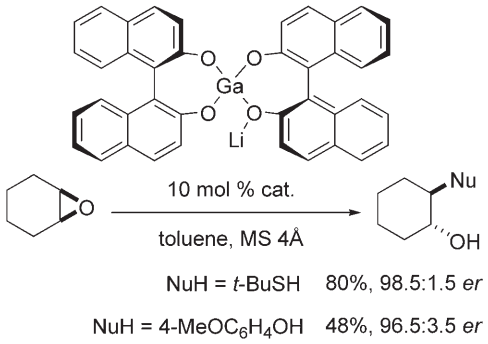
Scheme 2.



Scheme 3.



Scheme 4.



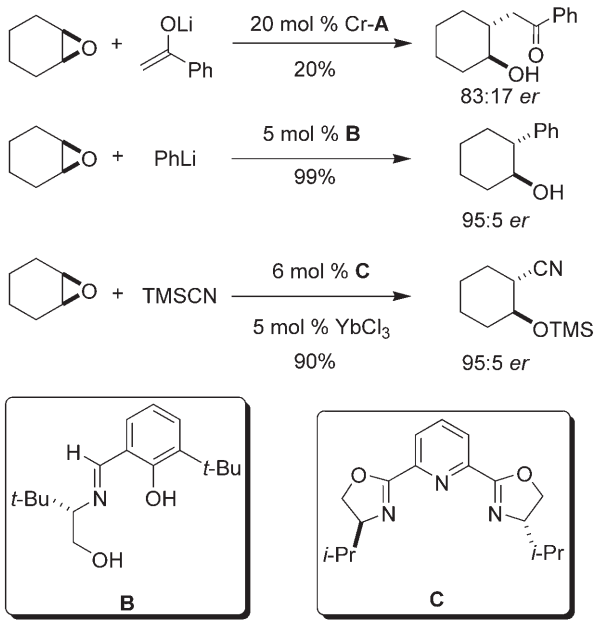
Scheme 5.

with only moderate levels of enantioselectivity. Sinou and co-workers extended this method to the use of a titanium tartrate complex to provide similarly modest levels of enantioselectivity.[8] The first highly-selective method for epoxide desymmetrization, published by Nugent in 1992, involves a zirconium(IV) trialkanolamine complex which catalyzes a highly enantioselective addition of *i*-$PrMe_2SiN_3$ to a variety of *meso*-epoxides, (Scheme 2).[9]

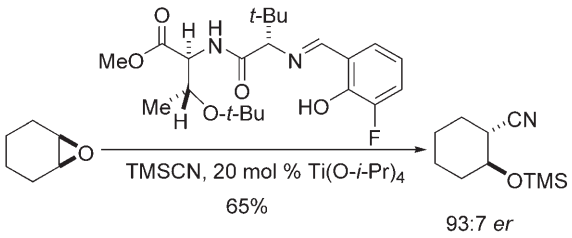
These pioneering studies on the desymmetrization of *meso*-epoxides were only capable of delivering nitrogen centered nucleophiles.[10] Although chiral amino alcohols are an important class of compounds, a more general method that would allow access to a wider variety of products derived from the additions of oxygen-, sulfur- and even carbon-centered nucleophiles would be a great advance. Jacobsen proposed that the manganese-(salen) complex that provides high enantioselectivity in the epoxidation of *cis*-olefins might also effect a highly enantioselective epoxide opening of *meso*-epoxides. This chiral metallo-(salen) complex developed by Jacobsen and co-workers for asymmetric epoxidations does allow for desymmetrization of *meso*-epoxides with a wide range of nucleophiles.[11] A thorough survey of transition metals revealed that chromium(III) uniquely led to high yields and enantioselectivities in the opening of a variety of epoxides with $TMSN_3$ (Scheme 3).[12] The versatility of this method was demonstrated by Ganem and co-workers in the synthesis of allosamidin.[13] Mechanistic studies on this and related systems have demonstrated that the reaction is second order in catalyst.[14] The cooperativity of the catalyst molecules in the transition structure led to the development of a variety of highly selective oligomeric and dendridic catalysts.[15]

The use of this chromium-(salen) complex is not limited to the addition of nitrogen-centered nucleophiles. The complex is the sole effective agent for the asymmetric synthesis of vicinal fluorohydrins albeit with a stoichiometric loading of the complex shown in Scheme 4.[16] Further extensions of the scope of this catalyst system for the additions of thiols to *meso*-epoxides employ the titanium-(salen) complex as also shown in Scheme 4.[17] Finally, a cobalt-(salen) complex catalyzes the highly selective addition of carboxylic acids.[18,19]

As part of their pioneering studies on the use of heterobimetallic complexes as catalysts for asymmetric synthesis, Shibasaki and co-workers reported the application of gallium-lithium bis(binaphthoxide) complexes for the enantioselective opening of *meso*-epoxides with thiols and phenols (Scheme 5).[6c-e]



Scheme 6.



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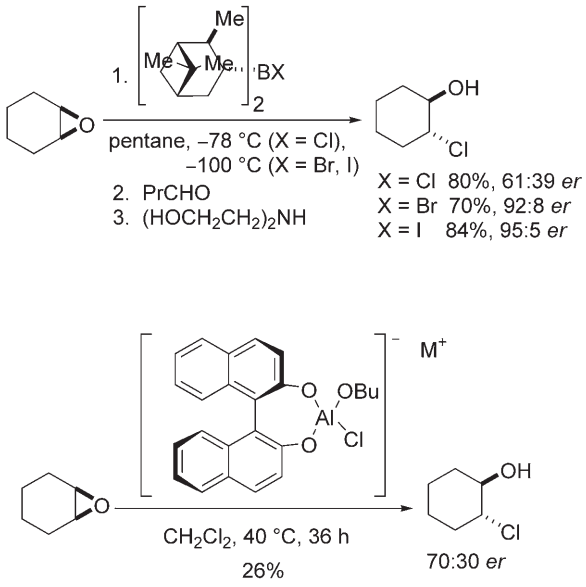
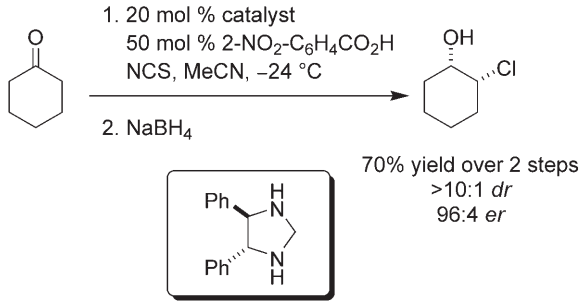


Scheme 8.



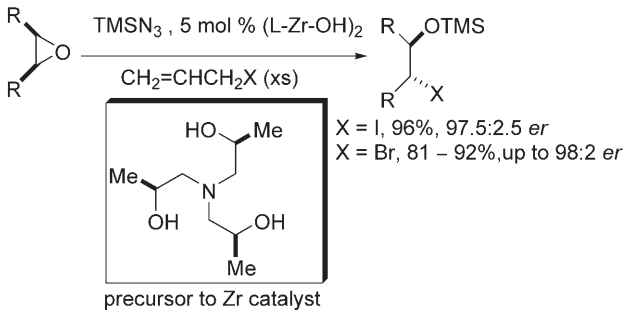
Scheme 9.

The addition of carbon-centered nucleophiles to *meso*-epoxides in a selective manner remains a synthetic challenge. In one of the first reports on the addition of a carbon nucleophile, Tomioka and co-workers described the enantioselective addition of phenyllithium to cyclohexene oxide in the presence of a stoichiometric amount of a chiral ligand.[20] The development of a catalytic method was reported by Crotti and co-workers who showed that the chromium-(salen) complex can promote the enantioselective addition of lithium enolates to *meso*-epoxides (Scheme 6).[21] Another method, developed by Oguni and co-workers, involves the addition of phenyllithium catalyzed by the chiral Schiff base complex **B** (Scheme 6).[22]

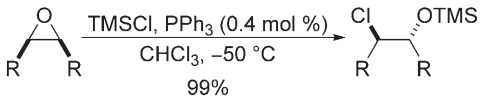
The opening of cyclohexene oxide with cyanide can be performed using either a polypeptide-based catalyst developed by Oguni, Snapper and Hoveyda[23] (Scheme7) or a ytterbium-pybox catalyst developed by Jacobsen and co-workers (Scheme 6).[24]

Curiously, less attention has been directed toward the asymmetric opening of *meso*-epoxides to afford the corresponding vicinal halohydrins. Halohydrins serve as important synthetic intermediates in their own right,[25] in addition to being key intermediates in the synthesis of halogenated natural products.[26] The classical reagents for halohydrin synthesis are strong Lewis[25] or hydrohalic acids[27] that provide powerful electrophilic activation. The asymmetric synthesis of chlorohydrins by enantioselective ring opening of epoxides relies on the use of stoichiometric amounts of chiral, Lewis acid halides (Scheme 8).[28] Alternatively, *cis*-halohydrins can be obtained by enantioselective α-chlorination of ketones followed by reduction (Scheme 9).[29]

At the time our work was initiated, no catalytic procedure for desymmetrization of *meso*-epoxides with halide nucleophiles had been developed. However, subsequently, Nugent reported a catalytic, enantioselective ring opening of *meso*-epoxides to afford the



Scheme 10.



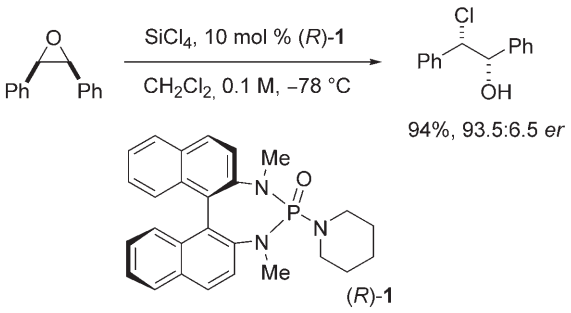
Scheme 11.

corresponding halohydrins, again employing the chiral zirconium catalyst, Scheme 10.[30]

A conceptually distinct approach for halide opening of an epoxide involves activation of Lewis acids (e.g., TMSCl) by Lewis bases. This method offers unique opportunities for asymmetric catalysis by disconnecting the roles of activator and nucleophile.[31] In one of the few examples in the literature, Andrews and coworkers found that epoxide ring opening with TMSCl could be very efficiently catalyzed with as little as 0.4 mol % of Ph_3P, Scheme 11.[32]

The use of a more reactive silicon species, $SiCl_4$,[33] allows for a similar reaction to proceed under milder conditions and opens the possibility for the introduction of an asymmetric environment during the enantiodetermining event. The Lewis base-catalyzed formation of chlorohydrins mediated by $SiCl_4$ has been studied in several laboratories and a wide variety of chiral Lewis bases have proven successful in providing high selectivities. In 1998, the first example of catalytic, enantioselective opening of epoxides with chlorosilanes to afford the corresponding chlorohydrins was reported from these laboratories.[34] The use of the chiral phosphoramide (*R*)-**1** in combination with $SiCl_4$ led to the enantioselective synthesis of chlorohydrins, Scheme 12. Following our initial report, other groups described the use of *N*-oxides,[35,36] phosphines,[37] and phosphine oxides[38] (Scheme 13).

As part of an ongoing program in these laboratories on Lewis base-catalyzed reactions of silicon tetrachloride, we sought to investigate a number of preparative and mechanistic features of the epoxide ring opening reaction to garner a clearer understanding of the role of each of the reaction components and potentially the origin of enantioselectivity.

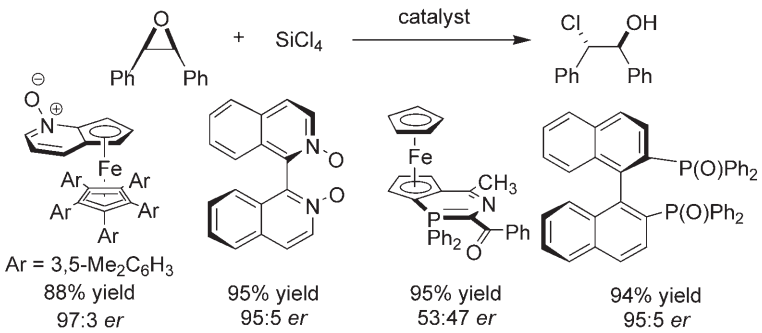


Scheme 12.

Results

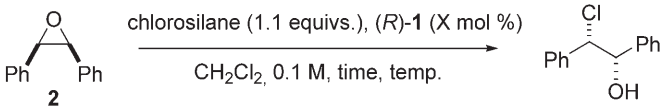
Chlorosilane Sources

The first phase of these studies probed the influence of chlorosilane structure on the rate and selectivity of the epoxide opening. For these studies, cyclohexene oxide was chosen as the test substrate under the standard reaction conditions [0.1 equiv. of (*R*)-**1**, 0.1 M cyclohexene oxide in CH_2Cl_2 at −78 °C for 2 h, then pouring into saturated aqueous KF/KH_2PO_4]. All of the following chlorosilanes afforded *trans*-2-chlorocyclohexanol: $SiCl_4$, $HSiCl_3$, $PhSiCl_3$, CH_3SiCl_3, $(CH_3)_2SiCl_2$, $(CH_2)_3SiCl_2$, $(CH_2)_3SiCH_3Cl$, $(CH_3)_3SiCl$, $PhCO_2SiCl_3$, *t*-$BuCO_2SiCl_3$. However, only $SiCl_4$ and



Scheme 13.

Table 1. Survey of chlorosilane sources.



Entry	Chlorosilane	(*R*)-**1** [mol %]	Time [h]	Temperature [°C]	*er*[a]	Conversion [%][b]
1	$SiCl_4$	10	3	−78	93.5/6.5	100
2	$HSiCl_3$	10	3	−78	76.0/24.0	68
3	$HSiCl_3$	100	3	−78	76.0/24.0	100
4	$AcOSiCl_3$[c]	10	17	−78	-	42
5	$MeSiCl_3$	10	3	24	0	100
6	$(CH_2)_3SiCH_3Cl$	10	6	24	0	70

[a] Determined by CSP-SFC analysis.
[b] Conversion determined by ^1H NMR analysis.
[c] 0.1 equiv. of HMPA employed as catalyst.

$HSiCl_3$ afforded the chlorohydrin product in an enantiomerically enriched form; all the other chlorosilanes gave rise to racemic *trans*-2-chlorocyclohexanol.

The formation of racemic products from all other chlorosilane sources was extremely puzzling, but closer consideration of the process revealed several factors that could explain this outcome. Hydrogen chloride is a potential contaminant in all of these chlorosilanes and because the corresponding background reactions were not examined in this initial screening, it was possible that the products could be formed as an artifact of opening with HCl (and are therefore racemic). After establishing that HCl could be removed by continuously refluxing the chlorosilanes in a still, a few of the other chlorosilanes were reinvestigated.[39] Because *cis*-stilbene oxide **2** led to the most enantioselective opening, and is also one of the least acid-sensitive, a number of chlorosilanes were reinvestigated with this epoxide, and the results are compiled in Table 1.

Entries 2 and 3 show that $HSiCl_3$ afforded the corresponding chlorohydrin with 76:24 *er* when either 10 mol % or 100 mol % of (*R*)-**1** was employed as the catalyst. However, there was a significant decrease in rate and selectivity upon switching from $SiCl_4$ to $HSiCl_3$ (entries 1 and 2). Acetoxytrichlorosilane reacted even slower, affording a 42 % conversion after 17 h at −78 °C when 10 mol % HMPA was employed as the catalyst (entry 4).

Surprisingly, $MeSiCl_3$ failed to induce any reaction at −78 °C after 24 h with either 10 or 100 mol % of (*R*)-**1** whilst $(CH_2)_3SiCH_3Cl$ provided a mere 17 % conversion after 4 d at −78 °C with 100 mol % of (*R*)-**1**. However, at room temperature, full conversion was observed with $MeSiCl_3$ after 3 h with 10 mol % of (*R*)-**1**. Unfortunately, the product was racemic (entry 5). Use of $(CH_2)_3SiCH_3Cl$ with 10 mol % of (*R*)-**1** led to 70 % conversion after 6 h, and again, the product was racemic (entry 6).

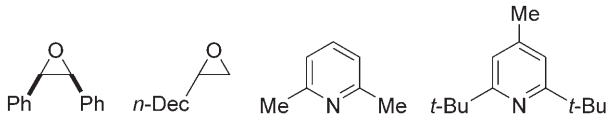
Internal Quench

During the course of these investigations, it was found that if the reactions had not proceeded to completion, then quenching under the standard conditions (pouring the reaction mixture into a 1/1 mixture of saturated aqueous KF/KH_2PO_4 solution at 0 °C) generated HCl which rapidly opened the unreacted epoxide to the chlorohydrin. The racemate thus formed then led to erroneous conversions and enantiomerically diluted products. Therefore, it was critical to establish a highly reproducible, internal quench that avoided the problem of generating HCl. The results of the quenching study are compiled in Table 2.

Two epoxides were chosen for study: *cis*-stilbene oxide **2** and 1,2-epoxydodecane **3**. These two epoxides behave very differently toward opening and would represent a spectrum of reactivities for subsequent studies. Initial experiments with **3** employed hindered amines **4** and **5**, and various fluoride sources as bases. Entries 1–3 show that quenching the reactions with alcohols in the presence of either of these amines or CsF led rapidly to the formation of HCl which opened **3** to the corresponding chlorohydrin. The use of TASF was ineffective for the faster reacting epoxide **3** (entry 4) leading to 43 % of the chlorohydrin, although this quench method proved more effective for the slower reacting epoxide **2** (entry 5).

These results showed that epoxide **3** was more effective at scavenging the HCl than a hindered, tertiary amine base. Logically therefore, a faster-reacting epoxide (e.g., propylene oxide) would serve as a suitable HCl scavenger for quenching with MeOH. Indeed, entries 6 and 7 show that a pre-mixed solution of propylene oxide and MeOH led to only 7 % conversion of **3** after the quench. Even better results were obtained by adding propylene oxide rapidly before the dropwise addition of MeOH. These conditions reproducibly led to only 3 % conversion. In ad-

Table 2. Internal quench of reaction mixtures.[a]



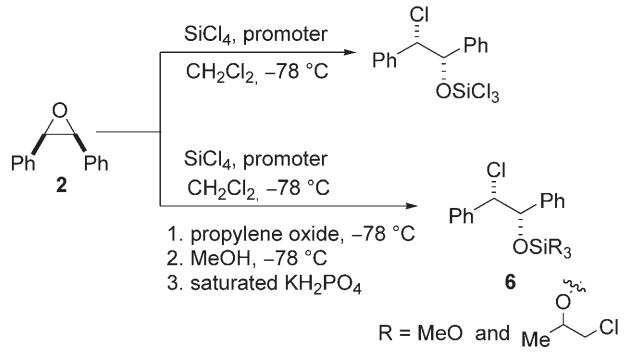
2 **3** **4** **5**

Entry	Epoxide	Quench conditions	Ring opening [%][b]
1	**3**	8 equivs. **4**, 50 equivs. MeOH, −78 °C	100
2	**3**	10 equivs. **5**, 10 equivs. *i*-PrOH, −78 °C	100
3	**3**	10 equivs. CsF, 37 equivs. MeOH, −78 °C	89
4	**3**	5 equivs. TASF, −78 °C	43
5	**2**	10 equivs. TASF, −78 °C	12
6	**2**	10 equivs. propylene oxide pre-mixed with 10 equivs. MeOH, −78 °C	7
7	**2**	15 equivs. propylene oxide pre-mixed with 10 equivs. MeOH, −78 °C	7
8	**2**	**10 equivs. propylene oxide, −78 °C, 30 s, *then* 5 equivs. MeOH, −78 °C**	**3**
9[c]	**2**	15 equivs. propylene oxide, −78 °C, *then* 5 equivs. MeOH, −78 °C	5

[a] 1.0 equiv of $SiCl_4$ in CH_2Cl_2.
[b] Determined by ^1H NMR analysis.
[c] Contained 10 mol% HMPA prior to quench.

dition to this, it was important to establish that the quench was instantaneous. Entry 9 shows that when 10 mol% of HMPA was added to a mixture of *cis*-stilbene oxide and $SiCl_4$ at −78 °C, followed immediately by the addition of propylene oxide, and then MeOH, only 5% of the chlorohydrin was formed. Thus, the quench was indeed rapid.

By use of this quenching protocol for a reaction either in progress or at completion leads to the isolation of the corresponding *silyloxy chlorohydrin* **6** (Scheme 14). In this product, both MeOH and the chlorohydrin derived from the HCl opening of propylene oxide have exchanged the chloride ligands at the silicon center. Therefore, conversions could be obtained, but desilylation of **6** was required to isolate the pure chlorohydrins for determination of enantiomeric composition. This maneuver was conveniently achieved by treatment of the silyloxychlorohydrin with TBAF buffered with AcOH (since TBAF alone was basic enough to effect ring closure of the chlorohydrin to the starting epoxide). Development of the internal quench allowed for reproducible conversions to be obtained at any time point throughout the course of the reaction. This tactic proved to be instrumental in validating and interpreting the data and also enabled the following investigation on the stoichiometry requirements of $SiCl_4$.



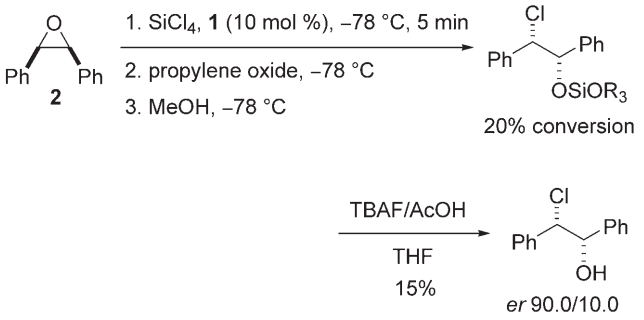
Scheme 14.

Stoichiometry of $SiCl_4$

Although $SiCl_4$ was not the only chlorosilane source that afforded enantiomerically enriched products, it did prove superior to all others both in terms of rates and selectivity. Therefore $SiCl_4$ was employed for all subsequent mechanistic studies.

The mechanistic inquiry began by establishing the stoichiometry of the reaction, i.e., to determine how many of the chlorines in $SiCl_4$ are transferrable. It is conceivable that the initial product, a trichlorosilyloxychlorohydrin, could also be susceptible to the same Lewis base promotion, leading to a dialkoxydichlorosilane, etc. If this were the case, then the reaction would not require a full equivalent of $SiCl_4$ for full conversion. To test this hypothesis, the loading of $SiCl_4$ was varied in the reaction of *cis*-stilbene oxide **2**, employing HMPA as the catalyst. The reactions were then quenched internally and the conversion examined by ^1H NMR analysis. The standard conditions involved stirring a solution of **2** (0.1 M in CH_2Cl_2) with $SiCl_4$ and 0.1 equiv. of HMPA at −78 °C for 3 h, then quenching with 15 equivs. of propylene oxide at −78 °C, followed by 5 equivs. of MeOH at −78 °C.

Surprisingly, the use of 0.52 equiv of $SiCl_4$ reproducibly led to 55% conversion, suggesting that only one



Scheme 15. Scheme 16

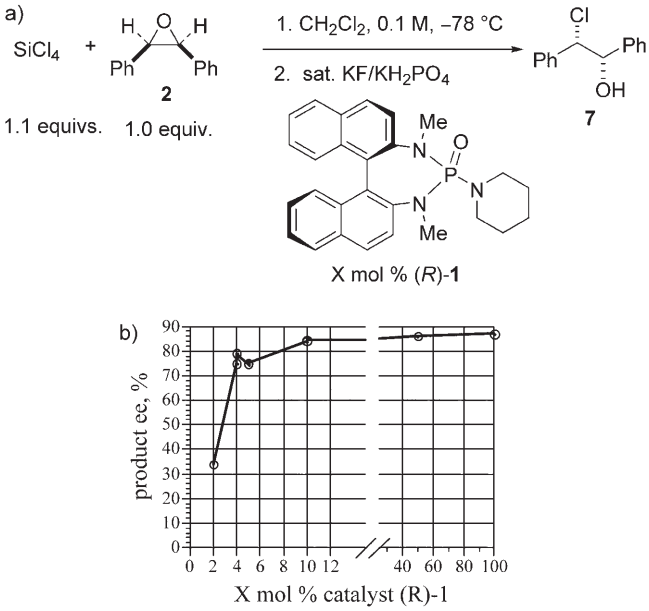


Figure 1. Loading study with $SiCl_4$ and (*R*)-**1**.

chlorine per $SiCl_4$ is delivered under these conditions. Moreover, 0.25 equivs. of $SiCl_4$ led to 29% conversion, which upon desilylation afforded a 22% yield of pure chlorohydrin. Likewise, 0.75 equivs. of $SiCl_4$ led to 76% conversion, affording a 64% yield of the isolated chlorohydrin after desilylation.

Even though only one chlorine per $SiCl_4$ is active, it is still possible that the nature of the reactive species changes as a function of conversion. To test this scenario, 10 mol% of (*R*)-**1** was combined with 1.1 equivs. of $SiCl_4$ and *cis*-stilbene oxide **2**, then the reaction was quenched internally after 5 min. This experiment provided a 20% conversion of **2**, which upon desilylation afforded a 15% yield of the chlorohydrin in a 90:10 *er*, along with 74% of recovered **2**, Scheme 15. Because essentially the same enantiomeric composition was observed at early conversion or full conversion, the ring opening species would appear to be consistent throughout the course of the reaction.

Catalyst Loading

The enantiomeric composition of the chlorohydrin from the reactions of **2** and $SiCl_4$ was determined as a function of catalyst loading with (*R*)-**1** and the results are depicted in Figure 1. As the graph clearly shows, only a slight erosion in enantioselectivity is observed from 100 mol% to 4 mol% of (*R*)-**1**. However, the enantioselectivity is greatly eroded at catalyst loadings less than 4 mol%. Although the rates were greatly reduced at these lower loadings, *control experiments established that the low selectivity observed was not due to a background reaction*. Experiments using 2 mol% of (*R*)-**1** were repeated many times and the results were highly variable until the internal quench method was developed. Once the internal quench had been established, the 2 mol% loading experiment led to a 71% conversion (after 40 h), which afforded the chlorohydrin **7** in 63% yield and with 34% *ee*. The background for this reaction was 3.5% after 40 h.

The reason for this precipitous drop in selectivity from 4 mol% to 2 mol% of (*R*)-**1** is difficult to rationalize because the rates and selectivities should fall off proportionally. Clearly, this is not the case, and currently, no explanation is available. That not withstanding, at catalyst loadings from 100 mol% to 4 mol%, primarily one catalytic pathway is operative.

Investigation of the Order in Catalyst

Kinetic Studies

To determine the order in the catalyst, the rapid injection NMR (RINMR) technique was employed because of the high rates and the sensitivity of the reaction to adventitious moisture. This technique has proven applicable to the study of a number of reactions employing highly reactive species and therefore seemed the method of choice for study of this Lewis base-catalyzed reaction process.[40]

The kinetic experiments were performed using 1.1 equiv of $SiCl_4$, epoxide **2** and HMPA as the catalyst in dichloromethane-d_2 at −78 °C and an overall concentration 0.2 M.[41] First, the order of each reagent was determined using the method of initial rates. Data from the 15% conversion run were employed to assess changes in initial rate as the concentration of a particular reagent was varied.[42] Each experiment was performed in triplicate to assure that the results were reproducible. However, despite extensive optimization, the extreme sensitivity of the reaction to traces of acid led to a degree of irreproducibility in the results. Although this problem hampered the collection of data, a number of conclusions can still be drawn.

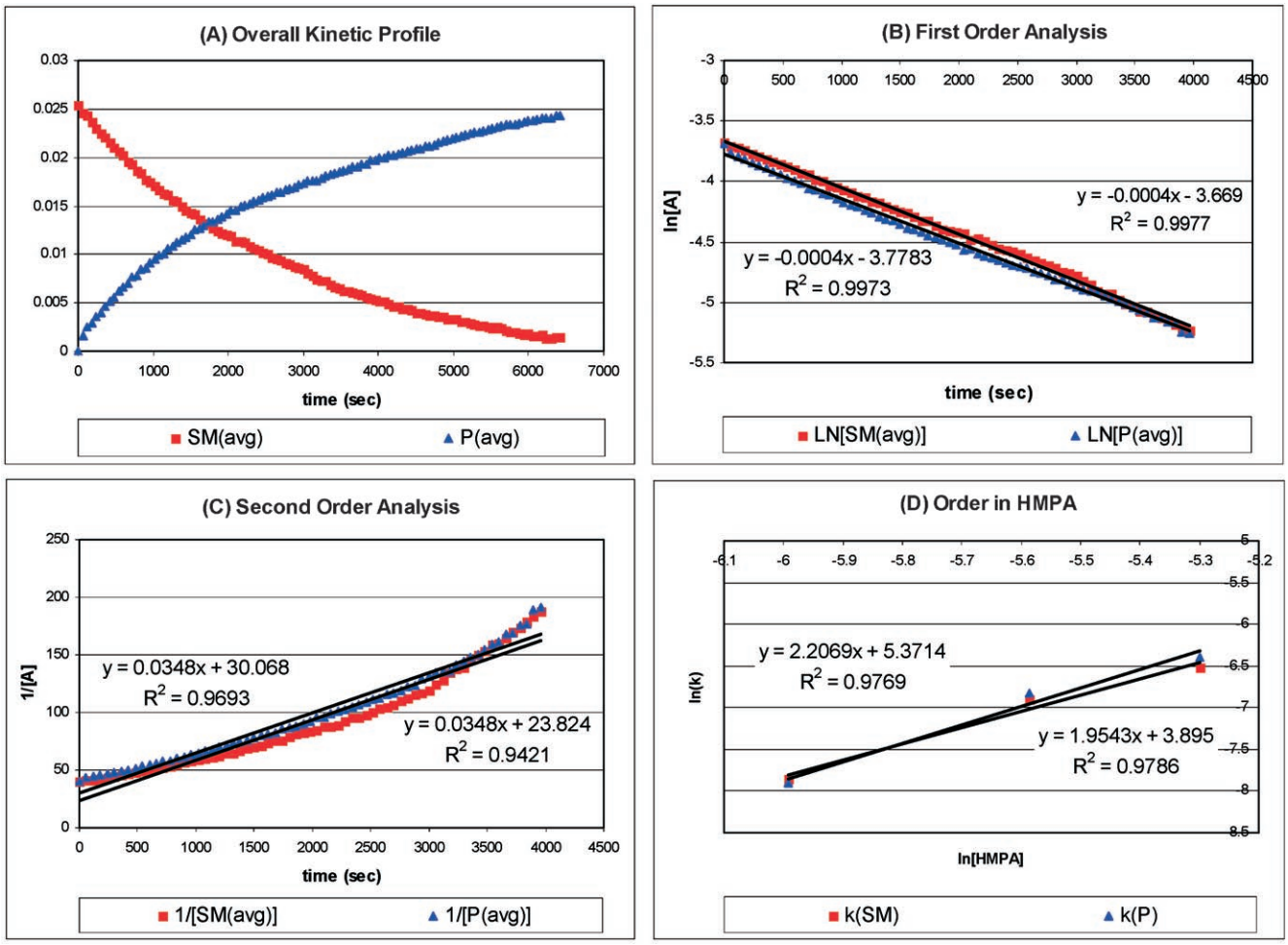


Figure 2. Kinetic analysis of the HMPA-catalyzed opening of **2**.

Examination of the reaction using the integral method revealed that the reaction exhibited good, overall 1st order behavior (Figure 2). The possibility of overall 2nd order behavior was ruled out by comparison of graphs of $\ln(\mathbf{2}_t)$ and $1/(\mathbf{2}_t)$ *versus* time out to 70% conversion [$R^2(\ln(\mathbf{2}_t)) = 0.9977$ *vs.* $R^2(1/(\mathbf{2}_t) = 0.9421$]. The linearity of the $\ln(\mathbf{2})$ *vs.* time plot was clearly higher than that of the $1/(\mathbf{2})$ *vs.* time plot. A similar conclusion could be drawn from plots of $\ln(\mathbf{2}_i - \mathbf{2}_t)$ and $1/(\mathbf{2}_i - \mathbf{2}_t)$ out to 70% conversion. By employing the method of initial rates, the order in $SiCl_4$ was determined to be zero. From 1.0 to 10 equivs. of $SiCl_4$, only small changes in initial rate were observed and overall 1st order behavior was maintained throughout [v_i(1 equiv. $SiCl_4$) $= (1.3 \pm 0.1) \times 10^{-6}\,s^{-1}$ *vs.* v_i(10 equivs. $SiCl_4$) $= (3.5 \pm 0.3) \times 10^{-6}\,s^{-1}$]. To determine the order in HMPA, changes in the first order rate constant (k_{obs}) were examined within the range of 10–20 mol% catalyst. This narrow range of catalyst concentrations was employed because of changes in the rate of these reactions and the unexpected problems associated with lower catalyst loadings. Despite these limitations, this concentration range still contains synthetically relevant catalyst loadings. Plotting ln[HMPA] against $\ln(k_{obs})$ revealed that the order in HMPA was between 1.95 and 2.2, depending on whether the analysis was performed on the basis of the disappearance of **2** or the appearance of the trichlorosilyl ether trichlorosiloxychlorohydrin, respectively ($0.9769 < R^2 < 0.9786$). On the basis of these results, the following rate equation for the epoxide opening is proposed: $-d(\mathbf{2})/dt = k[HMPA]^2[SiCl_4]^0[\mathbf{2}]^1$. Fu and co-workers reported similar observations in their studies of the *N*-oxide-catalyzed opening of *meso*-epoxides with $SiCl_4$.[35b]

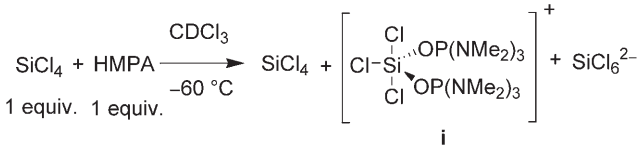
These results suggest the intriguing possibility that the Lewis base catalyst is saturated with $SiCl_4$ and that a 2:1 complex between the phosphoramide and $SiCl_4$ may be the catalyst resting state. Binding of the epoxide to this intermediate complex or attack of chloride on complex of HMPA, $SiCl_4$ and **2** is the rate-determining step, although no further conclusions can be drawn at this point.

The observed zero order rate dependence on the concentration of $SiCl_4$ also implies that under the standard reaction conditions, the majority of the cata-

lyst exists as a complex with $SiCl_4$ rather than as free catalyst. Therefore, it may be possible to observe the Lewis base-Lewis acid adduct spectroscopically. Indeed, ^{29}Si NMR spectroscopy is a powerful and well-understood technique that has proven to be the tool of choice in the search for silyl cations.[43] This nucleus has an extremely large dynamic range (~600 ppm) and the chemical shift is strongly effected by the coordination number of the silicon species under observation. The identity of the peripheral ligands has a smaller, albeit predictable effect on chemical shift. One factor that has almost no effect on the value of the chemical shift for a particular silicon species is charge. A chemical shift that can be predicted on the basis of coordination number rather than overall charge or consideration of the identity of the peripheral ligands is extremely useful. Interestingly, few ^{29}Si NMR chemical shifts have been reported for Lewis base complexes of a trichlorosilyl species. Kobayashi and co-workers, during their investigation of allylations with allyltrichlorosilane catalyzed by formamides, reported observation of a new signal at −170 ppm, assigned as the hexacoordinate complex, allyl$SiCl_3(DMF)_2$.[44] A closer analogy to systems relevant to this work is provided by the pentacoordinate trichlorosilylamidinate complexes reported by Karsch and co-workers ($-89 < \delta < -99$ ppm).[45]

Initial studies with $SiCl_4$ and HMPA confirmed the results of the kinetic analysis. At −60 °C in $CDCl_3$ solution, (conditions intended to approximate those used in the preparative reactions) an equimolar mixture of $SiCl_4$ and HMPA showed three majors signals (Scheme 16).[31a] The signal appearing at −19 ppm was assigned as free $SiCl_4$ while other signals appeared far upfield at −110 and −206 ppm. The signal at −110 ppm was a triplet with a coupling constant of 9 Hz, consistent with those spectra observed by Cremer and Bassindale for HMPA complexes of trialkylsilyl cations.[46] The signal at −110 ppm was tentatively assigned as the bis-HMPA complex of a trichlorosilyl cation **i**, with its chemical shift falling squarely in the middle of the range for a pentacoordinate silicon species (−50 to −150 ppm).[43a] The signal at −206 ppm can then be assigned as the dianion hexachlorosilicate ($SiCl_6^{2-}$).[47] These results indicate the presence of a fairly complex ion in solution: $[SiCl_3HMPA_2^+]_2[SiCl_6^{2-}]$ (**i**). Inspection of the ^{31}P NMR spectrum of this mixture in $CDCl_3$ revealed that the signal corresponding to free HMPA (27 ppm) had completely disappeared, only to be replaced by a single, new signal at 19 ppm.

Although these results suggest that a 2:1 complex between $SiCl_4$ and a Lewis basic phosphoramide is the active catalytic intermediate in these epoxide openings, the significant structural and catalytic efficiency differences between HMPA and (*R*)-**1** still leave open the question of whether a similar analysis



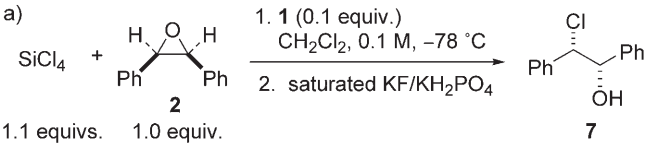
Scheme 16.

applies to the latter. Although kinetic studies of the epoxide opening of **2** with (*R*)-**1** would directly address this question, problems of irreproducibility precluded any analysis of the reaction order in (*R*)-**1**. In the absence of such data, we resorted to the use of enantiomeric composition experiments to provide insight into the molecularity of the chiral catalyst.

Non-Linear Effect Studies

Following Kagan,[47] a series of experiments was performed to establish the relationship of *ee* product as a function of *ee* catalyst, employing 10 mol% of (*R*)-**1**. Varying amounts of accurately weighed (*S*)-**1** and (*R*)-**1** were mixed but in addition, the *ee* of the catalyst was accurately assayed using CSP-SFC.[48] This analysis was conveniently carried out by sampling 50 μL of the pre-mixed catalyst directly from the reaction flask, prior to adding $SiCl_4$. The results are depicted in Figure 3.

All experiments were duplicated with good reproducibility. The graph clearly demonstrates a weak "negative non-linear effect," which supports the hypothesis that more than one phosphoramide is involved in the stereodetermining transition structure. However, there are two other mechanistic scenarios



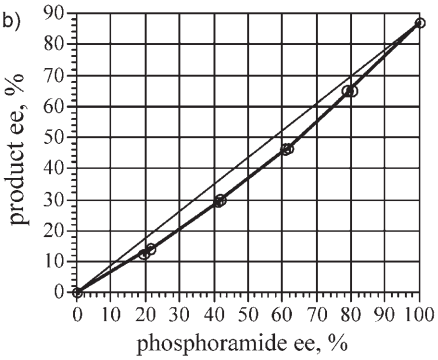


Figure 3. Non-linear effect study with (*R*)-**1**.

that can lead to a non-linear effect that do not involve a higher order in the molecularity of the catalyst.[48]

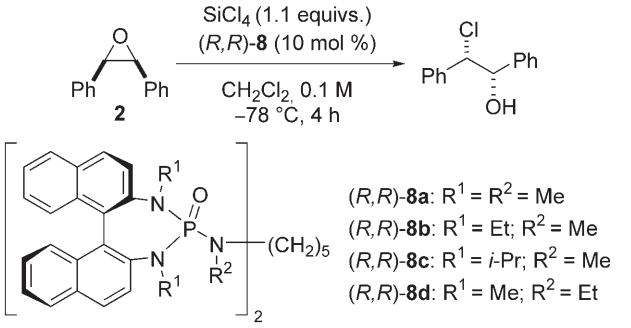
The first of the alternative scenarios is referred to as the *reservoir effect*. This phenomenon can give rise to a non-linear effect if the catalyst molecules are aggregated in the resting state, but not in the transition structure. If a reservoir effect were responsible for the observed non-linear effect, then its magnitude should be catalyst concentration-dependent. To test for this eventuality, an experiment employing 100 mol% of (*R*)-**1** of 42.0% *ee* afforded the product in 94% yield and with a 30.9% *ee*. Thus, the deviation from linearity is the same at 100 mol% loading as for 10 mol% loading, and therefore the ee_{prod} is independent of catalyst concentration over a 10-fold range. Therefore, the observed non-linear behavior is not a result of the reservoir effect.

The other mechanistic scenario is referred to as *product inhibition*. In this case, a non-linear effect arises because one enantiomer of the catalyst binds selectively with the chiral, non-racemic product. If this were the case, then one would expect the extent of the non-linear deviation to change as a function of conversion. Thus, an experiment using 100 mol% (*R*)-**1** with 52.4% *ee* was quenched after 7 min to afford the chlorohydrin in 28% yield and 39.6% *ee*. Thus, quenching the reaction at low conversion affords the chlorohydrin with the same *ee* as for the reaction at full conversion. Therefore, the non-linear behavior is not the result of product inhibition.

Catalyst Structure Survey

The combination of kinetic and non-linear effect studies suggests that two phosphoramides are involved in both the rate and stereochemistry determining steps of the epoxide opening. Therefore, it was hoped that the use of a chiral, dimeric phosphoramide catalyst would lead to improvements in enantioselectivity. In all of the other reactions that employ the combination of silicon tetrachloride and a chiral Lewis base for enantioselective addition reactions, dimeric ligands deliver higher selectivities when compared to the related monomers.[31] Accordingly, dimeric bisphosphoramides of the general structure (*R,R*)-**8** were prepared and assayed in the opening of **2** under the optimized reaction conditions. The results collected in Table 3 show that none of these structures gave results superior to those from (*R*)-**1**. Although this does not eliminate the possibility that two catalyst molecules are involved in the transition structure, it does suggest that the two are not in close proximity to each other (*vide infra*).

Table 3. Survey of dimeric catalysts.



Catalyst	Yield [%][a]	*er*[b]
(*R,R*)-**8a**	93	69.3/30.7
(*R,R*)-**8b**	93	47.4/52.6
(*R,R*)-**8c**	98	53.5/46.5
(*R,R*)-**8d**	68	31.0/69.0

[a] Yield of isolated, purified product.
[b] Determined by CSP-SFC analysis.

Discussion

Chlorosilane Source

In the survey of chlorosilane structure, the three agents, $SiCl_4$, $HSiCl_3$ and $AcOSiCl_3$ all induced the opening of **2** with 10 mol% of (*R*)-**1** at −78 °C. With $SiCl_4$ the reaction was complete after 3 h, however, $HSiCl_3$ afforded only 68% conversion over the same time. Although $AcOSiCl_3$ did react at −78 °C, this silane required 17 h to reach 42% conversion. An even greater difference in reactivity was observed in with the alkylchlorosilanes. For example, neither $MeSiCl_3$ nor $(CH_2)_3SiCH_3Cl$ reacted at −78 °C, even with a full equivalent of (*R*)-**1**. However, both these chlorosilanes did react at room temperature with 10 mol% of (*R*)-**1**; full conversion was observed for $MeSiCl_3$ after 3 h and 70% conversion for $(CH_2)_3SiCH_3Cl$ after 6 h. These results lead to the following reactivity trend: $SiCl_4 > HSiCl_3 > MeSiCl_3 > (CH_2)_3SiCH_3Cl$, where substitution of a chloride by H or AcO still allows the reaction to take place (albeit slower) at −78 °C, but substitution for an alkyl group shuts down the reaction at −78 °C. It would appear that replacement of a chloride with an alkyl substituent disfavors ionization. In addition, it was established that the lack of selectivity observed in the reactions with alkyl-substituted chlorosilanes was not due to a competing background reaction.

Stoichiometry of $SiCl_4$

From the loading study, it was clearly established that only one chlorine per $SiCl_4$ is available, which in turn implies that the product, a trichlorosilyloxychlorohydrin, is not capable of delivering a chloride under the

same conditions. This result is consistent with the conclusions of the chlorosilane survey which demonstrated that other reagents, particularly $AcOSiCl_3$ are less active than $SiCl_4$.

Furthermore, the enantioselectivity of the opening does not change as a function of conversion. This outcome further substantiates the conclusion that the product alkoxytrichlorosilane does not materially contribute to the reaction pathway. The stoichiometry study rules out the involvement of such intermediates, and shows that the nature of the reactive species does not change throughout the course of the reaction.

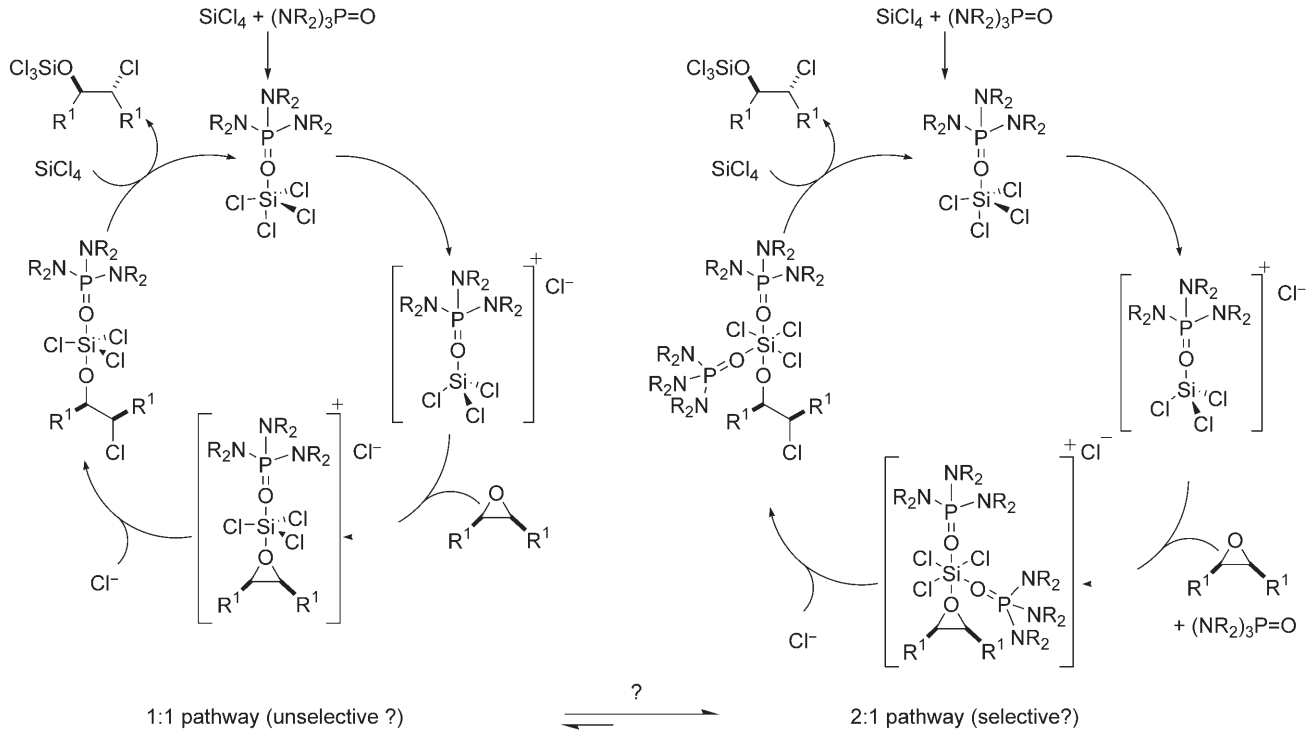
Catalyst Loading Studies

From the survey of chlorosilane structure, both $SiCl_4$ and $HSiCl_3$ were found to be the only enantioselective reagents. This outcome leads to the hypothesis that these agents are unique in their ability to be ionized by the catalysts at low temperature and perhaps even bind two phosphoramides. This pentacoordinate or hexacoordinate silicon species, now possessing a more crafted chiral environment, gives rise to enantioenriched products. By contrast, the other chlorosilanes were not sufficiently Lewis acidic and hence bind only one phosphoramide, leading to an unselective reaction. However, even if this proposition were true, we were still concerned that a competitive pathway may be operative with $SiCl_4$ that also involves a 1:1 complex. This hypothesis is supported by the catalyst loading study which showed decreasing enantioselectivity at relatively low catalyst loading. At higher catalyst concentrations the more selective 2:1 pathway should be favored and conversely, the less selective 1:1 pathway should only intervene at low catalyst concentrations (Scheme 17).

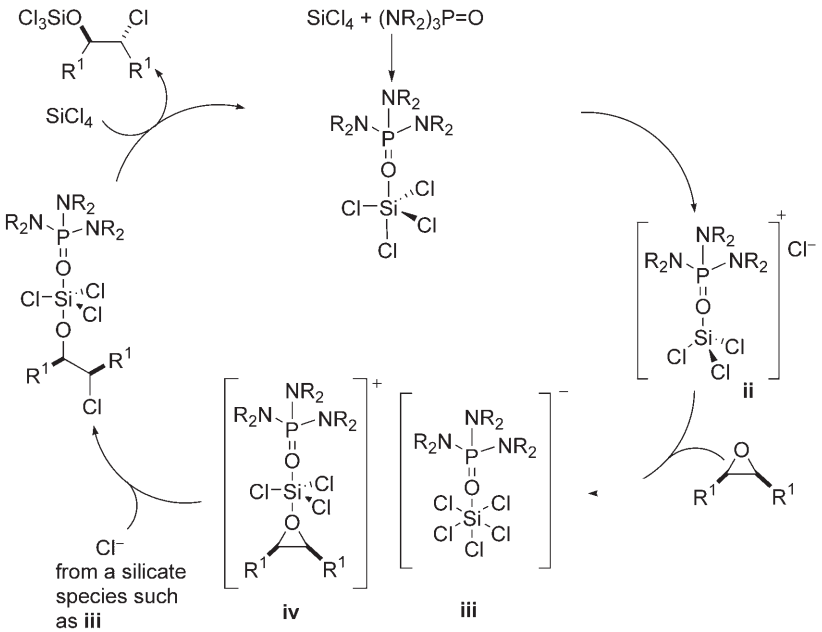
The results of the loading study establish that little erosion is observed for catalyst concentrations down to 4 mol% of (*R*)-**1**, but that a precipitous drop off is observed below 4 mol%. It is difficult to explain the dramatic change observed in both the rates and enantioselectivities. Catalyst turnover, although slow, is still sufficient to afford 71% conversion after 40 h at −78 °C. In addition, the product is obtained with 34% *ee*, and the fact that any level of stereoinduction is observed is clearly indicative of a phosphoramide-promoted pathway. However, even if this is the result of a 1:1 pathway, it still does not explain why there is such a sharp change in going from 4 mol% to 2 mol% of (*R*)-**1**. Nevertheless, in conjunction with the results of the kinetic studies, it is clear that at catalyst concentrations down to 4 mol% catalyst, a singular pathway is operative.

Kinetic and Non-Linear Effect Studies

The results of the kinetic studies combined with the non-linear effects studies indicate that two phosphor-



Scheme 17.



Scheme 18.

amides are likely involved in both the rate and stereochemistry determining steps of the epoxide opening. The observation of the siliconium ion $[SiCl_3HMPA_2]^+$ by ^{29}Si NMR supports the observed saturation kinetics in $SiCl_4$, but also provides insights into the true nature of the active, catalytic intermediate in these reactions.

Although the kinetic studies with HMPA helped to clarify the role of the catalyst, the questions regarding the role of the *chiral* catalyst (*R*)-**1** remain open. The results of the non-linear effect experiments demonstrate a weak, negative deviation from linearity which suggests that subtle interactions are involved, possibly with participation from a higher order species. A weak negative deviation indicates that the heterochiral complex is more kinetically competent than the homochiral complex.

The two other mechanistic interpretations of the data that could explain this effect, namely a reservoir effect and product inhibition, were ruled out by appropriate control experiments and assured the conclusion that more than one phosphoramide molecule is likely involved in the stereodetermining transition structure.

In spite of these two pieces of information regarding the role of the catalyst, it is still not possible to state whether the two phosphoramides are bound to the same silicon atom. It is possible that there are two silicon species, each with one phosphoramide bound to them that would also give the same molecularity in phosphoramide, such as shown in Scheme 18. A cationic silicon species such as **ii** would serve to activate the epoxide, whilst the chloride that dissociates in the ionization combines with the $SiCl_4$/phosphoramide complex to form the silicate species **iii**, which serves to activate the chloride to nucleophilic attack.[49] In this scenario, with the chiral phosphoramide now intimately involved with the nucleophile, it is somewhat easier to rationalize the observed asymmetric induction. In the initial hypothesis, it is hard to envisage how the chloride is able to distinguish between the two enantiotopic centers of the epoxide when the chiral phosphoramide is distal to the approaching nucleophile.[51] The current kinetic studies are unable to differentiate between these two mechanistic scenarios due to the observed, zeroth order behavior in $SiCl_4$. However, the failure of bisphosphoramide to improve the enantioselectivity of the opening also supports the notion that, if two phosphoramides are involved, then they are not acting on the same silicon atom.

Conclusions

A number of key mechanistic insights into the enantioselective opening of meso epoxides with silicon tetrachloride have been identified. First, silicon tetrachloride is unique in its ability to give highly enantiomerically enriched chlorohydrins. Second, only one of the four chlorines in $SiCl_4$ is active. Third, a single mechanistic pathway is operative between 4 and 100 mol% catalyst [(*R*)-**1**], but the selectivity drops off significantly at 2 mol% of (*R*)-**1**. Fourth, kinetic studies suggest that the reaction is second order in HMPA. Finally, a weak, negative non-linear effect has been demonstrated, again suggesting that more than one catalyst molecule is involved in the stereochemistry determining transition structure. Unlike many

other reactions promoted[52] by $SiCl_4$, dimeric phosphoramide catalysts did not improve the enantioselectivity of the epoxide opening, suggesting that if two catalyst molecules are involved, they may not be bound to the same silicon atom.

Further mechanistic investigations, including kinetic analysis with (*R*)-**1** and the identification of reaction parameters that will allow addition of other nucleophiles are currently underway, as are continuing studies to expand the preparative scope of the reaction.

Experimental Section

General Experimental Methods

^{1}H NMR spectra were recorded on a Varian Unity 400 (400 MHz) spectrometer. Spectra are referenced to residual chloroform ($\delta = 7.26$ ppm, ^{1}H) in $CDCl_3$. Chemical shifts are reported in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz.

All reactions were performed in oven and/or flame-dried glassware under an atmosphere of dry nitrogen. Dichloromethane (CH_2Cl_2) was distilled from P_2O_5, $SiCl_4$, $HSiCl_3$ and $MeSiCl_3$ were heated to reflux overnight then distilled immediately before use from a still. $(CH_2)_3SiCH_3Cl$ and $AcOSiCl_3$ were distilled immediately before use. Diethyl ether (Et_2O) was of reagent grade and used as received; other solvents for chromatography and extraction were technical grade and distilled from the indicated drying agents: hexane, and dichloromethane ($CaCl_2$); ethyl acetate (K_2CO_3). Analytical thin-layer chromatography was performed on Merck silica gel plates with QF-254 indicator. Column chromatography was performed using EM Science 230–400 mesh silica gel by the method of Still. Analytical supercritical fluid chromatography (SFC) was performed on a Berger Instruments packed-column SFC with built-in photometric detector ($\lambda = 220$ nm) using Daicel Chiralpak AD and AS columns. Retention times (t_R) and peak ratios were determined with a Hewlett Packard 3396 Series II integrator. *cis*-Stilbene oxide **2** was prepared by epoxidation of the corresponding alkenes with mCPBA. (*R*)-**4** and (*R*)-**1** were prepared as previously reported.[52]

General Procedure for Ring-Opening of *cis*-Stilbene Oxide with Chlorosilanes

To a cooled (−78 °C), stirred solution of *cis*-stilbene oxide (**2**) (196 mg, 1.0 mmol) and promoter [either (*R*)-**1** or HMPA] (0.10 mmol, 0.10 equiv.) in CH_2Cl_2 (10.0 mL) was added chlorosilane (1.1 mmol, 1.1 equivs.) dropwise over 1 min. After the addition was complete, the mixture was stirred at −78 °C (for time see Table 1) and then was quenched by the rapid addition of propylene oxide (1.0 mL, 16.5 mmol, 15 equivs. with respect to chlorosilane). After 1 min, MeOH (222 μL, 5.5 mmol, 5 equivs. with respect to chlorosilane) was added. After 30 min at −78 °C, the mixture was poured into cold (0 °C), rapidly stirring saturated aqueous KF/KH_2PO_4 solution (1/1, 20 mL), then was diluted with Et_2O (40 mL) and was allowed to warm to room temperature. The organic layer was separated, and the aqueous layer extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The resulting pale-yellow liquid was analyzed by ^{1}H NMR spectroscopy (for conversion), prior to desilylation as follows: to a solution of the crude silyloxy chlorohydrin in THF (5 mL) was added a premixed solution of TBAF (1 M in THF, 1.2 mL, 1.2 mmol, 1.2 equivs.) and AcOH (0.15 mL). After 15 min, the reaction was poured onto saturated aqueous $NaHCO_3$ solution (10 mL). The organic layer was separated, and the aqueous layer extracted with CH_2Cl_2 (4 × 25 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The resulting pale-yellow liquid was purified by silica gel chromatography (hexane/Et_2O, 9/1) to afford (*S*,*S*)-2-chloro-1,2-diphenyl-1-ethanol. Spectroscopic data matched those from the literature.[34] ^{1}H NMR (400 MHz): $\delta = 7.25$–7.13 (m, 8H), 7.13–7.07 (m, 2H), 5.01 (d, $J = 8.3$ Hz, 1H), 4.95 (dd, $J = 8.3$ Hz, 2.7, 1H), 3.02 (d, $J = 2.7$ Hz, 1H).

Representative Procedure for Stoichiometry Studies using the Internal Quench

To a cooled (−78 °C), stirred solution of *cis*-stilbene oxide (**2**) (196 mg, 1.0 mmol) and HMPA (20 μL, 0.11 mmol, 0.11 equivs.) in CH_2Cl_2 (10.0 mL) was added $SiCl_4$ (86 μL, 0.75 mmol, 0.75 equivs.) dropwise over 1 min. After the addition was complete, the mixture was stirred at −78 °C for 3 h and then was quenched by the rapid addition of propylene oxide (680 μL, 11.25 mmol, 15 equivs. with respect to $SiCl_4$). After 1 min, MeOH (152 μL, 3.75 mmol, 5 equivs. with respect to $SiCl_4$) was added. After 30 min at −78 °C, the mixture was poured into cold (0 °C), rapidly stirring saturated aqueous KF/KH_2PO_4 solution (1/1, 20 mL), then was diluted with Et_2O (40 mL) and was allowed to warm to room temperature. The organic layer was separated, and the aqueous layer extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The resulting pale-yellow liquid was analyzed by ^{1}H NMR spectroscopy (which showed 76% conversion), prior to desilylation as follows: to a solution of the crude silyloxychlorohydrin in THF (5 mL) was added a premixed solution of TBAF (1 M in THF, 0.9 mL, 0.90 mmol, 1.2 equivs.) and AcOH (0.1 mL). After 15 min, the reaction was poured onto saturated aqueous $NaHCO_3$ solution (10 mL). The organic layer was separated, and the aqueous layer extracted with CH_2Cl_2 (4 × 25 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The resulting pale-yellow liquid was purified by silica gel chromatography (hexane/Et_2O, 9/1) to afford (*S*,*S*)-2-chloro-1,2-diphenyl-1-ethanol; yield: 0.148 g (64%). Spectroscopic data matched those from the literature.[34]

Representative Procedure for Loading Studies with (*R*)-1

To a cooled (−78 °C), stirred solution of *cis*-stilbene oxide (**2**) (392 mg, 2.0 mmol) and catalyst (*R*)-**1** (44 mg, 0.1 mmol, 0.1 equiv.) in CH_2Cl_2 (20.0 mL) was added $SiCl_4$ (250 μL,

2.2 mmol, 1.1 equivs.) dropwise over 1 min. After the addition was complete, the mixture was stirred at −78 °C for 19 h and then was quenched by pouring into cold (0 °C), rapidly stirring saturated aqueous KF/KH_2PO_4 solution (1/1, 30 mL), then was diluted with Et_2O (50 mL), and was allowed to stir for 15 min. The organic layer was separated, and the aqueous layer extracted with Et_2O (3×25 mL). The combined organic extracts were washed with brine (25 mL) and the brine wash was back extracted with Et_2O (15 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The resulting pale-yellow liquid was purified by silica gel chromatography (hexane/Et_2O, 86/14) to afford (+)-(*S*,*S*)-2-chloro-1,2-diphenyl-1-ethanol [(+)-(**7**)]; yield: 0.437 g (94 %). Spectroscopic data matched those from the literature.[34] SFC: t_R (*S*,*S*)-**7**, 3.34 min (87.3 %); t_R (*R*,*R*)-**7** 3.88 min (12.7 %) (Chiralpak AS, 150 bar, 30 °C, 10 % CH_3OH in CO_2, 2.5 mL min^{-1}).

Representative Procedure for Non-Linear Effect Studies with Promoter 1

A mixture of promoter (*R*)-**1** (35.3 mg) and (*S*)-**1** (8.9 mg) [total of 44.2 mg (to make 60 % *ee*), 0.1 mmol, 0.1 equiv.] were added to a Schlenk flask, followed by *cis*-stilbene oxide (**2**) (196 mg, 1.0 mmol). To this was added CH_2Cl_2 (10.0 mL), and then a 50 μL aliquot was removed *via* a gas-tight syringe (SFC analysis of **1** shows 60.8 % *ee R*). The stirred solution was cooled to −78 °C before the addition of $SiCl_4$ (125 μL, 1.1 mmol, 1.1 equivs.) dropwise over 1 min. After the addition was completed, the mixture was stirred at −78 °C for 3.25 h and then was quenched by pouring into cold (0 °C), rapidly stirring, saturated aqueous KF/KH_2PO_4 solution (1/1, 20 mL), diluted with Et_2O (30 mL), and allowed to stir for 10 min. The organic layer was separated, and the aqueous layer extracted with Et_2O (3×25 mL). The combined organic extracts were washed with brine (15 mL) and the brine wash was back extracted with Et_2O (15 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The resulting pale-yellow liquid was purified by silica gel chromatography (hexane/Et_2O, 9/1) to afford (+)-(*S*,*S*)-2-chloro-1,2-diphenyl-1-ethanol [(+)-**7**]; yield: 0.217 g (93 %). SFC: t_R (*R*)-**1**, 2.59 min (80.4 %); t_R (*S*)-**1**, 3.48 min (19.6 %) (Chiralpak AD, 150 bar, 30 °C, 25 % CH_3OH in CO_2, 3.5 mL min^{-1}). SFC: t_R (*S*,*S*)-**7**, 3.34 min (87.3 %); t_R (*R*,*R*)-**7**, 3.88 min (12.7 %) (Chiralpak AS, 150 bar, 30 °C, 10 % CH_3OH in CO_2, 2.5 mL min^{-1}).

Acknowledgements

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