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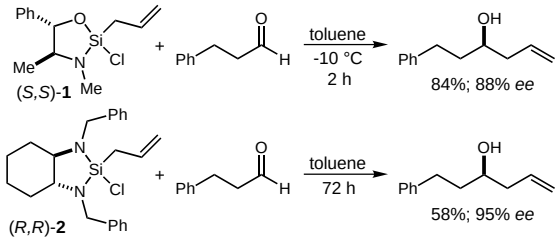
Allylation of Aldehydes

A Highly Practical and Enantioselective Reagent for the Allylation of Aldehydes**

*Katsumi Kubota and James L. Leighton**

Owing mainly to the prevalence of secondary alcohols in bioactive natural products, chemists have developed many moderately to highly enantioselective chiral reagents[1] and catalytic systems[2] for the allylation of aldehydes. In terms of practical utility, an ideal reagent should 1. be readily prepared in both enantiomeric forms, 2. be a stable/storable solid that can be prepared in bulk and employed at will by using only trivial procedures, 3. possess a good safety profile both for the user and environmentally, and 4. be generally effective in terms of both efficiency and enantioselectivity. Herein we report a new reagent that almost completely satisfies all of these conditions.

Based on our discovery that silicon—constrained in a five-membered ring by 1,2-diols, 1,2-aminoalcohols and 1,2-diamines—possesses Lewis acidity sufficient for clean, uncatalyzed allylation of aldehydes, we recently described the pseudoephedrine-derived strained silacycle **1** as a reagent for the enantioselective allylation of aldehydes (Scheme 1).[3] Whereas this reagent is trivially prepared and employed, and the enantioselectivities for aliphatic aldehydes are good (87–89% *ee*, typically), they are unacceptably low for aromatic and conjugated aldehydes (60–81% *ee*, typically). This reagent thus falls short of ideal mainly in terms of condition 4 (see above). Also reported were preliminary data regarding reagent **2**, which was found to provide improved enantioselectivity, but also low reactivity. We therefore initiated a full investigation into the potential of the diamine-based system.



Scheme 1. Reagents for asymmetric allylation.

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[**] Financial support was provided by the Sumitomo Corp. (postdoctoral support of K.K.). We thank Merck Research Laboratories for generous financial support. J.L.L. is a recipient of a Pfizer Award for Creativity in Organic Chemistry.

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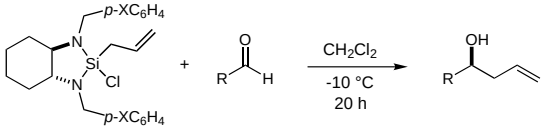
We began by optimizing the performance of reagent **2**, and were surprised to find that the use of CH_2Cl_2 as solvent led to a substantial increase in both efficiency and enantioselectivity (Table 1, entries 1 and 2), a result that did not hold for reagent **1**. With optimal conditions identified, the bis-(*p*-methoxybenzyl) and bis-(*p*-bromobenzyl) analogues of **2** were prepared[4] and screened for any effect on efficiency and selectivity. Interestingly, the latter sytem did provide a small but significant increase in efficiency and enantioselectivity with an aliphatic aldehyde (entry 1 versus entry 4) and with benzaldehyde (entry 2 versus entry 5). Perhaps more importantly, the bis-(*p*-bromobenzyl) substituted reagent is a moderately air-stable solid, and it was therefore selected for further study.

Table 1: Optimization of the diamine auxiliary.

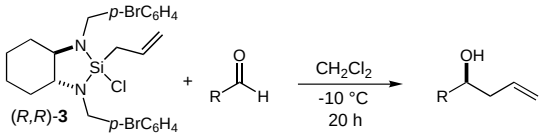


Entry[a]	X	R	Yield [%][b]	*ee* [%][c]
1	H	$PhCH_2CH_2$	79	96
2	H	Ph	61	94
3	OMe	$PhCH_2CH_2$	77	98
4	Br	$PhCH_2CH_2$	90	98
5	Br	Ph	69	98

[a] Reactions run with silane (1.0 equiv) and aldehyde (1.0 equiv) in CH_2Cl_2 at −10 °C for 20 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis or by the Mosher ester method. See the Supporting Information.

With the bis-(*p*-bromobenzyl)–diamine system identified as the most effective and convenient system, we examined the scope of the reaction (Table 2). With respect to aliphatic aldehydes reagent **3** is generally effective and provides good to excellent yields and uniformly excellent enantioselectivities that are among the highest observed for this reaction. The conditions were carefully optimized to maximize yield and enantioselectivity. Reactions at room temperature are only slightly less selective, but the yields are significantly lower because of partial decomposition of the reagent.

Table 2: Enantioselective allylation of aliphatic aldehydes.

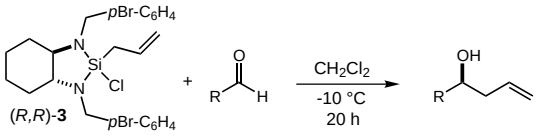


Entry[a]	R	Yield [%][b]	*ee* [%][c]
1	$PhCH_2CH_2$	90	98
2	$(CH_3)_2CHCH_2$	80[d]	96
3	*c*Hex	93	96
4	$PhCH_2OCH_2$	67	97
5	$PhCH_2OCH_2CH_2$	87	98
6	*t*$BuMe_2SiOCH_2$	61	98

[a] Reactions run with silane **3** (1.0 equiv) and aldehyde (1.0 equiv) in CH_2Cl_2 at −10 °C for 20 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis or by the Mosher ester method. See the Supporting Information. [d] Because of product volatility, an alternative workup and purification was employed. See the Supporting Information.

We next turned to an investigation of the scope with respect to aromatic and conjugated aldehydes, a substrate class for which reagent **1** proved ineffective. A series of benzaldehydes were treated with reagent **3** and in every case moderate to good yields and excellent enantioselectivities could be obtained (Table 3, entries 1–3). Interestingly, *p*-anisaldehyde required 60 h to give a similar yield to that obtained with benzaldehyde and *p*-trifluoromethylbenzaldehyde after 20 h. Conjugated aldehydes proved less efficient still, but when the reaction was carried out at 8 °C for 72 h good yields and excellent enantioselectivities could be obtained (entries 4 and 5).

Table 3: Enantioselective allylation of aromatic and conjugated aldehydes.

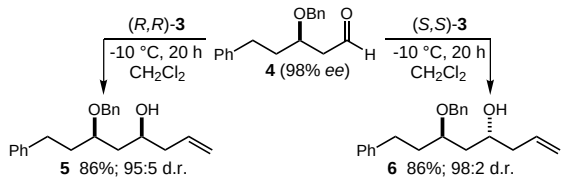


Entry[a]	R	Yield [%][b]	*ee* [%][c]
1	Ph	69	98
2[d]	*p*-$MeOC_6H_4$	62	96
3	*p*-$CF_3C_6H_4$	66	96
4[e]	(*E*)-PhCH=CH	75	96
5[e]	(*E*)-*n*PrCH=CH	71[f]	95

[a] Reactions run with silane **3** (1.0 equiv) and aldehyde (1.0 equiv) in CH_2Cl_2 at −10 °C for 20 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis or by the Mosher ester method. See the Supporting Information. [d] Reaction run for 60 h. [e] Reaction run at 8 °C for 72 h. [f] Because of product volatility, an alternative workup and purification was employed. See the Supporting Information.

Especially in the context of applications in natural product synthesis, it was also of interest to investigate the use of reagent **3** with chiral aldehydes as the ability of this reagent to override any inherent substrate bias would add to its utility. Subjection of aldehyde **4** (98 % *ee*) to the standard allylation conditions with (*R,R*)-**3** gave protected *syn*-alcohol **5** in 86 % yield and 95:5 d.r. (Scheme 2). Subjection of aldehyde **4** (98 % *ee*) to the standard allylation conditions with the enantiomeric reagent (*S,S*)-**3** gave protected *anti*-alcohol **6** in 86 % yield and 98:2 d.r. Thus, although the expected substrate bias for 1,3-*anti* induction[5] was observed, excellent selectivity for either diastereomer may be achieved.

We have described a new reagent for the highly enantioselective allylation of a broad range of aldehydes. While the



Scheme 2. Asymmetric allylation of chiral aldehydes.

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reaction time (typically 20 h) would ideally be shorter, and aromatic and conjugated aldehydes tend to require even longer reaction times (Table 3), the four conditions for an ideal reagent outlined above have otherwise been met fully. In this context it is especially noteworthy, and bears repeating, that reagent **3** is a readily prepared stable solid that may be briefly handled in air with no apparent decomposition, and may be stored in a freezer under N_2 or Ar for long periods of time (> 1 month). Investigations into the mechanistic basis for the sluggish reactivity of some aromatic and conjugated aldehydes and a method to overcome this limitation have been initiated.

Experimental Section

Preparation of reagent (*R,R*)-**3**: To a cooled (0 °C) solution of allyltrichlorosilane (2.05 mL, 14.1 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (4.24 mL, 28.4 mmol) in dichloromethane (50 mL) was added (*R,R*)-*N,N′*-bis-(4-bromobenzyl)cyclohexane-1,2-diamine (5.37 g, 11.9 mmol) in dichloromethane (20 mL) over 50 min. After 2 h, the mixture was warmed to room temperature, and was stirred for 13 h. The reaction mixture was concentrated. After diethyl ether (60 mL) was added, the mixture was stirred for 1 h and filtered through a pad of celite, and the residue was washed with diethyl ether (2 × 10 mL). The filtrate was concentrated. Benzene (10 mL) was added, and the solution was concentrated. This procedure was repeated to give the product as an oil (5.37 g, 88 %). Upon standing (under Ar) in a freezer, the oil solidified to a white solid that may be stored in a freezer (under Ar) and used as needed. ^{1}H NMR (300 MHz, C_6D_6): $\delta = 7.43$ (d, $J = 8.4$ Hz, 2H; Ar-H), 7.42 (d, $J = 8.4$ Hz, 2H; Ar-H), 7.18 (d, $J = 8.5$ Hz, 2H; Ar-H), 7.17 (d, $J = 8.5$ Hz, 2H; Ar-H), 5.72 (m, 1H; C*H*=CH_2), 5.00–4.92 (m, 2H; CH=CH_2), 3.98 (d, $J = 16.2$ Hz, 1H; one of NCH_2Ar), 3.95 (d, $J = 15.1$ Hz, 1H; one of NCH_2Ar), 3.65 (d, $J = 15.1$ Hz, 1H; one of NCH_2Ar), 3.64 (d, $J = 16.2$ Hz, 1H; one of NCH_2Ar), 2.63–2.75 (m, 2H; two of C*H*N), 1.42–1.79 (m, 6H; four of Cy and SiCH_2CH=CH_2), 0.83–1.05 ppm (m, 4H; four of Cy); ^{13}C NMR (75 MHz, C_6D_6): $\delta = 141.7$, 140.7, 131.7, 131.4, 130.3, 129.5, 128.7, 121.2, 120.9, 116.6, 66.8, 65.8, 48.3, 47.5, 31.1, 30.7, 25.1, 25.0 ppm; ^{29}Si NMR (60 MHz, C_6D_6): $\delta = -4.4$ ppm.

General procedure for the reaction of (*R,R*)-**3** with aldehydes: To a cooled (−10 °C) solution of (*R,R*)-**3** in CH_2Cl_2 (0.2 M) was added the aldehyde (1.0 equiv). The reaction mixture was transferred to a freezer (−10 °C) and maintained at that temperature for 20 h. To this cooled solution was added 1N HCl and EtOAc, and the mixture was vigorously stirred at room temperature for 15 min. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic layers were diluted with hexane, dried ($MgSO_4$), filtered, and concentrated. The homoallylic alcohol products may be purified further by chromatography on silica gel. All yields listed in Tables 1–3 are for chromatographed, analytically pure material.

Received: October 24, 2002 [Z50425]

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One-Step Route to Tetrahydrofurans

A General Oxidative Cyclization of 1,5-Dienes Using Catalytic Osmium Tetroxide**

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The oxidative cyclization of 1,5-dienes to produce tetrahydrofurans has been known for some time, and is a unique method for making these heterocycles. The reaction is

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[**] We thank the EPSRC and Merck, Sharp, and Dohme for funding this project. AstraZeneca, GlaxoSmithKline, Pfizer, and Novartis are thanked for unrestricted donations.

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