Catalytic, Enantioselective Addition of Substituted Allylic Trichlorosilanes Using a Rationally-Designed 2,2′-Bispyrrolidine-Based Bisphosphoramide

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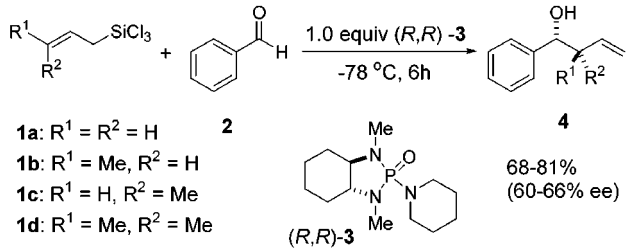
The enantioselective addition of allylmetal reagents to aldehydes is an often-employed and powerful method for stereoselective carbon−carbon bond formation.[1] The overwhelming majority of examples that operate catalytically are chiral Lewis acid-promoted additions of allylic silanes and stannanes which often proceed with excellent enantioselectivity.[2] However, these transformations are less useful for the introduction of γ-substituted allylic species, because the open-transition structure characteristic of these reactions does not allow for controlled diastereoselection.[3]

A mechanistically distinct approach that addresses the problem of relative diastereocontrol is the Lewis base-promoted addition of allylic trichlorosilanes to aldehydes.[4,5] In 1994, the first examples of catalytic enantioselective addition of allylic trichlorosilanes to aldehydes by the use of chiral phosphoramides was reported from these laboratories (Scheme 1).[6] Since then, a number of groups have reported enantioselective additions promoted by chiral phosphoramides,[7a,b] formamides,[7c,d] *N*-oxides,[7e] ureas,[7f] and diamines.[7g] Despite significant efforts at empirical optimization of the enantioselectivity, a highly selective and reactive catalyst has yet to be discovered. Herein, we report the design and implementation of a new 2,2′-bispyrrolidine-based bisphosphoramide that catalyzes the addition of many kinds of allylic trichlorosilanes to aldehydes with excellent diastereo- and enantioselectivity. We also report the first examples of catalytic, enantioselective construction of *quaternary carbon centers* by this technology.

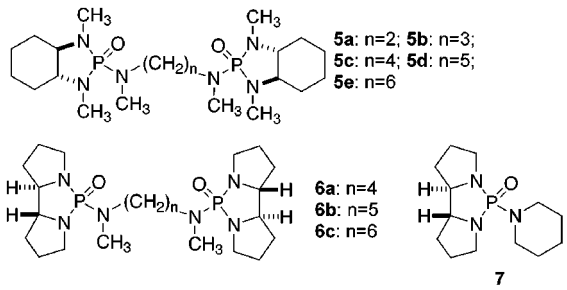
Mechanistic studies on the allylation promoted by phosphoramide **3** indicated that the reaction can proceed by two pathways involving either one or two phosphoramides bound to the

Scheme 1



chlorosilane.[8] An important consequence of this duality is that the rate of the more selective "two-phosphoramide" pathway decreases as [cat]^2. Thus, at catalytic loadings, the rate and selectivity (due to the intervention of the one-phosphoramide pathway) of the addition are adversely affected. This problem was addressed by utilizing bisphosphoramide **5** with the expectation of increasing the effective concentration of the second catalyst molecule through proximity (Chart 1). A systematic investigation of the tether revealed that bisphosphoramide **5d** (in which the two base functions are separated by a five-methylene unit) was able to provide a higher, yet still modest ee (72%).

Chart 1



Further modifications of the catalyst structure focused on the evaluation of dimeric phosphoramides with various chiral diamines as backbones. Employment of dimeric versions of catalysts that have served well in other processes were largely ineffective here.[9] To refine our understanding of the origin of asymmetric induction and assist in the design of more selective catalysts, we utilized $SnCl_4$ as a surrogate for silicon to study the complexation of a bisphosphoramide to a Lewis acid.[10] Examination of the X-ray crystal structure of **5d**·$SnCl_4$[11] revealed that the disposition of the internal, N-methyl substituents was significantly influenced by the chiral skeleton (Figure 1a). 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 1b,c, and thus suggested the use of a phosphoramide derived from 2,2′-bispyrrolidine.[12]

We were delighted to find that the dimeric bisphosphoramides **6a**−**c** induced the allylation of benzaldehyde at −78 °C with just 5 mol % loading. For this series as well, the dimer **6b** with a five-methylene tether provided superior selectivity and reactivity

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(11) The crystallographic coordinates of **5d**·$SnCl_4$ have been deposited with the Cambridge Crystallographic Data Centre; deposition no. CCDC 164277.

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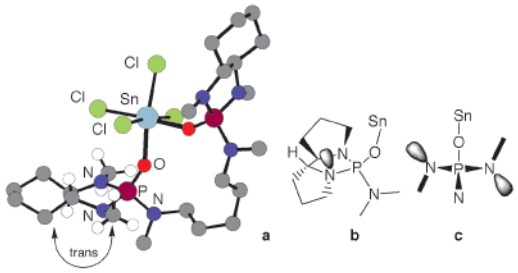


Figure 1. (a) Chem 3D image of **5d**·$SnCl_4$. Most hydrogens removed for clarity. (b) Nitrogen distortion in the hypothetical complex of phosphoramides **6/7**. (c) Front view.

compared to the bisphosphoramides **6a** and **6c** with different tether lengths and the monophosphoramide **7** (Table 1).[13] The strong cooperativity of the dimers and enhanced selectivity of **6b** compared to **7** support the hypothesis of a two-phosphoramide pathway.

Table 1. Allylation of Benzaldehyde with **1a** Catalyzed by 2,2′-Bispyrrolidine-Derived Phosphoramides[a]

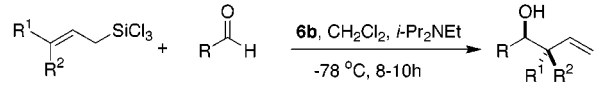
entry	catalyst	ee, %[b]	yield, %
1	**6a**	18 (*S*)	54
2	**6b**	87 (*S*)	85
3	**6c**	67 (*S*)	58
4[c]	**7**	56 (*S*)	56

[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] 20 mol % catalyst was used.

With an efficient catalyst in hand, we explored the scope of the allylation with various aldehydes (Table 2). Aromatic, heteroaromatic, and unsaturated aldehydes underwent allylation in good yields and selectivities (Table 2, entries 1−6). However, the more important demonstration of scope was in the extension to the reactions of γ-substituted allylic trichlorosilanes. The additions of (*E*)- or (*Z*)-2-butenyltrichlorosilanes (**1b** and **1c**) are known to be highly diastereoselective and the results with **6b** were no exception (entries 7−16). The proposed chairlike transition structure for these additions is apparently operative as reflected in the excellent correlation of geometrical purity of the silanes with the diastereomeric composition of the products (*E* → anti; *Z* → syn). The results in Table 2 show clearly that **1c** leads to much higher enantioselectivity compared to **1b**. Furthermore, γ-disubstituted allylic trichlorosilane **1d** also reacted under these conditions to provide prenylation products with excellent selectivity (Table 2, 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 aldehydes seemed to react with higher enantioselectivities compared to electron poor substrates (cf. entries 3 vs 4, 12 vs 13).

The successful and highly enantioselective addition of **1d** promoted by **6b,** together with the strong stereochemical coupling of geometry with diastereoselectivity (for **1b** and **1c**), suggested the opportunity to construct quaternary stereogenic centers[14] by the addition of unsymmetrically γ-disubstituted allylic trichlorosilanes to aldehydes. As test substrates we chose trisubstituted silanes (*E*)-**8** and (*Z*)-**8**, which were synthesized from geraniol and nerol, respectively, in geometrically pure form in two steps.[5c] The catalyzed addition of these agents to benzaldehyde provided adducts *anti*-**9** and *syn*-**9** with excellent diastereo- and enantioselectivities (Scheme 2). Since the γ-disubstituted allylic alcohols are widely accessible, this method represents a versatile route for the construction of quaternary stereogenic centers.[15]

Table 2. Allylations Catalyzed by **6b**[a]



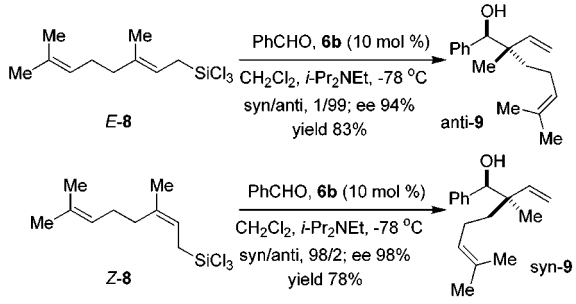
1a: R^1=H, R^2=H; **1b**: R^1=Me, R^2=H;
1c: R^1=H, R^2=Me; **1d**: R^1=Me, R^2=Me.

4

entry	silanes[b]	R	yield, %	syn/anti[c]	ee, %[d]
1	**1a**	Ph	85		87[e]
2	**1a**	2-naphthyl	92		87[e]
3	**1a**	4-$CH_3OC_6H_4$	84		88[e]
4	**1a**	4-$CF_3C_6H_4$	79		80[e]
5	**1a**	(*E*)-C_6H_5CH=CH	86		81[e]
6	**1a**	2-furyl	59		81[e]
7	**1b**	Ph	82	1/99	86[e]
8	**1b**	2-naphthyl	83	1/99	81
9	**1b**	(*E*)-C_6H_5CH=CH	57	1/99	80
10	**1c**	Ph	89	99/1	94[e]
11	**1c**	2-naphthyl	88	99/1	94
12	**1c**	4-$CH_3OC_6H_4$	91	99/1	94
13	**1c**	4-$CF_3C_6H_4$	85	99/1	82
14	**1c**	(*E*)-C_6H_5CH=CH	78	99/1	88
15	**1c**	(*E*)-C_6H_5CH=C(CH_3)	62	95/5	92
16	**1c**	2-furyl	82	99/1	95
17	**1d**	Ph	89		96[e]
18	**1d**	(*E*)-C_6H_5CH=CH	70		88
19	**1d**	2-furyl	71		95

[a] Reactions done at −78 °C for 8−10 h with 5 mol % of **6b**. [b] **1b** and **1c** both >99/1 isomerically pure by ^{1}H NMR analysis. [c] Determined by ^{1}H NMR (400 or 500 MHz) analysis. [d] Determined by CSP-SFC or chiral CSP-GC. [e] Absolute configuration assigned by comparison to the literature value of optical rotation; see Supporting Information.

Scheme 2



In summary we have developed a highly efficient bisphosphoramide catalyst (derived from readily available (*R*,*R*)-2,2′-bispyrrolidine) for the addition of allylic trichlorosilanes to aldehydes. This catalyst effectively promotes the diastereo- and enantioselective addition of various γ-substituted silanes to unsaturated aldehydes at low loadings and in high yield. Further extension of the reaction to aliphatic aldehydes and the application to problems in synthesis are under investigation.

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Supporting Information Available: Full characterization of all catalysts and products, procedures for the preparation of (*R*,*R*)-2,2′-bispyrrolidine, **6a**−**6c**, **7**, (*E*)-**8**, and (*Z*)-**8**, along with a general procedure for the addition reaction (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The preparation of (*R*,*R*)-2,2′-bispyrrolidine was easily accomplished on a large scale by photodimerization of pyrrolidine followed by resolution with tartaric acid; see Supporting Information. For photodimerization of pyrrolidine see: (a) Krajnik, P.; Ferguson, R. R.; Crabtree, R. H. *New J. Chem.* **1993**, *17*, 559. (b) Ferguson, R. R.; Boojamra, C. G.; Brown, S. H.; Crabtree, R. H. *Heterocycles* **1989**, *28*, 121. For resolution of bispyrrolidine see: (c) Oishi, T.; Hirama, M.; Sita, L. R.; Masamune, S. *Synthesis* **1991**, 789. For alternative syntheses see: (d) Alexakis, A.; Tomassini, A.; Chouillet, C.; Roland, S.; Mangeney, P.; Bernardinelli, G. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 4093. (e) Kotsuki, H.; Kuzume, T.; Ghoda, H.; Fukuhara, M.; Ochi, M.; Oishi, T.; Hirama, M.; Shiro, M. *Tetrahedron: Asymmetry* **1995**, *6*, 2227.

(13) It is interesting to note that the X-ray structure of **5d**·$SnCl_4$ also reveals the probable basis for the superiority of the $(CH_2)_5$ tether in that the methylenes can occupy a nicely staggered syn-pentane alignment.

(14) For a review on catalytic enantioselective construction of quaternary centers see: Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 388.

(15) The absolute configuration of the products was assured by X-ray crystallography of the 4-bromobenzoate derivative of the adduct of (*E*)-**8** with 2-naphthaldehyde, see Supporting Information.