Asymmetric Allylation of Aldehydes with Chiral Lewis Bases

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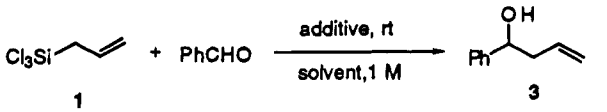
Summary: The asymmetric allylation and crotylation of aromatic aldehydes with allylic trichlorosilanes can be promoted by chiral phosphoramides in high yield and modest enantiomeric excess. The reaction likely proceeds via a hexacoordinate siliconate species.

The asymmetric addition of allylmetal reagents to aldehydes has evolved into a powerful and selective tactic in modern organic synthesis.[1] Among the most common strategies to accomplish asymmetric allylation is the use of reagents in which the metal is ligated by chiral modifiers. This approach has been extensively developed with excellent results for boron[2] and titanium,[3] but with more modest results for silicon[4] and tin.[5,6] The reason for this dichotomy rests squarely in the mechanistic differences in these transformations; i.e., allylboranes and titanium reagents are type 1[7] reagents which react through associative cyclic transition structures while allylsilanes and -stannanes are type 2 reagents which react (under Lewis acid catalysis) through less rigid, open transition structures.[8]

Recently, a number of laboratories have recorded a significant advance in asymmetric additions of allylsilanes[9] and -stannanes[10] by the use of chiral Lewis acid catalysts.[11] While good to excellent enantiomeric excesses have been reported, these transformations are fundamentally less general than type 1 reactions for the introduction of γ-substituted allylic species (i.e., crotylation). We, therefore, sought to develop a catalytic allylation reaction that proceeded through a type 1 pathway and disclose herein preliminary results on the use of chiral *Lewis bases* (phosphoramides) as promoters for the asymmetric allylation and crotylation of aldehydes with allyl- and crotyltrichlorosilanes.

Table 1. Allylation of Benzaldehyde Using Allyltrichlorosilane and Additives



1 3

entry	additive (equiv)	solvent[a]	$t_{1/2}$,[b] min	conversion (time)[b]	yield,[c] %
1	DMF (1)	C_6D_6		83 (70 h)	
2	HMPA (1)	C_6D_6	18		77
3	HMPA (1)	$CDCl_3$		63 (4 min)	85
4	HMPA (1)	CD_3CN		63 (4 min)	86
5	HMPA (0.1)	C_6D_6	529	60 (46 h)	
6	HMPA (0.1)	d_8-THF	350	80 (124 h)	
7	TPPA[d] (1)	C_6D_6	26		71

[a] Reaction run at 1 M concentration. [b] Reaction monitored by ^{1}H NMR. [c] Yield of purified material. [d] Tripiperidinephosphoric triamide.

The addition of allyl- and crotyltrifluorosilanes promoted by fluoride ion as well as catecholates has been extensively developed by Sakurai.[12] The intermediacy of siliconate complexes and closed, type 1 transition states has been convincingly documented.[12–14] Recently, Kobayashi has shown that allyl- (**1**) and crotyl*trichloro*silanes (**2**) can be successfully employed in additions if DMF is used as solvent.[15] They suggest (and NMR experiments support) the role of DMF as a Lewis basic ligand to form the requisite siliconate complex.

To assay the ability of other additives to promote the allylation, we surveyed a variety of Lewis bases as stoichiometric reagents in 1 M solution with **1** and benzaldehyde at room temperature, Table 1. While DMF

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(6) The more common strategy for the Group 14 allylmetals is the use of reagents in which the metal is attached to a stereogenic center. See ref 1a,g for examples.

(7) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655.

(8) (a) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1994**, *59*, 5130. (b) Denmark, S. E.; Hosoi, S. *J. Org. Chem.* **1994**, *59*, 5133.

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(11) For an early example of a chiral Lewis acid promoted addition of an allylalane see: Minowa, N.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3697.

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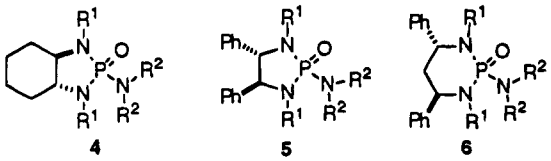
Table 2. Allylation of Benzaldehyde Using Allyltrichlorosilane and Additives[a]



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entry	additive[b]	R^1	R^2	solvent[c]	ee,[d] %
1	**4a**	CH_3	CH_3	THF	59
2	**5**	CH_3	CH_3	CH_2Cl_2	33
3	**6**	CH_3	CH_3	CH_2Cl_2	41
4	**4a**	CH_3	CH_3	CH_2Cl_2	56[e]
5	**4a**	CH_3	CH_3	toluene	54
6	**4a**	CH_3	CH_3	C_2H_5CN	61
7	**4b**	Et	CH_3	CH_2Cl_2	59
8	**4c**	*i*-Pr	CH_3	THF[f]	0
9	**4d**	Bn	CH_3	CH_2Cl_2	31
10	**4e**	CH_2t-Bu	CH_3	THF[f]	NR
11	**4f**	CH_3	*i*-Pr	CH_2Cl_2	17
12	**4g**	CH_3	$-(CH_2)_5-$	CH_2Cl_2	63[g]

[a] All reactions carried out at −78 °C for 6 h. [b] 1 equiv used. [c] 1 M in each component. [d] Determined by GC using Astec B-PA 50 m column. [e] Yield of purified product 78%, $[\alpha]_D = +29.8$ (*c* 2.50, C_6H_6). [f] Reaction run at −78 °C to room temperature. [g] Yield of purified product 85%, $[\alpha]_D = +31.9$ (*c* 2.51, C_6H_6).

is an efficient allylation promoter as solvent, 1 equiv of DMF in benzene is relatively ineffective, requiring 70 h for 83% conversion. The most effective additive examined[16] was HMPA which promoted complete conversion within minutes ($t_{1/2}$ = 18 min), entry 3. A modest solvent effect was noted, and it was found that substoichiometric amounts of HMPA could also promote efficient conversion (entries 5 and 6). The more hindered phosphoramide TPPA was a slightly less potent promoter. Control experiments without additives gave no conversion, clearly showing the lack of uncatalyzed processes.

Having demonstrated the superiority of phosphoramides as allylation promoters, we immediately turned our efforts to a survey of chiral phosphoramide structures.[17-19] These phosphoramides were evaluated for their ability to promote asymmetric allylation of benzaldehyde in stoichiometric amounts using 1 equiv of **1**. The results in Table 2 show that the parent structures **4a**, **5**, and **6** are all more potent than HMPA since the reactions were complete in <6 h at −78 °C. Since **4a** was clearly more enantioselective, we further optimized this structure by evaluating the solvent effect (for **4a**) and changing the R^1 and R^2 groups (**4a**−**g**). The results in Table 2 also show that there is little solvent effect for **4a** (entries 1 and 4−6). More importantly, increasing the bulk of any substituents reduced the rate and/or selectivity of the allylation (entries 7−11). After extensive optimization we found that the piperidine

Scheme 1

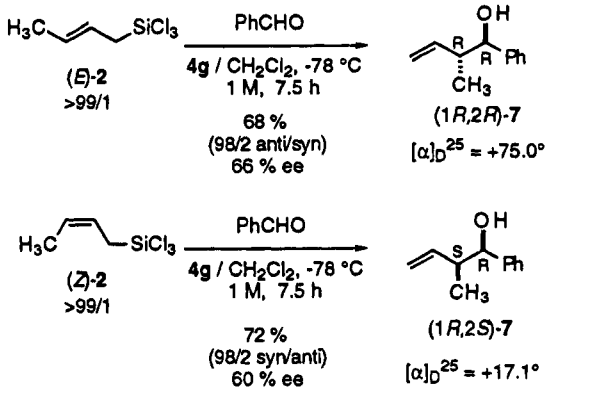
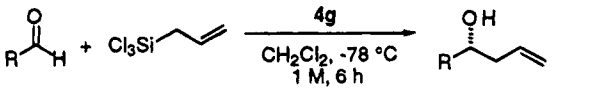


Table 3. Asymmetric Allylation of Selected Aldehydes Using Allyltrichlorosilane and 4g



entry	R	yield,[b] %	ee,[c] % (config)[d]	$[\alpha]_D$[e]
1	C_6H_5	81	60 (*R*)	+31.7 (C_6H_6)[21a]
2	2-MeC_6H_4	81	65 (*R*)[f]	+30.4 (EtOH)
3	4-$NO_2C_6H_4$	76	21 (*R*)	+14.9 (C_6H_6)[21b]
4	4-$MeOC_6H_4$	80	50 (*R*)	+20.2 (C_6H_6)[21c]
5	4-$NMe_2C_6H_4$	69	33 (*R*)[f]	+5.4 (EtOH)
6	PhCH=CH	67	38 (*R*)	+6.1 (C_6H_6)[21d]

[a] All reactions carried out at −78 °C for 6 h with 1 equiv of **4g**, 0.5 M in each component. [b] Yield of analytically pure product. [c] Determined by HPLC analysis employing either a Diacel Chiracel OD or AD column. [d] Assignment by comparison to literature $[\alpha]_D$ values. [e] Observed rotations and literature references. [f] Assignment by analogy.

derivative **4g** was marginally superior to **4a**. The absolute configuration of the major enantiomer from (*R*,*R*)-**4g** was established to be (+)-(*R*)-**3** by comparison to the literature rotation.[2a,b,3a] Surprisingly, allyltrifluorosilane (93% yield, 10% ee), allyltrichlorostannane (51% yield, 16% ee), and methallyltrichlorosilane (90% yield, 14% ee), all participated effectively in promoted allylations at −78 °C, but with poor selectivities.

To establish that the phosphoramide-promoted process is mechanistically related to the previously described reactions of haloallylsilanes, we carried out asymmetric crotylations of benzaldehyde with (*E*)- and (*Z*)-2-propenyltrichlorosilanes, (*E*)-**2** and (*Z*)-**2**,[12c] using **4g** as the promoter, Scheme 1. The reactions proceeded smoothly at −78 °C to afford the known homoallylic alcohols with 98/2 diastereoselectivity and similar levels of enantioselectivity as in the allylation.[20] The sense of internal stereoinduction ((*E*)-**2** to *anti*-**7**, (*Z*)-**2** to *syn*-**7**) clearly supports the intermediacy of a siliconate complex and reaction via a hexacoordinate silicon species. The absolute configurations of (1*R*,2*R*)-**7** and (1*R*,2*S*)-**7** were established by comparison to literature rotations.[20] The stereochemical outcome at the hydroxy center in all reactions is consistent with a common cyclic siliconate transition structure.

The generality of the reaction using **4g** (1 equiv, CH_2Cl_2, −78 °C, 6 h) was briefly surveyed for aldehyde structure. While aliphatic aldehydes reacted sluggishly, aromatic aldehydes underwent allylation in good yields but with variable selectivity, Table 3. The rate and

(16) Other additives examined (DMSO and pyridine *N*-oxide) were incompatible with **1**.

(17) A variety of phosphoramide, phosphoramidate, phosphonamide, phosphine, and phosphine oxides were surveyed, and the results will be detailed in a full account.

(18) The diamines were prepared by literature procedures. (a) Hanessian, S.; Delorme, D.; Beaudoin, S.; LeBlanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754. (b) Mangeney, P.; Tejero, T.; Alexakis, A.; Grosjean, F.; Normant, J. *Synthesis* **1988**, 255. (c) Denmark, S. E., Kim, J.-H. *Synthesis* **1992**, 229. (d) The enantiomeric purity of (*R*,*R*)-cyclohexane-1,2-diamine used for the preparation of all derivatives of **4** was shown to be >99% by chiral HPLC analysis of the derived bis-(*m*-toluamide).

(19) The phosphoramides were prepared from the chiral diamine with corresponding phosphoramic dichlorides in the presence of triethylamine, as described by: Setzer, W. N.; Black, B. G.; Hovanes, B. A.; Hubbard, J. L. *J. Org. Chem.* **1989**, *54*, 1709.

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Table 4. Asymmetric Allylation of Benzaldehyde with 1 Using Substoichiometric Amounts of 4g[a]

entry	equiv of **4g**	time, h	yield,[b] %	ee,[c] %
1	1.0	6	81	60
2	0.5	24	78	57
3	0.25	24	74	59
4	0.1	24	40	53

[a] All reactions carried out at −78 °C for 24 h 0.5 M in each component. [b] Yield of isolated purified product. [c] Determined by GC using Astec B-PA 50 m column.

selectivity of allylation of benzaldehyde was not influenced by the addition of 2,6-*tert*-butylpyridine, thus ruling out catalysis by adventitious acid. Both electron-donating and electron-withdrawing substituents dramatically reduced selectivity (entries 3−5) while steric effects (entry 2) had little influence. The absolute configurations of the homoallylic alcohols were consistent for all substrates as established by comparison to literature values.[21]

Finally, the potential for catalysis has been demonstrated using substoichiometric quantities of **4g** by allowing the reactions to run for 24 h at −78 °C. With as little as 25 mol % (entry 3) the yield is only slightly eroded and the enantioselectivity essentially the same.

In summary, the potential for nucleophilic catalysis in asymmetric allylations with chiral Lewis bases has been demonstrated. The yields are good, but enantioselectivities are still modest. Since the reactions most likely proceed through closed transition structures involving hexacoordinate siliconates, modification of the promoter structure to improve selectivity can be rationally based and is underway.

Acknowledgment. We are grateful to the National Science Foundation (NSF CHE 9121631) for support of this research. D.M.C. thanks the Fulbright Commission for a travel grant.

Supplementary Material Available: Preparation and full characterization of **4a**, **4g**, and all homoallylic alcohols along with a representative allylation procedure are provided (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(21) (a) Reference 2a: $[\alpha]^{20}_D$ −17.48 (c = 7.38, C_6H_6) for 30% ee (*S*). (b) Reference 11: $[\alpha]^{25}_D$ −19.3 (c = 2.14, C_6H_6) for 84% ee (*S*). (c) Reference 11: $[\alpha]^{23}_D$ −65.8 (c = 3.56, C_6H_6) for 80% ee (*S*). (d) Reference 2a: $[\alpha]^{20}_D$ +3.6 (c = 10.08, Et_2O) for 24% ee (*S*).