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Chiral Phosphoramide-Catalyzed Enantioselective Addition of Allylic Trichlorosilanes to Aldehydes. Preparative Studies with Bidentate Phosphorus-Based Amides

Scott E. Denmark,* Jiping Fu, and Michael J. Lawler

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

denmark@scs.uiuc.edu

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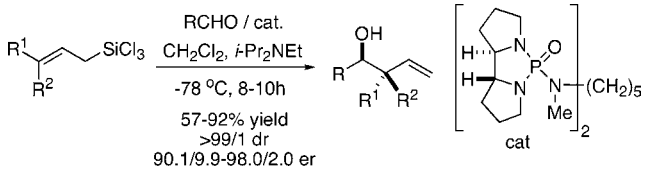
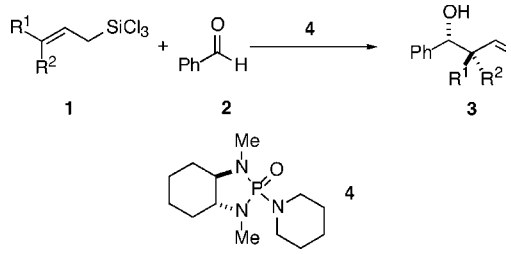


On the basis of the mechanistic insight that more than one Lewis basic moiety (phosphoramide) is involved in the rate- and stereochemistry-determining step of enantioselective allylation, bidentate chiral phosphoramides were developed. Different chiral phosphoramide moieties were connected by tethers of methylene chains of varying length. The rate and enantioselectivity of allylation with allyltrichlorosilane promoted by the bidentate phosphoramides was found to be highly dependent on the tether length. A new phosphoramide based on a 2,2′-bispyrrolidine skeleton has been designed and afforded good yield, efficient turnover, and high enantioselectivity in allylation reactions. The synthesis of enantiopure 2,2′-bispyrrolidine was easily accomplished on large scale by photodimerization of pyrrolidine followed by resolution with L(or D)-tartaric acid. The scope of the allylation reaction was examined with variously substituted allylic trichlorosilanes and unsaturated aldehydes. This method has been applied to the construction of stereogenic, quaternary centers by the addition of unsymmetrically γ-disubstituted allylic trichlorosilanes.

Introduction and Background

It is axiomatic that the invention of new, catalytic enantioselective transformations is inexorably bound to the design and development of highly selective and efficient catalysts.[1] In the development Lewis base catalyzed, enantioselective allylation[2] of aldehydes, ketones, and azomethine derivatives, the design of chiral Lewis bases has met with modest success. Chirally modified formamides, aromatic and aliphatic *N*-oxides, ureas, diamines, sulfoxides, and phosphine oxides have been described for this transformation.[3] In 1994, we described the first chiral Lewis base promoted allylation by the use of chiral phosphoramides for this transformation.[4a] Since that time, we have been engaged in a broadly based program on the design and testing of different structures of phosphoramides derived primarily from chiral 1,2-diamines (Scheme 1). The addition of allyltrichlorosilanes **1** to aldehydes is promoted by chiral phosphoramide **4** to give chiral, nonracemic homoallylic alcohols **3** with high diastereocontrol yet with only modest enantioselectivity. Although the yield and enantioselectivity were modest, the reaction was still judged to have great potential because (1) the uncatalyzed reaction does not proceed in the absence of promoter, (2) the allylation displays high diastereocontrol suggesting a rigid, closed transition structure, and (3) the reaction could be promoted with a substoichiometric amount of Lewis base.

SCHEME 1



Unfortunately, extensive empirical optimization did not provide either a better catalyst or even a framework for structural

(1) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999; Vols. I−III.

(2) For reviews of catalytic enantioselective allylation, see: (a) Denmark, S. E.; Fu, J. *Chem. Commun.* **2003**, 167−170. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763−2793. (c) Yanagisawa, A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999; Vol. II, Chapter 27. (d) Kobayashi, S.; Sugiura, M.; Ogawa, C. *Adv. Synth. Catal.* **2004**, *346*, 1023−1034.

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modification.[5] This failure stimulated an in-depth mechanistic study to probe the origins of activation and stereoselection. It was demonstrated that the reaction proceeds through simultaneously operating pathways that involve either one or two phosphoramides in the rate- and stereochemistry-determining steps (Figure 1).[4b] Although mechanistically intriguing, these dual mechanistic pathways are disadvantageous in a catalytic process for both selectivity and reactivity reasons. First, because the reaction is second order in catalyst, the rate of the reaction falls off as the square of catalyst concentration. Second, at lower catalyst loadings, a competing, less selective pathway can compromise the overall reaction selectivity. Third, structural modification of the catalyst often requires increasing steric bulk that disfavors the binding of two catalyst molecules to the silicon center.

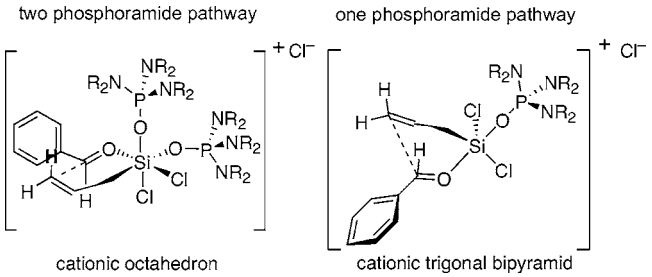


FIGURE 1. Dual mechanistic pathways for the allylation reaction.

To address these problems, we envisioned the utilization of bidentate ligands with the expectation of increasing the effective concentration of the second catalyst molecule through approximation.[6] In designing these bidentate chiral phosphoramides, we envisioned two distinct types of bisphosphoramides (Figure 2), namely (1) Type A, the two chiral phosphoramide units separated with achiral linker, and (2) Type B, chiral linkages employed to connect two achiral phosphoramide units.

With the conformational restriction provided by the linkage, the selectivity and reactivity of the catalyst would depend on not only the phosphoramide subunit but also the connecting tether.[7] We describe herein studies on the optimization of the phosphoramide unit as well as the linkage that led to the development of a highly selective catalyst.[4b−d]

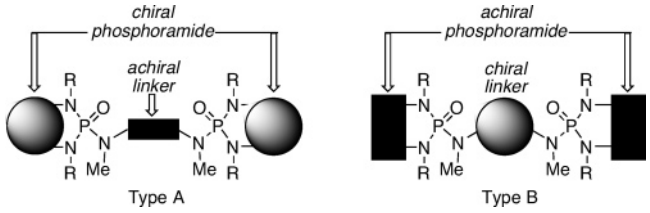
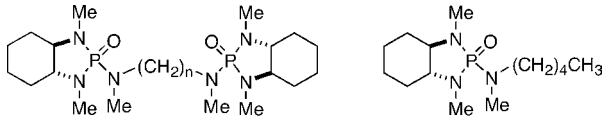


FIGURE 2. Design of chiral phosphoramides.

Results

1. Bidentate Ligands Derived from (*R*,*R*)-1,2-*trans*-Cyclohexanediamine. 1.1. Bisphosphoramides. Although prior studies in these laboratories provided a good notion of the geometric requirements to accommodate *cis* coordination by phosphoramides,[8] it was difficult to predict, a priori, the ideal type and length of linker to connect the two participating functions. Thus, our initial design of bidentate ligands focused on the utilization of Type A chiral bisphosphoramides. Specifically, polymethylene tethers were utilized as linkages that would allow a broad survey of optimal tether length for chelation. In addition, (1*R*,2*R*)-*N*,*N*-dimethyl-1,2-*trans*-cyclohexanediamine was chosen as the chiral phosphoramide subunit because the corresponding monophosphoramide **4** provided one of highest enantioselectivities in the allylation reaction promoted by monophosphoramide.[5] These considerations led to the formulation of bisphosphoramides **5**. In addition, monophosphoramide **6** was prepared to closely mimic the behavior of dimeric ligands **5** if they bound in only a monodentate fashion (Chart 1).

CHART 1

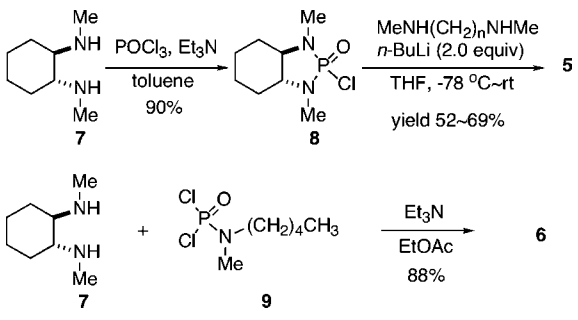


5a: n=2; **5b**: n=3; **5c**: n=4; **5d**: n=5; **5e**: n=6

6

The bisphosphoramides **5** were prepared by condensation of (1*R*,2*R*)-*N*,*N*-dimethyl-1,2-*trans*-cyclohexanediamine **7** with phosphorus oxychloride to afford the diaminophosphoryl chloride **8**.[9] This chiral diaminophosphoryl chloride was subsequently combined with dilithiated *N*,*N*-dimethyldiamine linkers ($n = 2-6$) (Scheme 2). The bisphosphoramides with shorter tethers (**5a** ($n = 2$), **5b** ($n = 3$), **5c** ($n = 4$)) were crystalline, whereas the bisphosphoramides **5d** ($n = 5$) and **5e** ($n = 6$) were

SCHEME 2



(3) (a) Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron* **1999**, *55*, 977−988. (b) Hellwig, J.; Belser, T.; Muller, J. F. K. *Tetrahedron Lett.* **2001**, *42*, 5417−5419. (c) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419−6420. (d) Malkov, A. V.; Bell, M.; Orsini, M.; Pernazza, D.; Massa, A.; Herrmann, P.; Meghani, P.; Kocovsky, P. *J. Org. Chem.* **2003**, *68*, 9659−9668. (e) Shimada, T.; Kina, A.; Ikeda, S. Hayashi, T. *Org. Lett.* **2002**, *4*, 2799−2801. (f) Chataigner, I.; Piarulli, U.; Gennari, C. *Tetrahedron Lett.* **1999**, *40*, 3633−3634. (g) Angell, R. M.; Barrett, A. G. M.; Braddock, D. C.; Swallow, S.; Vickery, B. D. *Chem. Commun.* **1997**, 919−920. (h) Massa, A.; Malkov, A. V.; Kocovsky, P. Scettri, A. *Tetrahedron Lett.* **2003**, *44*, 7179−7181. (i) Traverse, J. F.; Zhao, Y.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2005**, *7*, 3151−3154. (j) Pignataro, L.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Celentano, G. *Chirality* **2005**, *17*, 396−403. (k) Müller, C. A.; Hoffart, T.; Holbach, M.; Reggelin, M. *Macromolecules* **2005**, *38*, 5375−5380. (l) Nakajima, M.; Kotani, S.; Ishizuka, T.; Hashimoto, S. *Tetrahedron Lett.* **2005**, *46*, 157−159.

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(5) Denmark, S. E.; Fu, J.; Coe, D. M.; Su, X.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **2006**, *71*, 1513−1522.

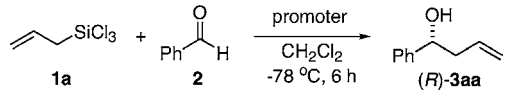
(6) For another study on dimeric catalysts tethered with methylene units, see: Konsler, R. G.; Karl, J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 10780−10781.

(7) For a review on the effect of ligand bite angle effect in phosphine ligands, see: van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741−2769.

oils. For convenience of manipulation, stock solutions of phosphoramides in CH_2Cl_2 were prepared and used in the allylation reactions. The synthesis of **6** was accomplished by direct condensation of the diamine **7** with the phosphoryl dichloride **9**.[10]

With these new phosphoramides in hand, the addition of allyltrichlorosilane (**1a**) to benzaldehyde (**2**) was then carried out, and the results are collected in Table 1. Because compounds **5** are bisphosphoramides, 0.5 equiv was used for comparison to the monophosphoramide **6**. The dependence of the product er on the linker length was striking. Whereas the monophosphoramide **6** gave an er of 75.5/24.5, nearly racemic product was obtained with **5a** (entries 1 and 2). A dramatic increase in er was seen in the change from **5c**, where the er of the product was only 58.5/41.5, to **5d**, wherein the er was 82.5/17.5 (entries 4 and 6). The er decreased again to 73.0/26.0 when **5e** was used (entry 8). This behavior implies a cooperativity of binding with bisphosphoramides, because if there were no chelation with silicon, the er of **5** would be chain-length independent and similar to that obtained with **6**. For reasons that were not at all obvious, bisphosphoramide **5d** tethered with five methylene units gave the highest enantioselectivity.

TABLE 1. Allylation with 1a Promoted by Bisphosphoramides[a]



entry	promoter	tether, *n*	equiv	er[b]	yield, %
1	**6**		1.0	75.5/24.5	73
2	**5a**	2	0.5	50.0/50.0	60
3	**5b**	3	0.5	62.5/17.5	72
4	**5c**	4	0.5	58.5/41.5	82
5	**5c**	4	0.1	55.0/45.0	52
6	**5d**	5	0.5	82.5/17.5	78
7	**5d**	5	0.1	86.0/14.0	54
8	**5e**	6	0.5	73.0/26.0	75
9[c]	**5d**	5	0.1	86.0/14.0	73

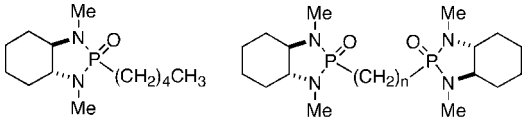
[a] Reaction performed at 1.0 M concentration at −78 °C for 6 h using 100% ee promoter. [b] Determined by CSP-SFC. [c] 5.0 equiv of *i*-Pr_2NEt was used as an additive.

Foregoing studies with monophosphoramide **4** showed that the allylation selectivity could be dependent on the promoter loading.[5] Thus, the dependence of the product enantiomeric composition on the promoter loading (concentration) was then studied with bisphosphoramides **5c** and **5d**, which gave the lowest and highest enantioselectivities, respectively. Entries 4−5 in Table 1 show that when the loading of **5c** was decreased to 0.1 equiv, the er of the product obtained also decreased from 58.5/41.5 to 55.0/45.0. On the other hand, a similar lowering of the loading of **5d** (entries 6−7) brought about an increase in the er of **3aa** from 82.5/17.5 to 86.0/14.0. It was rather surprising that in the reaction promoted by **5d**, even higher ee was achieved at lower promoter concentration, but this clearly suggested a different mode of binding of **5d** compared to **4** and **5c**.

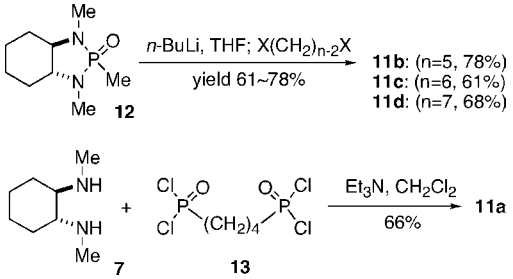
Finally, to further improve the yield of **3aa** obtained with substoichiometric amounts of **5d**, *i*-Pr_2NEt was used as an additive in the reaction. The use of *i*-Pr_2NEt in reactions of allylic trichlorosilanes was initially developed by Nakajima for reactions catalyzed by bis-*N*-oxides, wherein it was found that *i*-Pr_2NEt could enhance the reaction rate without affecting the enantioselectivity.[3c] Nakajima proposed that *i*-Pr_2NEt functions to assist turnover by releasing the catalyst from the product trichlorosilyl ether. This effect is clearly seen by comparing entries 7 and 9 (Table 1). In the reaction catalyzed by 0.1 equiv of **5d**, the addition of 5.0 equiv of *i*-Pr_2NEt improved the reaction yield to 73% without affecting the enantioselectivity.

1.2. Bisphosphonamides. The allylation reaction clearly manifested the beneficial effect of uniting the two phosphoramide units through a diaminoalkyl chain presumably as a consequence of chelation. Because phosphonic amides such as **10** are also effective promoters for the allylation reaction,[5] the dimeric phosphonic amides **11** tethered with various methylene units were prepared as well (Chart 2). The bidentate ligands **11b**−**d** were prepared by treatment of the lithiated phosphonamide **12**[11] with 1,*n*-dihalides (Scheme 3). Attempts to synthesize **11a** by adding the anion to 1,2-diiodoethane, however, did not provide the desired dimeric product. Instead, **11a** was synthesized by condensation of diamine **7** with bisphosphonic acid chloride **13** in the presence of triethylamine.

CHART 2



SCHEME 3



The addition of **1a** to **2** was then carried out with 0.1 equiv of catalyst at −78 °C, and the results are collected in Table 2. The reactions gave rather low yields of **3aa** with a catalytic amount of promoter. In the reaction catalyzed by bidentate ligands **11**, the enantioselectivity was also found to be dependent on the tether length. The magnitude of er variation in **11** was much less than that with chiral bisphosphoramides **5**. The bisphosphonic diamide with four methylene tether **11a** gave an er of 77.0/23.0, and the er increased to 87.0/13.0 with **11b** (entries 2 and 3). The enantioselectivity decreased to 81/19 when **11c** was used, and the highest selectivity (89.0/11.0 er) was observed with **11d** tethered by seven methylene units (entires 4 and 5). Again, the effect of tether length on the enantioselectivity and the enhanced enantioselectivity observed with **11d**

(8) For previous studies of monophosphoramide/Lewis acid complexes, see: Denmark, S. E.; Su, X. *Tetrahedron* **1999**, *55*, 8727−8738.

(9) Alexakis, A.; Mutti, S.; Magneney, P. *J. Org. Chem.* **1992**, *57*, 1224−1237.

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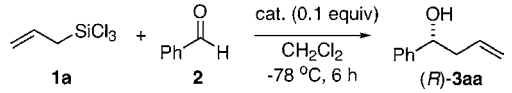
(11) Lawrence, R. M.; Biller, S. A.; Dickson, J. K., Jr.; Logan, J. V. H.; Magnin, D. R.; Sulsky, R. B.; DiMarco, J. D.; Gougoutas, J. Z.; Beyer, B. D.; Taylor, S. C.; Lan, S.-J.; Cioseck, C. P., Jr.; Harrity, T. W.; Jolibois, K. G.; Kunselman, L. K.; Slusarchyk, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 11668−11669.

TABLE 2. Addition of Allyltrichlorosilane to Benzaldehyde Catalyzed by Bidentate Phosphonic Amides[a]



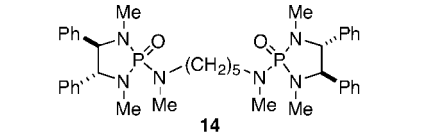
entry	cat.	yield, %	er[b]
1	**10**	27	83.0/17.0
2	**11a**	37	77.0/23.0
3	**11b**	42	87.0/13.0
4	**11c**	40	81.0/19.0
5	**11d**	39	89.0/11.0

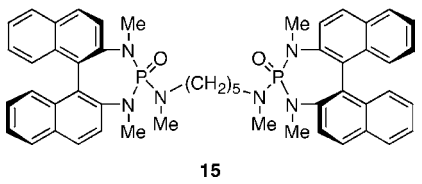
[a] Reaction performed at −78 °C for 6 h at 1.0 M concentration. [b] Determined by CSP-SFC.

again suggested the operation of chelation. However, in this series, high enantioselectivity was also seen with the monomeric phosphonamide **10**, so the magnitude of the cooperativity is less compelling than with the phosphoramide series **5**.

2. Bidentate Ligands Derived from Stilbene and Binaphthyl Diamines. The chain length dependence observed with bidentate ligands **5** successfully established that the two phosphoramide subunits can behave cooperatively to enhance selectivity. Accordingly, we next investigated the development of Type A bisphosphoramides bearing a pentamethylene tether that would bring together different phosphoramide units to further improve the stereoselectivity. In contemporaneous investigations in these laboratories on the catalytic enantioselective aldol addition reaction,[12] we have documented good success with both monomeric[13] and dimeric[14] phosphoramide catalysts derived from readily available diamines (*R*,*R*)-1,2′-stilbenediamine and (*R*)-1,1′-binaphthyl-2,2′-diamine (Chart 3). Thus, the bisphosphoramides **14** and **15** derived were prepared and tested in the allylation.

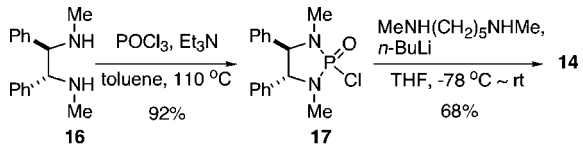
CHART 3

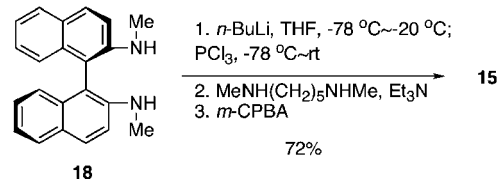




Phosphoramide **14** was synthesized in a straightforward manner by the route developed for the *trans*-1,2-cyclohexanediamine-based bisphosphoramides **5**.[10] Thus, starting from diamine **16**, formation of diaminophosphoryl chloride **17** (from $POCl_3$),[9] followed by reaction with the dilithiated *N*,*N*′-dimethyldiamine linker gave the bisphosphoramide **14** in 68% yield (Scheme 4). The synthesis of **15** was achieved in a one-pot procedure, in which the two phosphorus atoms were linked with the diamine at the P(III) stage.[10]

SCHEME 4

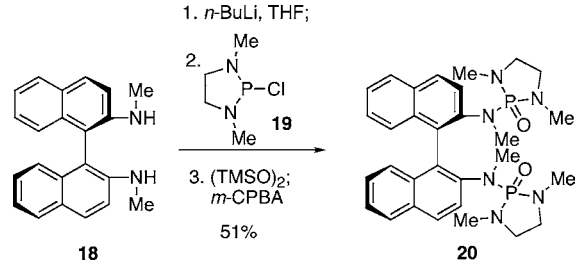




These two new bisphosphoramides, unfortunately, were rather ineffective in the allylation reaction, giving low enantioselectivities and/or reactivities. In the test reaction with **1a** and **2**, catalyst **14** (5 mol %) provided **3aa** in 82% yield but only with 60.0/40.0 er. With catalyst **15** (5 mol %), the reaction was rather sluggish, affording **3aa** in only 4% yield.

3. Bisphosphoramides Linked by Chiral Diamines (Type B). Although seven atom tethers were found to be the ideal tether length for chelation, the Type B chiral bisphosphoramide **20**, was first tested in which two achiral subunits are separated by *six* atoms comprising four carbon and two nitrogen atoms. The bisphosphoramide **20** was synthesized from 1,1′-binaphthyl-2,2′-diamine **18** by coupling the dilithiated diamide with **19** followed by oxidation with $(TMSO)_2$ and *m*-CPBA (Scheme 5).

SCHEME 5



The bisphosphoramide **20** catalyzed the addition of **1a** to **2** and provided the adduct **3aa** with up to 90/10 er, and more importantly, the enantioselectivity was independent of the loading of the catalyst (Table 3). The insensitivity of the enantioselectivity on the catalyst strongly supported the operation of chelation. Under the optimized reaction condition with 10 mol % of **20** and 5.0 equiv of *i*-Pr_2NEt as an additive, the homoallylic alcohol **3aa** was obtained in 67% yield and 90.0/10.0 er.

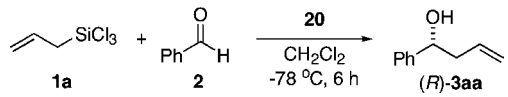
4. Bidentate Ligands Derived from 2,2′-Bispyrrolidine and 2,2′-Bispiperidine. 4.1. Design and Preparation. The failure to improve the enantioselectivity of allylation by empirical modification with conventional diamines (in Type A or Type B ligands) suggested the need to better understand the origin

(12) Denmark, S. E.; Fujimori, S. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vol. 2, Chapter 7.

(13) Monophosphoramides derived from **14** and **15** have provided excellent enantioselectivities in reactions with other chlorosilane species such as the aldol reaction of enoxytrichlorosilanes and epoxide-opening reactions (silicon tetrachloride). For aldol reaction, see: (a) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res*. **2000**, *33*, 432−440. Epoxide-opening reaction, see: (b) Denmark, S. E.; Barsanti, P. A.; Wong, K.-T.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 2428−2429.

(14) These bisphosphoramides have been employed with good success in aldol addition reactions of enoxytrichlorosilanes (**14**) and Mukaiyama-type aldol addition with silicon tetrachloride (**15**). See: (a) Denmark, S. E.; Pham, S. M. *J. Org. Chem.* **2003**, *68*, 5045−5055. (b) Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 3774−3789.

TABLE 3. Addition of Allyltrichlorosilane Catalyzed by Bisphosphoramide 20[a]



entry	loading	additive	yield, %	er[b]
1	0.5		76	90.0/10.0
2	0.1		49	90.0/10.0
3	0.1	*i*-Pr_2NEt	67	90.0/10.0

[a] Reaction performed at 1.0 M concentration at −78 °C for 6 h. [b] Determined by CSP-SFC.

of asymmetric induction in this process. Thus, to refine our understanding and assist in the design of more selective catalysts, we first chose to study the structure of our Group 14 Lewis acid complexes of the chiral phosphoramides. Because no suitable crystals could be obtained from silicon-based Lewis acids,[15] we employed tin tetrachloride as a surrogate, fully cognizant of the difference between silicon and tin.[16] For this study, we selected one of the more selective bisphosphoramide catalysts, **5d**. Examination of the X-ray crystal structure of **5d**·$SnCl_4$ revealed that the disposition of the internal, *N*-methyl substituents was significantly influenced by the cyclohexane-1,2-diamine skeleton (Figure 3a). We reasoned that connecting the substituent on the stereogenic center to the nitrogen atom by enclosure in a ring should enforce a more rigid control of the orientation of the N-substituents and thus impose a more highly dissymmetric coordination environment. This notion of backbone-induced nitrogen distortion is presented in Figure 3b,c. To accomplish this structural modification, we envisioned the utilization of 2,2′-bispyrrolidine (*R*,*R*)-**21** and bispiperidine (*R*,*R*)-**22** (Chart 4) as entries into a new class of chiral diamine-derived phosphoramides.

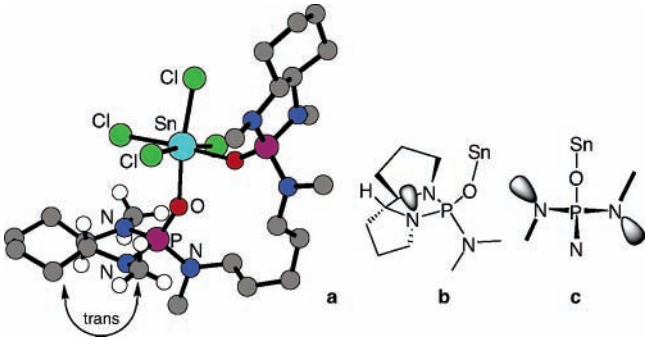
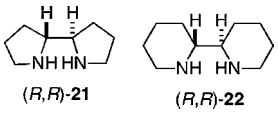


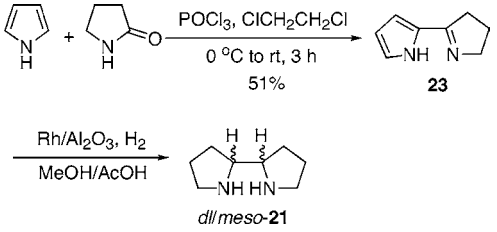
FIGURE 3. (a) Chem 3D presentation of **5d**·$SnCl_4$, hydrogens omitted for clarity. (b) Nitrogen distortion in the ring-fused phosphoramide tin complex. (c) Up−down geometry of phosphoramide in the hypothetical phosphoramide tin complex.

CHART 4



(*R*,*R*)-2,2′-Bispyrrolidine **21** was initially developed by Hirama and has been successfully applied in the asymmetric dihydroxylation of olefins[17] and also for catalytic enantioselective additions to nitroalkenes.[18] Several syntheses of enantiopure 2,2′-bispyrrolidine have been previously reported. Most of these routes required a multiple-step synthesis from chiral starting materials. For example, the synthesis developed by Hirama and co-workers requires 11 steps from D-tartaric acid.[17c] Alternatively, Alexakis has developed a synthesis of (*R*,*R*)-2,2′-bispyrrolidine by an organometallic addition to a chiral diimine that required five steps.[18b] In a simpler synthesis reported by Masamune, the *dl*/*meso* mixture 2,2′-bispyrrolidine was synthesized in two steps, which was then resolved with tartaric acid.[19] In our initial attempts to prepare this compound, the Masamune approach was chosen for the initial synthesis of (*R*,*R*)-2,2′-bispyrrolidine because of its apparent simplicity (Scheme 6). Condensation of pyrrole with 2-pyrrolidinone under the action of phosphorus oxychloride gave **23**, which was subsequently hydrogenated with rhodium on alumina to provide a *dl*/*meso* mixture of 2,2′-bispyrrolidine **21**. The hydrogenation step, however, was found to be very sluggish and irreproducible. When carried out on a 12 g scale, the reaction required 5 days to achieve a 90% conversion. Furthermore, attempts to scale-up the synthesis to 100 g led to even slower reactions, in which only 40% conversion was obtained after 30 days.

SCHEME 6



These problems encouraged us to reconsider an alternative preparation of **21** that was initially dismissed as being less preparatively useful. In 1989, Crabtree reported an intriguing oxidative photodimerization of amines.[20] It was reported that 2,2-bispyrrolidine could be obtained by heating neat pyrrolidine to reflux in under ultraviolet irradiation in the presence of a trace amount of mercury. Surprisingly, despite many efforts on the synthesis of (*R*,*R*)-2,2′-bispyrrolidine, this method had not been developed. If this reaction were scalable, then given the direct resolution of the resulting 2,2′-bispyrrolidine established by Masamune, it would provide a very convenient, practical method for the synthesis of (*R*,*R*)-2,2′-bispyrrolidine.

Ultimately, it was found that the photodimerization reaction was amenable to scale-up with a rather simple apparatus: a 500-mL flask equipped with quartz refluxing columns and water condensers (Scheme 7).[21] To this flask were added 200 mL of

(15) For a recent X-ray crystal structure of a bis-*N*-oxide complex of silicon tetrachloride, see: Denmark, S. E.; Fan, Y.; Eastgate, M. D. *J. Org. Chem.* **2005**, *70*, 5235−5248.

(16) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2003**, *125*, 2208−2216.

(17) (a) Hirama, M.; Oishi, T.; Ito, S. *J. Chem. Soc., Chem. Commun.* **1989**, 665−666. (b) Oishi, T.; Hirama, M. *J. Org. Chem.* **1989**, *54*, 5834−5835. (c) Kotsuki, H.; Kuzume, H.; Ghoda, T.; Fukuhara, M.; Ochi, M.; Oishi, T.; Hirama, M.; Shiro, M. *Tetrahedron: Asymmetry* **1995**, *6*, 2227−2236.

(18) (a) Andrey, O.; Alexakis, A.; Tomassini, A.; Bernarindelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147−1168. (b) Alexakis, A.; Tomassini, A.; Chouillet, C.; Roland, S.; Mangeney, P.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4093−4095.

(19) Oishi, T.; Hirama, M.; Sita, L. R.; Masamune, S. *Synthesis* **1991**, 789−792.

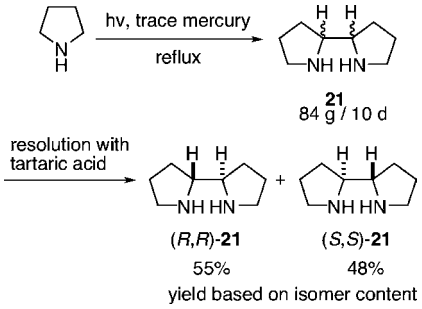
(20) (a) Ferguson, R. R.; Boojamra, C. G.; Brown, S. H.; Crabtree, R. H. *Heterocycles* **1989**, *28*, 121−124. (b) Krajnik, P.; Ferguson, R. R.; Crabtree, R. H. *New J. Chem.* **1993**, *17*, 559−566.

(21) Denmark, S. E.; Fu, J.; Lawler, M. J. *Org. Synth.* **2005**, *83*, in press.

pyrrolidine, a drop of mercury, and boiling chips. The flask was placed in a Rayonet photoreactor with 14 × 8-W low-pressure Hg lamps (254 nm). The mixture was then heated to reflux before the lamps were turned on, after which the mixture was heated to reflux under irradiation for 10 days. After the unreacted pyrrolidine was separated by simple distillation, 84.0 g of the 2,2′-bispyrrolidine **21** was obtained by vacuum distillation.

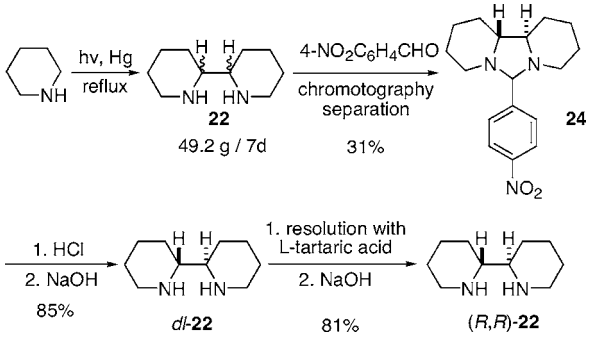
The crude product containing a 1/1 *dl*/*meso* mixture of 2,2′-bispyrrolidine was of sufficient purity to continue to the resolution step. Addition of L-tartaric acid to an aqueous solution of 2,2′-bispyrrolidine produced (*R*,*R*)-2,2′-bispyrrolidine•L-tartaric salt as prismatic crystals, which after neutralization gave (*R*,*R*)-**21** in 55% overall yield (based on isomer content). The mother liquor from the resolution step was also basified to recover the rest of 2,2′-bispyrrolidine, from which (*S*,*S*)-**21** was obtained in 48% yield with the use of D-tartaric acid as the resolving reagent. Thus, through sequential resolution using L- or D-tartaric acid, both (*R*,*R*)-**21** and (*S*,*S*)-**21** could be obtained in enantiopure form in two steps.

SCHEME 7



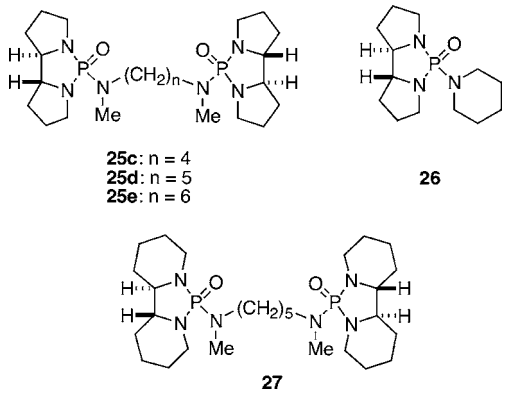
By the same method, *dl*/*meso*-2,2′-bispiperidine **22** (*dl*/*meso*, 1/1) was synthesized on a large scale (Scheme 8). To simplify the resolution of *dl*-2,2′-bispiperidine, diastereomerically pure *dl*-2,2′-bispiperidine was required.[22] Thus, the *dl*/*meso* mixture of 2,2′-bispiperidines was derivatized with 4-nitrobenzaldehyde, and the chiral diastereomer **24** was obtained in 31% yield after chromatographic separation.[23] Hydrolysis of **24** with an aqueous solution of HCl provided the *d*,*l*-2,2′-bispiperidine (85%), which was then resolved with L-tartaric acid to give (*R*,*R*)-**22** in 81% yield (based on available isomer content).

SCHEME 8

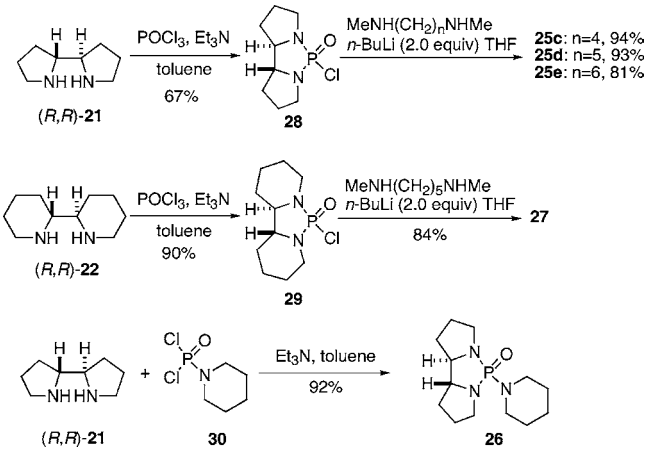


With enantiopure diamines (*R*,*R*)-**21** and (*R*,*R*)-**22** in hand, the bisphosphoramides **25c**−**e** and **27** were synthesized (Chart 5, Scheme 9). As shown in Scheme 9, formation of phosphoryl chlorides **28** and **29** with $POCl_3$ from diamines (*R*,*R*)-**21**/**22**, respectively, followed by reaction with dilithiated *N*,*N*′-dimethyl-1,*n*-diamine linkers provided the bisphosphoramides **25c**−**e** and **27**. In the phosphoramides derived from 2,2′-bispyrrolidine, the monophosphoramide **26** was also prepared for comparison. The synthesis of **26** was achieved by direct condensation of (*R*,*R*)-**21** with piperidinophosphoric dichloride **30**.

CHART 5

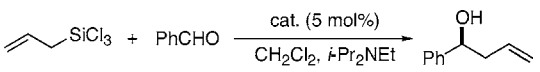


SCHEME 9



4.2. Allylations with (*R*,*R*)-25, (*R*,*R*)-26, and (*R*,*R*)-27. These new phosphoramides were then evaluated in the addition of allyltrichlorosilane (**1a**) to benzaldehyde (**2**) in the presence of 5.0 equiv of *i*-Pr_2NEt was an additive. With 20 mol % of monophosphoramide **26** as the catalyst, the adduct was obtained only in modest yield and enantioselectivity (Table 4, entry 1).

TABLE 4. Allylation of Benzaldehyde Catalyzed by Phosphoramides[a]



entry	catalyst	er[b] (*S*/*R*)	yield,[c] %
1[d]	**26**	78.0/22.0	56
2	**25c**	59.0/41.0	54
3	**25d**	93.5/6.5	85
4	**25e**	83.5/16.5	58
5	**27**	79.0/21.0	72

[a] All reactions run at 1.0 M concentration in CH_2Cl_2/*i*-Pr_2NEt, 1/1 at −78 °C for 8 h, using 5 mol % catalyst. [b] Determined by CSP-SFC. [c] Yield of chromatographically homogeneous product. [d] 20 mol % of catalyst was used.

(22) Sato, M.; Sato, Y.; Yano, S.; Yoshikawa, S. *J. Chem. Soc., Dalton Trans.* **1985**, 895−898.

(23) Chivers, P. J.; Crabb, T. A.; Williams, R. O. *Tetrahedron* **1968**, *24*, 4411−4421.

In the reaction catalyzed by bisphosphoramides **25**, a dependence of product enantioselectivity on tether length was observed. The enantioselectivity variation on the tether length followed the same trend as that seen with bisphosphoramides **5**. Whereas **25c** gave only 59.0/41.0 er in the reaction, **25d**, bearing a five-methylene tether dramatically improved the enantioselectivity to 93.5/6.5 er (entries 2 and 3). In this case, the enantioselectivity observed with **25d** was significantly higher than that obtained with **5d** and **11d** derived from *trans*-cyclohexane-1,2-diamine, which clearly illustrated the success of the design. When **25e** was used, the enantioselectivity decreased slightly to 83.5/16.5 er. In addition, the bisphosphoramide **25d** proved to be much more reactive than the bisphosphoramides with other tethers as well as the monophosphoramide, giving an 85% yield with only 5 mol % catalyst loading. Compared to **25d**, the bisphosphoramide **27d** derived from 2,2-bispiperidine, however, provided a lower selectivity and yield (entry 5).

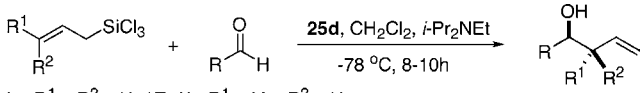
5. Scope of the Reaction. The successful design and implementation of bisphosphoramide **25d** derived from (*R*,*R*)-2,2′-bispyrrolidine demonstrated our understanding of the origin of stereochemical induction in the allylation reactions and produced high enantioselectivity in the addition of allyltrichlorosilane to benzaldehyde. To establish the generality of the bisphosphoramide **25d** in the catalytic enantioselective allylation reaction, a survey of aldehydes and allylic trichlorosilanes was undertaken, and the results are collected in Table 5. Under the established reaction condition with 5 mol % of **25d**, **1a** underwent addition to aromatic (entries 1−4), heteroaromatic (entry 6), and unsaturated aldehydes (entry 5) to give homoallylic alcohols in good selectivities and yields. 2-Naphthaldehyde and 4-methoxybenzaldehyde provided enantioselectivities similar to that with benzaldehyde, whereas 4-trifluoromethylbenzaldehyde, cinnamaldehyde, and 2-furaldehyde gave slightly diminished enantioselectivities.

An important demonstration of scope was in the extension to the reactions of γ-substituted allylic trichlorosilanes. An excellent correlation of geometrical homogeneity of the silanes with the diastereomeric composition of the products ((*E*)-**1b** → *anti*-**3**; (*Z*)-**1b** → *syn*-**3**) was seen. The results in Table 5 show clearly that (*Z*)-**1b** leads to much higher enantioselectivity compared to (*E*)-**1b** (compare entries 7−9 and 10−12). Furthermore, γ-disubstituted allylic trichlorosilane **1c** also reacted under these conditions to provide prenylation products with excellent selectivity (Table 5, entries 17−19). Apparently, the *Z*-substituent on the allylic trichlorosilane has a beneficial effect as evidenced by the highly selective *syn*-butenylation and prenylation processes. Further, electron-rich aromatic aldehydes seemed to react with higher enantioselectivities compared to electron-deficient aromatic substrates (cf. entries 3 vs 4, 12 vs 13).

6. Quaternary Stereogenic Centers. The successful and highly enantioselective addition of **1c** promoted by **25d**, together with the strong stereochemical coupling of geometry with diastereoselectivity (for (*E*)-**1b** and (*Z*)-**1b**), suggested the opportunity for enantioselective construction of quaternary stereogenic centers by the addition of unsymmetrical γ-disubstituted allylic trichlorosilanes to aldehydes.[24] Trisubstituted silanes (*E*)-**33** and (*Z*)-**33** were chosen as test substrates and were readily synthesized from commercial available geraniol (*E*)-**31** and nerol (*Z*)-**31**, respectively (Scheme 10). The geometrically homogeneous alcohols (*E*)- and (*Z*)-**31** were converted to the corresponding chlorides (*E*)-**32** and (*Z*)-**32** by the Corey−Kim procedure[25a,b] or with PPh_3/CCl_4[25c] which were then treated with diisopropylethylamine, trichlorosilane, and a catalytic amount of CuCl to provide allylic trichlorosilanes (*E*)-**33** and (*Z*)-**33** also in geometrically homogeneous form.[26] The catalyzed additions of (*E*)-**33** and (*Z*)-**33** to benzaldehyde provided adducts *anti*-**34** and *syn*-**34** with excellent diastereo- and enantioselectivities (Scheme 10).

The configurational assignment in the formation of quaternary centers was unambiguously confirmed by X-ray crystallographic analysis of the adduct of (*E*)-**33** with 2-naphthaldehyde. The addition of (*E*)-**33** to 2-naphthaldehyde catalyzed by (*R*,*R*)-**25d** provided the homoallylic alcohol **35** with high diastereo- and enantioselectivity (Scheme 11). Treatment of the **35** with 4-bromobenzoyl chloride and a stoichiometric quantity of DMAP in the presence of Et_3N led to the acylated product **36**. Repeated recrystallization provided enantiomerically pure **36** which was suitable for single-crystal X-ray diffraction.[27] The

TABLE 5. Addition of Allylic Trichlorosilanes to Aldehydes Catalyzed by 25d[a]



1a: $R^1 = R^2 = H$; (*E*)-**1b**: R^1 = Me, R^2 = H
(*Z*)-**1b**: R^1 = H, R^2 = Me; **1c**: $R^1 = R^2$ = Me

3

entry	silanes[b]	R	product	yield,[c] %	syn/anti[d]	er[e]
1	**1a**	C_6H_5	**3aa**	85		93.5/6.5
2	**1a**	2-naphthyl	**3ab**	92		93.4/6.6
3	**1a**	4-$CH_3OC_6H_4$	**3ac**	84		94.0/6.0
4	**1a**	4-$CF_3C_6H_4$	**3ad**	79		90.1/9.9
5	**1a**	(*E*)-$C_6H_5CH{=}CH$	**3ae**	84		90.7/9.3
6	**1a**	2-furyl	**3af**	59		90.3/9.7
7	(*E*)-**1b**	C_6H_5	**3ba**	82	1/99	92.8/7.2
8	(*E*)-**1b**	2-naphthyl	**3bb**	83	1/99	90.4/9.6
9	(*E*)-**1b**	(*E*)-$C_6H_5CH{=}CH$	**3be**	59	1/99	90.4/9.6
10	(*Z*)-**1b**	C_6H_5	**3ba**	89	99/1	96.7/3.3
11	(*Z*)-**1b**	2-naphthyl	**3bb**	88	99/1	96.8/3.2
12	(*Z*)-**1b**	4-$CH_3OC_6H_4$	**3bc**	91	99/1	97.3/2.7
13	(*Z*)-**1b**	4-$CF_3C_6H_4$	**3bd**	85	99/1	92.3/7.7
14	(*Z*)-**1b**	(*E*)-$C_6H_5CH{=}CH$	**3be**	78	99/1	94.0/6.0
15	(*Z*)-**1b**	(*E*)-$C_6H_5CH{=}C(CH_3)$	**3bg**	62	95/5	96.1/3.9
16	(*Z*)-**1b**	2-furyl	**3bf**	82	99/1	97.8/2.2
17	**1c**	C_6H_5	**3ca**	89		98.0/2.0
18	**1c**	(*E*)-$C_6H_5CH{=}CH$	**3ce**	71		94.1/5.9
19	**1c**	2-furyl	**3cf**	71		97.3/2.6

[a] Reaction performed at −78 °C for 8−10 h with 5 mol % of **25d**. [b] (*E*)-**1b** and (*Z*)-**1b** both greater than 99/1 isomerically pure by ^1H NMR analysis. [c] Yield of chromatographically homogeneous product. [d] Determined by ^1H NMR (400 or 500 MHz) analysis. [e] Determined by CSP-SFC or CSP-GC.

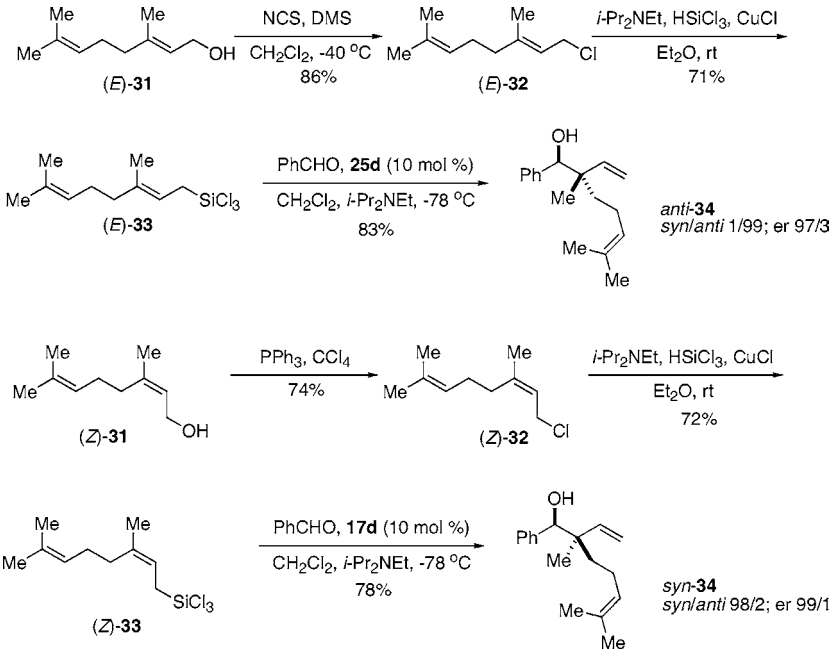
(24) For reviews on enantioselective construction of quaternary stereocenters, see: (a) Christoffers, J.; Barao, A. *Adv. Synth. Catal.* **2005**, *347*, 1473−1482. (b) Douglas, C. J. Overman, L. E. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5363−5367. (c) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591−4597. (d) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (e) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066.

(25) (a) Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, *13*, 4339−4342. (b) Davisson, V. J.; Woodside, A. B.; Neal, T. R.; Stremler, K. E.; Muehlbacher, M.; Poulter, C. D. *J. Org. Chem.* **1986**, *51*, 4768−4779. (c) Calzada, J. G.; Hooz, J. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, pp 634−637.

(26) Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620−6628.

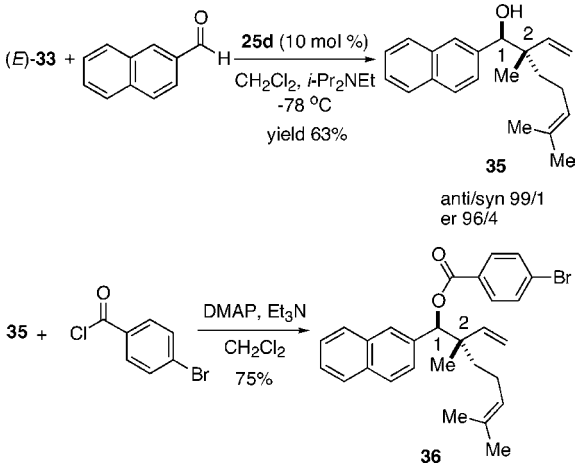
(27) The crystallographic coordinates of **36** have been deposited with the Cambridge Crystallographic Data Centre; deposition no. CCDC 165491. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

SCHEME 10



configuration of **36** was determined to be (1*S*,2*S*). The sense of relative stereoinduction clearly supported the intermediacy of a siliconate complex which reacts through a closed, chair-like transition structure. In addition, the observation that the major adduct had the *S* configuration at the hydroxyl center is also consistent with the results obtained in the addition of allylsilanes **1**.

SCHEME 11



Because geometrically defined γ-disubstituted allylic alcohols are widely accessible, this method represents a versatile route for the construction of quaternary stereogenic centers. As a demonstration of such a method in synthesis, it was applied to the enantioselective synthesis of serotonin antagonist (LY426965) (**46**)[28] which contains an α-carbonyl quaternary center (Scheme 12). LY426965 belongs to a family of arylpiperazines that are effective pharmaceutical agents for the treatment of conditions related to or affected by the serotonin 1A receptor. Preclinical studies indicated that LY426965 is a selective, full 5-HT1A antagonist that may have clinical use as pharmacotherapy for smoking cessation and depression-related disorders.

The key steps in the synthesis of LY426965 are shown in Scheme 12.[4d] To generate the *S* configuration of the quaternary center required the combination of *E*-configured allylic silane **40** under the action of chiral catalyst (*S*)-(*l*,*l*)-**25**. The synthesis of (*E*)-**39** began by zirconium-catalyzed carbometalation of phenylacetylene **37** followed by activation and trapping of the resulting alane with formaldehyde to provide the homoallyl alcohol **38** as a single geometrical isomer.[29] Alcohol **38** was converted by the Corey−Kim procedure[25] to the corresponding chloride **39**, which was then treated with diisopropylethylamine, trichlorosilane, and a catalytic amount of CuCl to give trichlorosilane **40** in geometrically homogeneous form in 78% yield for the two steps. The addition of this chlorosilane to benzaldehyde was effectively catalyzed by (*S*)-(*l*,*l*)-**25d** and provided adduct **41** with excellent diastereoselectivity (*anti*/*syn* 99/1) and enantioselectivity (96.5/3.5). In this case, it was found that the addition of 0.2 equiv of tetrabutylammonium iodide could improve the yield without affecting the selectivity.[30] Selective hydroboration/oxidation of the terminal double bond afforded intermediate **42**.

The final stages of the synthesis of LY426965 required selective saturation of one of the phenyl rings. This maneuver could be accomplished by a two-stage hydrogenation, first with rhodium on alumina[31] and then at higher pressure with platinum on carbon to afford diol **43**. Adjustment of the oxidation state under Swern oxidation conditions afforded keto aldehyde **44**,

(28) (a) Rasmussen, K.; Calligaro, D. O.; Czachura, J. F.; Dreshfield-Ahmad, L. J.; Evans, D. C.; Hemrick-Luecke, S. K.; Kallman, M. J.; Kendrick, W. T.; Leander, J. D.; Nelson, D. L.; Overshiner, C. D.; Wainscott, D. B.; Wolff, M. C.; Wong, D. T.; Branchek, T. A.; Zgombick, J. M.; Xu, Y.-C. *J. Pharmacol. Exp. Ther.* **2000**, *294*, 688−700. (b) Godfrey, A. G.; Kohlman, T. D.; O'Toole, J. C.; Xu, Y.-C.; Zhang, T. Y. U.S. Pat. Appl. Publ. US2004044009, 2004.

(29) Okukado, N.; Negishi, E.-I. *Tetrahedron Lett.* **1978**, *19*, 2357−2360.

(30) (a) Short, J. D.; Attenoux, S.; Berrisford, D. J. *Tetrahedron Lett.* **1997**, *38*, 2351−2354. (b) Denmark, S. E.; Su, X.; Nishigaichi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 12990−12991.

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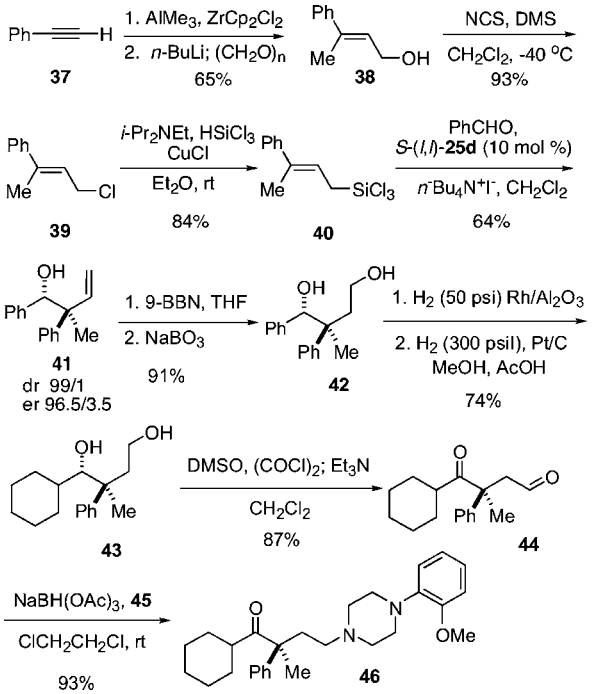
which underwent clean reductive amination with commercially available 4-(2-methoxyphenyl)piperazine (**45**) to complete the synthesis of LY426965.

SCHEME 12

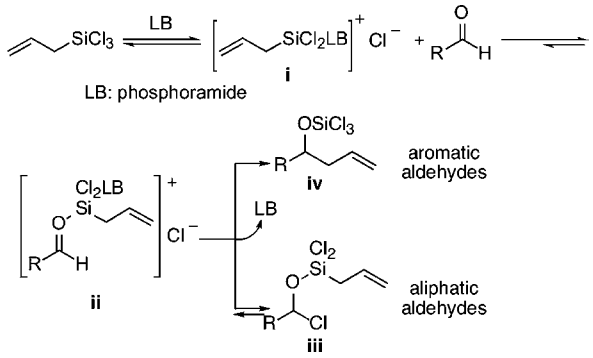


Clearly, a more direct approach to LY426965 would have been the addition of (*E*)-**39** to cyclohexanecarboxaldehyde. Unfortunately, when this aldehyde was employed under the standard allylation conditions, no desired product was formed. This outcome was not unexpected from previous studies on the scope of the addition reaction of simpler allylic silanes **1**. This limitation has plagued the Lewis base catalyzed allylation reactions of allylic trichlorosilanes, and therefore, a systematic study on the origins and potential solutions was initiated.

7. Allylation of Aliphatic Aldehydes. Under conditions by which aromatic and unsaturated aldehydes successfully reacted with allylic trichlorosilanes, aliphatic aldehydes did not undergo addition. This is surprising as aliphatic aldehydes should be more reactive substrates. Careful analysis of the reaction mixtures by ^{1}H NMR spectroscopy revealed that aliphatic aldehydes are immediately consumed in the formation of an α-chloro silyl ether **iii,** which is unreactive toward the allylating reagents (Scheme 13). In the preceding paper, it was shown that the mechanism of the allylation involves an ionization of a chloride ion from **1** to generate a cationic silicon species **i**. Binding of **i** to the aldehyde oxygen constitutes activation of the carbonyl group in species **ii**. With aromatic aldehydes, **ii** proceeds directly to the product (aromatic aldehydes show no tendency to form α-chloro silyl ethers by ^{1}H NMR spectroscopic analysis), whereas with aliphatic aldehydes, collapse of the zwitterion is much faster and only α-chloro silyl ether **iii** is observed.

The formation of α-chloro silyl ether has also been observed in reactions with other trichlorosilyl species.[14b,32] Nevertheless, even when the resting state of the aldehyde was shown to

SCHEME 13



be in the form of the α-chloro silyl ether, many stronger nucleophiles were capable of providing addition products, such as trichlorosilyl ketene acetals,[15] TBS ketene acetals,[14b] conjugated ketene acetals,[14b,33] and isocyanides.[34] Clearly, the α-chloro silyl ether **iii** exists in an equilibrium with the activated aldehyde **ii**. Thus, depending upon the position of that equilibrium and the reactivity of the competing nucleophile, measurable addition rates can be seen. However, because **1** and its relatives are on the lower end of the nucleophilicity scale,[35] our efforts to promote addition focused on shifting the position of the equilibrium toward **ii**. We envisioned that sequestering the chloride anion would affect the equilibrium to favor the complexed aldehyde and allow addition of the allyl group. Strategies such as ion pairing and solvation effects were considered.

The chloride anion is known to form ate complexes with various inorganic salts that have high chloride affinities.[36] Thus, we devised an empirical survey of the effect of various inorganic salts on the rate, yield, and selectivity of the addition of **1** to an aliphatic aldehyde. Hydrocinnamaldehyde was chosen as a representative aliphatic aldehyde, and the allylation was carried out in CH_2Cl_2 at 0.2 M concentration at room temperature for 1 h. After quenching the reactions with KF and aqueous workup, the reaction mixtures were subjected to GC analysis (internal standard) to determine the conversion (Table 6).

In absence of an inorganic salt, HMPA-promoted the allylation of hydrocinnamaldehyde at a rather slow rate at room temperature, reaching only 6% conversion after 2 h (Table 6). With addition of inorganic salts, the reaction was enhanced (entries 3−14), particularly with 10 mol % of $HgCl_2$ or $SbCl_3$ for which up to 28% conversion was achieved.

In subsequent studies to establish the optimal loading of the salt (entries 15−18), it was found that the reaction rate significantly dropped when the loading of $HgCl_2$ was decreased to 2 mol %. However, an increase of loading from 10 mol % to 50 mol % only gave a slightly improved reaction rate.

In addition, the effect of phosphoramide stoichiometry and structure on the reaction rate was also investigated (entries 18−

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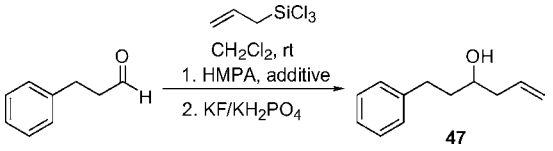
(36) (a) Larson, J. W.; McMahon, T. B. *J. Am. Chem. Soc.* **1985**, *107*, 766−773. (b) Kraus, K. A.; Moore, G. E. *J. Am. Chem. Soc.* **1953**, *75*, 1460−1462. (c) Strelow, F. W. E.; Rethemeyer, R.; Bothma, C. J. C. *Anal. Chem.* **1965**, *37*, 106−111. (d) Strelow, F. W. E.; Van Zyl, C. R.; Bothma, C. J. C. *Anal. Chim. Acta* **1969**, *45*, 81−92.

20). Without HMPA, there was essentially no reaction with $HgCl_2$ alone. Compared to the reaction with 20 mol % of HMPA, only a marginal improvement on the conversion was observed when the loading of the HMPA was increased to 50 mol %. The most promising result was obtained when bisphosphoramide **25d** was used. With 5 mol % of bisphosphoramide **25d** and 10 mol % of $HgCl_2$, the allylation of hydrocinnamaldehyde achieved 59% conversion after 1 h.

TABLE 6. Addition of Allyltrichlorosilane to Hydrocinnamaldehyde Catalyzed by HMPA and Inorganic Salts[a]

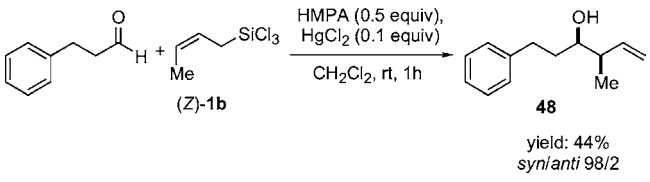


entry	HMPA, equiv	additive, equiv	conversion, %[b]
1			1.3
2	0.2		6
3	0.2	$SbCl_3$, (0.1)	28
4	0.2	$HgCl_2$, (0.1)	26
5	0.2	$ZrCl_4$, (0.1)	9
6	0.2	$CuCl_2$, (0.1)	13
7	0.2	$PdCl_2$(0.1)	5
8	0.2	$GeCl_4$, (0.1)	9
9	0.2	$NiCl_2$, (0.1)	9
10	0.2	$PtCl_2$, (0.1)	6
11	0.2	$BiCl_3$, (0.1)	19
12	0.2	$InCl_3$, (0.1)	13
13	0.2	$PbCl_2$, (0.1)	6
14	0.2	$HgCl_2$, (0.1)	26
15	0.2	$HgCl_2$, (0.02)	8.7
16	0.2	$HgCl_2$, (0.5)	31
17	0.2	$HgCl_2$, (1.0)	30
18		$HgCl_2$, (0.1)	1.3
19	0.5	$HgCl_2$, (0.1)	31
20	**25d** (0.05)	$HgCl_2$, (0.1)	59

[a] Reaction done at 0.20 M concentration at rt for 2 h. [b] Conversion determined by GC analysis.

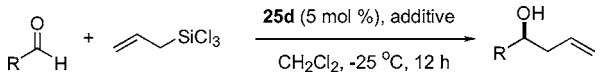
The catalyst system was further applied to the addition of 2-butenyltrichlorosilanes **1b** to examine the effect of $HgCl_2$ on the diastereoselectivity. With 50 mol % of HMPA and 10 mol % of $HgCl_2$, the silane (*Z*)-**1b** successfully added to the hydrocinnamaldehyde and provided the *syn* homoallyl alcohol **48** in 44% yield and high selectivity (*syn*/*anti*, 98/2) (Scheme 14). The high stereospecificity strongly suggested a closed, chairlike transition structure.

SCHEME 14



Because of the enhanced reaction rate observed with the addition of $HgCl_2$, the effect of $HgCl_2$ on the enantioselectivity was then investigated. At −78 °C, the bisphosphoramide **25d** did not promote the addition of allyltrichlorosilane to hydrocinnamaldehyde. Increasing the reaction temperature to −25 °C allowed the addition to take place, and the homoallylic alcohol adduct could be isolated in 25% yield and er of 66.0/34.0 (Scheme 15). Upon addition of 10 mol % of $HgCl_2$ salt, the reaction rate was significantly enhanced. The homoallyl alcohol adduct was isolated with up to 32% yield. Unfortunately, the enantioselectivity decreased only 55.5/44.5 er. A similar effect of $HgCl_2$ on the enantioselectivity was observed in the allylation of benzaldehyde. At −25 °C, the bisphosphoramide **25d** catalyzed the allylation reaction and gave the homoallylic alcohol in 86% yield and 85.0/15.0 er. In contrast, nearly racemic product was isolated when $HgCl_2$ was added.

SCHEME 15



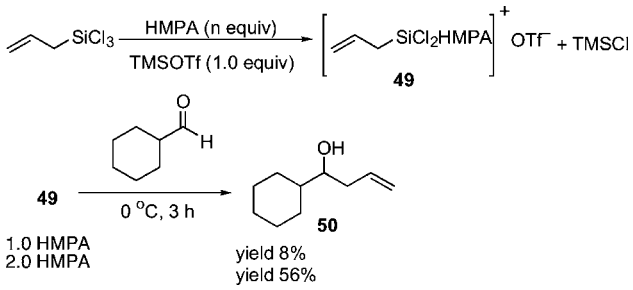
R	additive	yield, %	er
R = $PhCH_2CH_2$	none	25	66.0/34.0
	$HgCl_2$ (10 mol%)	32	55.5.0/44.5
R = Ph	none	86	85.0/15.0
	$HgCl_2$ (10 mol%)	74	51.0/49.0

As an alternative approach to solve the lack of reactivity of aliphatic aldehydes, it was reasoned that the formation of the α-chloro silyl ether might be disfavored if the chloride anion could be exchanged with a less nucleophilic anion such as a triflate anion. Thus, the equilibrium would favor the complexed aldehyde, which would allow addition of the allyl group. This exchange should be promoted by phosphoramides since the ionization of chloride took place only upon coordination of phosphoramides to allylic trichlorosilane.

Thus, to a solution of allyltrichlorosilane with a 20 mol % of HMPA was added TMSOTf as the triflate anion source. Upon addition, TMSOTf disappeared rapidly with the formation of TMSCl. The reaction, however proceeded to 20% conversion as judged by ^1H NMR analysis. To achieve complete reaction required the use of 1.0 equivalent of HMPA. The stoichiometries of the reagents utilized in the reaction suggested the formation of ionic HMPA/allyldichlorotriflate complex **49** (Scheme 16).

To test the reactivity of complex **49** toward aliphatic aldehydes, cyclohexanecarboxaldehyde was added to the reaction mixture. After 3 h at 0 °C, the allylation adduct **50** was obtained only in 8% yield (Scheme 16). The allylation rate could be significantly accelerated by the addition of another equivalent of HMPA. With 2 equiv of HMPA, the allylation product **50** was obtained in 56% yield after 3 h at 0 °C.

SCHEME 16



These studies demonstrated that the allylation of aliphatic aldehydes could be achieved by intercepting the chloride anion. Particularly, with $HgCl_2$ as an additive, a catalytic amount of phosphoramide could afford the allylation adduct with high

conversion. Unfortunately, in this case, the enantioselectivity observed was adversely affected.

Discussion

1. Reaction Promoted by Bidentate Ligands. The poor selectivities and reaction rates observed with monodentate phosphorus-based ligands as catalysts in allylation reactions was shown to arise from the intervention of two mechanistic pathways involving either one or two ligands in the rate- and stereochemistry-determining transition structure. The use of bidentate ligands addressed this problem by increasing the effective concentration of the second basic group through tethering. An important consequence of tethering is that the arrangement of the Lewis basic subunits in the complex is dictated by the tether length and flexibility. Not surprisingly, the selectivities were found to be quite different for two different phosphoramide subunits and one phosphonamide (Figure 4). The graphical presentation of the data clearly shows the dramatic chain length dependence of enantioselectivity, which strongly supports the hypothesis that the two subunits are cooperative. Both of the phosphoramide series **5** and **25** show significant increase in selectivity with the pentamethylene tether. Even the bisphosphonamide series **11** showed a dependence of the product er on the tether length albeit with a different pattern, perhaps reflecting the all-carbon chain that connects the two phosphonamide units. Nevertheless, the maximum was seen with a heptamethylene tether that corresponds to the same 12-membered chelate ring for complexation of the siliconium cation.

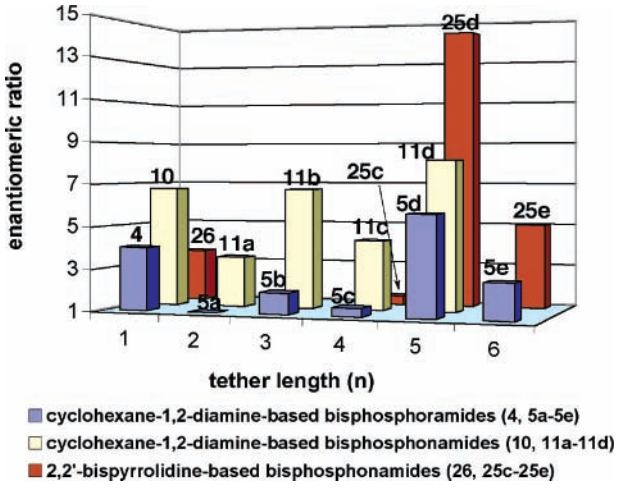


FIGURE 4. Tether length dependence of enantioselectivity for various dimeric catalysts.

The dependence of er on the promoter concentration provided additional support for the operation of chelation. In the allylation promoted by bisphosphoramides, there are two possible competing pathways involving two phosphoramide units in the transition structure: (a) one bisphosphoramide chelated to silicon and (b) two separate bisphosphoramides (nonchelated) bound in the transition structure (Figure 5). The rate of the pathway (b) is second order in phosphoramide concentration, while the rate of pathway (a) is first order in phosphoramide concentration. Therefore, the chelated pathways would be more favorable at lower phosphoramide concentration. Because the enantioselectivities of the chelated and nonchelated pathways were different, the net reaction selectivity would be concentration dependent. Indeed, loading studies with bisphosphoramides showed that when the loading of **5c** was decreased from 1.0 to 0.1 equiv, the er of product obtained also decreased from 58.5/41.5 to 55/45. On the other hand, a lower of the loading of **5d** brought about an increase in the ee of the product from 82.5/17.5 to 86/14. Thus, if the reaction catalyzed by **5c** primarily involved two separate bisphosphoramides because of the low propensity of **5c** to chelate, then lowering the concentration of **5c** would allow intervention of the unselective nonchelated one-phosphoramide pathway (Figure 5c). On the other hand, if **5d** reacts primarily through a chelated, one-bisphosphoramide pathway (Figure 5a) with some of the two-separate-bisphosphoramide pathway in competition, then lowering the concentration of **5d** would lead to enhanced selectivity by favoring the more selective chelated pathway. This is what was observed.

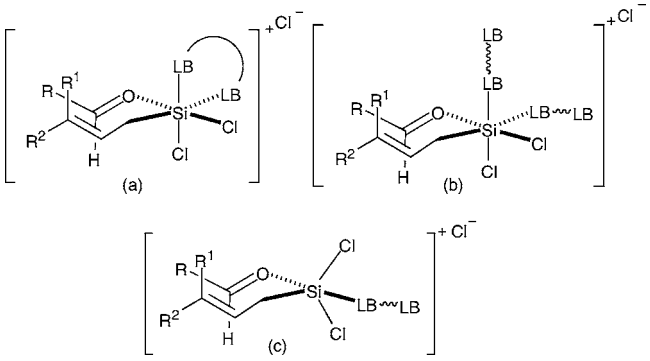


FIGURE 5. (a) Chelated one-phosphoramide pathway. (b) Nonchelated two-phosphoramide pathway. (c) Nonchelated one-phosphoramide pathway.

Structural support for the formation of these various complexes has been provided by solution NMR spectroscopic and solid X-ray crystallographic studies of the bisphosphoramide·$SnCl_4$ complexes.[16] From ^{119}Sn and ^{31}P NMR solution studies, it was found that the catalysts **5c**, **25c**, **5d**, and **25d** bearing four or five methylene units formed exclusively the *cis*-chelate complex with $SnCl_4$ at high concentration.

In addition, the NMR spectroscopic studies revealed that the formation of chelated complexes was not as favorable with bisphosphoramides **5a**, **5b**, **5e**, and **25e** containing other tether lengths. Instead these potentially chelating bisphosphoramides functioned as monodentate ligands. In the allylation reaction the bisphosphoramides, **5b**, **5e**, and **25e** provided rather similar enantioselectivity compared to the monophosphoramide **6**; therefore, it was most likely that these ligands behave as monodentate ligands in the reaction as well.

In the case of bisphosphoramide **5a**, upon coordination of one phosphoramide unit, the appended bulky phosphoramide is in close proximity to the coordinating phosphoramide unit. Thus, the bisphosphoramide could be viewed as a bulky monodentate phosphoramide. In the allylation reaction promoted by **5a**, the product was obtained in racemic form. Since the sterically bulky phosphoramides have been found give poor enantioselectivity, the reason for the low selectivity was presumably due to the steric bulk of this monodentate phosphoramide.

Clearly, tether length and the resulting chelation are not the only factors that influenced the stereoselectivity of the allylation. Obviously, the structure of the phosphorus-containing units that create the chiral environment are crucial for high facial

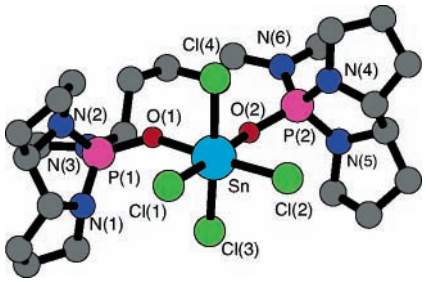


FIGURE 6. Chem 3D presentation of the X-ray structure of **25d**·$SnCl_4$.

differentiation. Compare, for example, the phosphoramides **5d**, **14**, **15**, **20**, **25d**, and **27**, all of which can achieve 12-membered ring chelation. The range of enantioselectivities is striking from 60/40 up to 93.5/6.5. Perhaps most illustrative of the sensitivity of these reactions to structural details is the drop in selectivity seen for the bispiperidine catalyst **27**. Given the generality and high selectivity observed with catalyst **25d**, a rationalization of preferred transition-structure arrangements is warranted.

2. Transition Structure for the Allylation Catalyzed by 25d. Among the bisphosphoramide examined, the bisphosphoramide **25d** derived from 2,2′-bispyrrolidine provided the highest enantioselectivity. To provide an understanding of the special features of **25d**, the complexation of **25d** with $SnCl_4$ as a Lewis acid has been studied, and the solid-state structure of **25d**·$SnCl_4$ complex is shown in Figure 6.[16] In this complex, the tin atom adopts an octahedral geometry with bisphosphoramide chelated in a cis manner. Most importantly, the two pyrrolidine rings adopt a stairlike geometry, creating a highly asymmetric environment.

A transition structure for the allylation reaction catalyzed by **25d** can be formulated by combining the coordinates from the X-ray crystal structure with our recently reported computational analysis of the preferences for coordination geometries in hypervalent silicon species.[15] These calculations revealed a strong preference for the trans arrangement of chlorines in one of the two 3-center-4-electron bonds and the placement of the coordinated aldehyde in the sp hybrid orbital. This geometry then places the allyl group in the second hypervalent bond, which is also where the electronic activation should be the strongest. Two limiting arrangements of the aldehyde and allyl groups in chairlike conformations (as must be the case because of the high diastereoselectivity) are shown in Figure 7.[37] In one of the possible chairlike assemblies (Figure 7b), leading to the *Re*-face attack, the benzaldehyde ring is located in a quadrant of the ligand environment that is occupied by a forward-pointing pyrrolidine ring, thereby creating unfavorable steric interactions. In the diastereomorphic chairlike arrangement (Figure 7a), the benzaldehyde ring is placed in a quadrant that is occupied by a rearward-pointing pyrrolidine ring, and no unfavorable steric interactions are evident. On the basis of this analysis, we propose that the reaction proceeds through a transition structure similar to the arrangement shown in Figure 7a, leading to the observed homoallyl alcohol of *S*-configuration at the hydroxyl center.

The bisphosphoramide **25d** possesses two features that contribute to the high enantioselectivities: (1) a 2,2′-bispyrrolidine as chiral diamine backbone and (2) five methylene units as the tether. Interesting, the bisphosphoramide **27d** derived from 2,2′-bispiperidine was much less selective than **25d**. It is conceivable that the longer linkage between the nitrogen and the stereogenic center (four ring methylenes vs three ring methylenes) and the attendant increased flexibility of the in the piperidine attenuates the influence of the backbone on the geometry of the piperidine ring, which leads to a decreased enantioselectivity. In addition, in a detailed solution- and solid-state study on the bisphosphoramide **25c**·$SnCl_4$ and **25d**·$SnCl_4$,

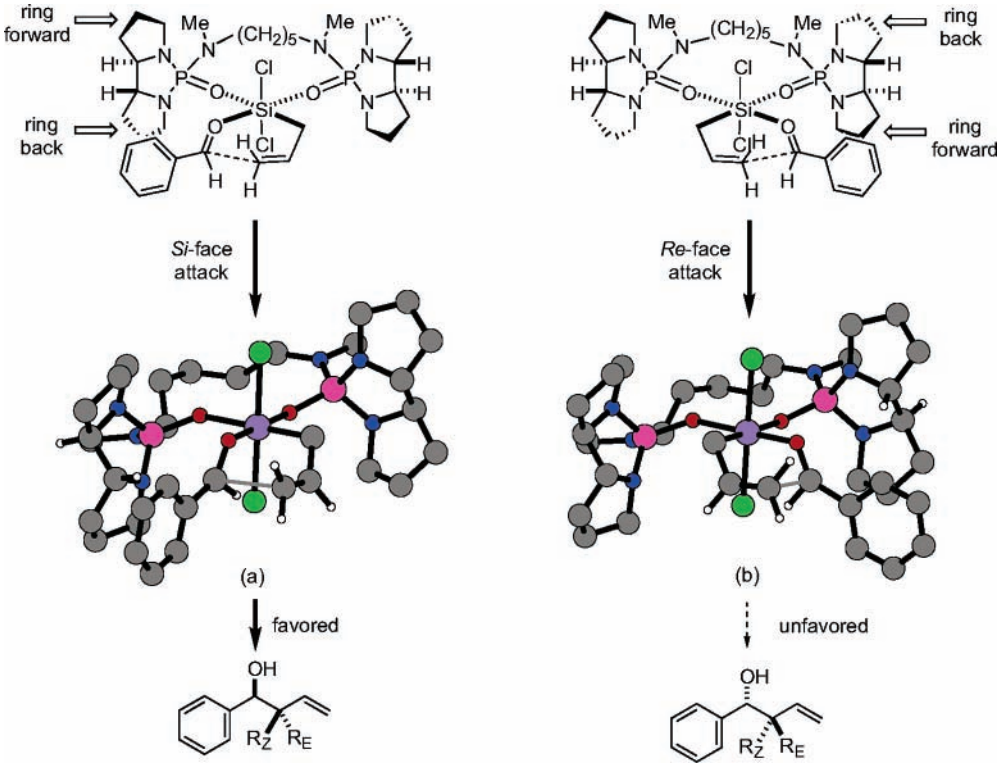


FIGURE 7. Hypothetical transition structure for the reaction promoted by **25d**.

it was found that a five methylene unit tether was not only important for chelation but also necessary to bring the chiral information close to the reaction center, thereby achieving high asymmetric induction.[16]

3. Reaction with γ-Substituted Allylic Trichlorosilanes. In the addition of allylic trichlorosilanes to aromatic aldehydes, the electron-rich aromatic aldehyde provided higher enantioselectivity than the electron-poor aromatic aldehydes. One might expect that an electron-rich aldehyde would coordinate more tightly to the silicon center, thus contracting the transition structure and intensifying steric interaction, leading to the higher selectivity. Alternatively, it is possible that the less reactive electron-rich aldehydes react via late transition states that can also enhance interactions of substrate and chiral catalyst.[38]

A more important demonstration of the chiral Lewis base catalyzed allylation is that uniformly high diastereoselectivities and enantioselectivities are observed in the addition of (*E*)- and (*Z*)-2-butenyltrichlorosilanes to aldehydes. The high stereospecificity clearly suggested a closed, chairlike transition structure. Although asymmetric allylation has seen wide application in organic synthesis, few applications of this method in the construction of quaternary centers have been reported. The challenges of performing such a reaction are as follows: (1) selective synthesis of geometrically pure 3,3-disubstitued allylic organometallic reagents; (2) correlation of the geometrical composition of the allylic organometallic reagents to the diastereomeric composition of the products; (3) control of asymmetric induction with internal chiral auxiliaries or external chiral catalysts. The allylation method described here has been proven to satisfy these requirements. This method provided a very versatile route for the construction of quaternary centers from the corresponding γ-disubstituted allylic alcohol. The application of this method to the synthesis of serotonin antagonists **46** demonstrated not only the efficiency of this allylation method but also the versatile functionality provided by the allylation adducts.

Conclusions

A new family of phosphorus-based bidentate ligands has been developed for catalytic enantioselective allylation reaction. From a combination of mechanistic insights and X-ray crystallographic analysis, it was found that linking two phosphonamide units through a pentamethylene tether leads to optimal cooperativity in the activation of allylic trichlorosilyl reagents. The bidentate phosphoramide derived from 2,2-bispyrrolidine provided the highest yield and enantioselectivity in the addition of various allylic trichlorosilyl species with aromatic and unsaturated aldehydes. Aliphatic aldehydes are prone to formation of unreactive α-chlorosilyl ethers and do not undergo addition in useful yields. The high stereochemical fidelity between allyl geometry and product configuration supports the hypothesis of a highly organized chairlike transition structure and also allowed for the development of catalytic enantioselective construction of quaternary stereogenic centers. This application was illustrated in the synthesis of serotonin agonist LY426965.

This technology represents the state of the art for catalytic, enantioselective allylation of aromatic and olefinic aldehydes. Extremely high enantio- and diastereoselectivity can be obtained from simple allylic reagents and from geometrically defined donors, even for the construction of quaternary stereogenic centers. The singular (albeit significant) shortcoming of this method is the inability to engage aliphatic aldehydes. Because this is a mechanism-based problem associated with the necessary ionization of chloride from the chlorosilyl reagents, future studies will focus on allylating agents that are capable of nucleophilic activation without the need for ionization of a ligand. These efforts along with applications of the chlorosilyl species in synthesis endeavors will be reported in due course.

Experimental Section

General Experimental Procedures. See the Supporting Information.

Preparation of (3a*R*,4a*R*)-7-Chlorooctahydro-6a,7a-diaza-7-phosphacyclopenta[*a*]pentalene 7-Oxide (28). In a 100-mL, two-neck, round-bottom flask with a nitrogen adapter and septum were added a solution of (*R*,*R*)-**21** (2.0 g, 14.3 mmol) in 80 mL of diethyl ether at 0 °C (ice bath) and triethylamine (4.0 mL, 28.6 mmol, 2.0 equiv) followed by the slow addition of phosphorus oxychloride (1.33 mL, 14.3 mmol, 1.0 equiv) by syringe. The mixture was stirred at room temperature for 2 h, whereupon the salt was filtered though a glass filter frit and the filtrate was concentrated to give 2.1 g (67%) of **28** as a light yellow oil. This crude material was used directly in the next step. An analytical sample was obtained by a chromatographic purification (silica gel, CH_2Cl_2/acetone, 19/1). Data for (+)-**28**: ^{1}H NMR (500 MHz, $CDCl_3$) 3.69−3.57 (m, 3 H, HC(3a), HC(4a), HβC(6)), 3.44−3.36 (m, 1 H, HαC(6)), 3.06−2.98 (m, 2 H, $H_2C(1)$), 2.06−1.89 (m, 6 H, $H_2C(2)$, $H_2C(5)$, H_2C-(3 or 4), 1.75−1.51 (m, 2 H, H_2C(3 or 4)); ^{13}C NMR (500 MHz, $CDCl_3$) 68.7 (d, J = 14.7, C(3a or 4a)), 66.1 (d, J = 17.5, C(3a or 4a)), 45.4 (d, J = 1.9, C(1 or 6)), 45.2 (d, J = 3.7, C(1 or 6)), 30.7 (d, J = 6.4, C(3 or 4)), 30.3 (d, J = 2.7, C(3 or 4)), 27.5 (d, J = 4.6, (C(2 or 5)), 27.1 (d, J = 5.5, C(2 or 5)); ^{31}P NMR (202 MHz, $CDCl_3$): 28.35; IR (NaCl): 2969 (m), 2879 (m), 1446 (w), 1278 (s), 1197 (m), 1110 (s), 1066 (m), 1033 (s), 993 (w), 910 (w); MS (FAB) 224 (3), 223 (29), 222 (10), 221 (100), 141 (33), 132 (16), 118 (23); $[\alpha]^{24}_D$ +37.25 (c = 1.21, benzene); TLC R_f 0.34 (CH_2Cl_2/acetone, 19/1) [$KMnO_4$]; HRMS calcd for $C_8H_{15}ClN_2OP$ (M^+ + H) 221.0610, found 221.0611.

Preparation of *N*,*N*′-Dimethyl-*N*,*N*′-bis((3′a*R*,4′a*R*)-7′-oxooctahydro-6′a,7′a-diaza-7′-phosphacyclopenta[*a*]pentalene-7′-yl)-pentane-1,5-diamine (25d). In a 50-mL, three-necked, round-bottom flask fitted with a nitrogen inlet adapter, septum, and thermocouple was placed a solution of *N*,*N*′-dimethyl-1,5-pentanediamine (476 μL, 3.0 mmol, 1.0 equiv) in 28.0 mL of THF, and the solution was cooled to −78 °C in a dry ice/*i*-PrOH bath. To this solution was added dropwise *n*-BuLi (4.0 mL, 1.55 M, 6.1 mmol, 2.0 equiv). The reaction mixture was warmed to 0 °C and was stirred at 0 °C in an ice bath for 30 min and then was cooled to −78 °C. To this solution was added a solution of **28** (1.50 g, 6.8 mmol, 2.3 equiv) in 17.0 mL of THF. The mixture was stirred at 0 °C in an ice bath for 1 h and then at room temperature for 2 h. After evaporation of the solvent, the product was purified by silica gel column chromatography (CH_2Cl_2/*i*-PrOH, 9/1 followed by CH_2Cl_2/*i*-PrOH, 4/1) to provide 1.41 g (93%) of **25d** as a clear, colorless oil. The product was pure by ^{1}H NMR (S/N > 100/1) and ^{31}P NMR (S/N > 60/1) analysis.

Data for (+)-**25d**: ^{1}H NMR (500 MHz, $CDCl_3$) 3.53−3.46 (m, 6 H, 2 × HC(3′a), 2 × HC(4′a), 2 × HβC(6′)), 3.05−2.92 (m, 8 H, 2 × H_2C(1′), H_2C(1), H_2C(5)), 2.75−2.70 (m, 2 H, 2 × HαC-(6′)), 2.57 (d, J = 10.3, 6 H, H_3C(Me)), 1.95−1.81 (m, 12 H, 2 × H_2C(2′), 2 × H_2C(5′), 2 × H_2C(3′ or 4′)), 1.62−1.47 (m, 8 H, H_2C(2), H_2C(4), 2 × H_2C(3′ or 4′)), 1.29−1.24 (m, 2 H, H_2C(3));

(37) This analysis is different from that presented in our previous account (ref 16) wherein the aldehyde was suggested to be coordinated trans to a chloride in an axial position. Our calculations strongly suggest that this is not a bound species and would also be deactivated for addition to the aldehyde group.

(38) For an in-depth mechanistic discussion of the addition of enoxytrichlorosilyl species to aldehydes, see: Denmark, S. E.; Bui, T. *J. Org. Chem.* **2005**, *70*, 10393−10399.

^{13}C NMR (126 MHz, $CDCl_3$) 68.6 (d, J = 10.1, C(3′a or 4′a), 66.6 (d, J = 9.4, C(3′a or 4′a), 49.1 (d, J = 3.6, C(1), C(5)), 45.4 (d, J = 2.8, C(1′ or 6′)), 43.5 (d, J = 3.6, C(1′ or 6′)), 33.0 (d, J = 3.7, C(Me)), 30.9 (d, J = 2.8, C(3′ or 4′)), 30.5 (d, J = 5.5, C(3′ or 4′)), 28.2 (d, J = 2.7, C(2′ or 5′)), 27.9 (d, J = 6.5, C(2′ or 5′)), 27.4 (d, J = 3.7, C(2), C(4)), 24.0 (C(3)); ^{31}P NMR (202 MHz, $CDCl_3$) 25.37; IR (NaCl) 3039 (w), 2958 (s), 2867 (s), 1714 (w), 1454 (m), 1328 (m), 1226 (s), 1207 (s), 1135 (s), 1091 (s), 1070 (s), 1027 (s), 985 (s), 730 (s); MS (FAB) 224 (3), 223 (29), 222 (10), 221 (100), 141 (33), 132 (16), 118 (23); $[\alpha]^{24}_D$ +12.26 (c = 1.11, EtOH); TLC R_f 0.45 (CH_2Cl_2/EtOH, 9/1) [$KMnO_4$]; HRMS calcd for $C_{23}H_{45}N_6O_2P_2$ (M^+ + H) 499.3079; found 499.3081.

Addition of Allylic Trichlorosilanes to Aldehydes. Preparation of (*S*)-1-Phenyl-3-buten-1-ol (3aa). In a 10-mL, three-necked, round-bottom flask fitted with a nitrogen inlet adapter, septum, and thermocouple was placed a solution of **25d** (50 mg, 0.1 mmol, 0.05 equiv) in 1.0 mL of dichloromethane and 1.0 mL of diisopropylethylamine under N_2 at −78 °C, and then allylic trichlorosilane **1a** (580 μL, 4.0 mmol, 2.0 equiv) was added. The solution was stirred at −78 °C for 10 min before benzaldehyde (200 μL, 2.0 mmol) was added. The resulting mixture was stirred at that temperature for 8 h, whereupon the cold solution was poured into a mixture of 10 mL of saturated aqueous $NaHCO_3$ and 10 mL of saturated aqueous KF solution at 0 °C with vigorous stirring. The mixture was stirred for 2 h at room temperature, and then it was filtered through Celite. The layers were then separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried (Mg_2SO_4), filtered, and concentrated. The oily residue was purified by column chromatography ((SiO_2), CH_2Cl_2/pentane, 3/1 followed by CH_2Cl_2) to give 254 mg (85%) of **3aa** as a colorless oil. Data for (*S*)-**3aa**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.37−7.26 (m, 5 H, HC(Aryl)), 5.80 (dddd, J = 17.5, 10.5, 7.7, 6.6, 1 H, HC(3)), 5.19−5.14 (m, 2 H, H_2C(4)), 4.75 (dd, J = 7.7, 5.0, 1 H, HC(1)), 2.57−2.46 (m, 1 H, HC(2)), 2.02 (br, 1 H, OH); ^{13}C NMR (126 MHz, $CDCl_3$) 143.8 (C(1′)), 134.4 (C(3)), 128.4 (C(3′)), 127.6 (C(4′)), 125.8 (C(2′)), 118.5 (C(4)), 73.2 (C(1)), 43.8 (C(2)); IR (NaCl) 3368 (s), 3076 (w), 3030 (w), 2906 (w), 1641 (m), 1493 (w), 1453 (m), 1315 (w), 1198 (w), 1047 (s), 916 (s), 757 (s), 700 (s); $[\alpha]^{24}_D$ −48.12 (c = 1.05, benzene) (lit.[39] $[\alpha]^{24}_D$ −17.8 (c = 7.38, benzene) for 30% ee of (*S*)-**3aa**); TLC R_f +0.39 (CH_2Cl_2) [$KMnO_4$]; SFC (*R*)-**3aa**, t_R 2.97 min (6.5%); (*S*)-**3aa**, t_R, 3.46 min (93.4%) (Chiralpak OD, 40 °C, 150 bar, 4% MeOH in CO_2, 3.0 mL/min, 258 nm).

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Supporting Information Available: Preparation and full characterization ofphosphoramide catalysts, all addition products, a representative allylation procedure, and crystallographic data for **36**. This material is available free of charge via the Internet at http://pubs.acs.org.

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