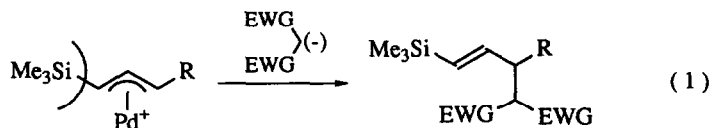# A Regiochemical Control in the π-Allylpalladium Substitution. Preparation of Optically Active γ-Silylallylamines

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Abstract: Optically active γ-trimethysilylallylamine derivatives were prepared from γ-trimethylsilylallyl alcohols via i. derivatization to carbonates and ii. palladium-catalyzed, regioselective allylic substitution by nitrogen nucleophiles without loss of the enantiomeric purities of the starting alcohols.

Control of regiochemistry in allylic systems is a long-standing, inevitable problem when allylic substitution is being attempted.[1] Palladium-catalyzed allylic substitution[2] is one of the most useful methodologies owing to its mild reaction conditions, but is not free from the above problem. A most straightforward devise seems to be the one that a sterically demanding group at one terminus of the allyl system blocks the incoming nucleophile. In fact, bulky trimethylsilyl group has been reported to fulfill such a purpose in the reaction with active methylene compounds (eq 1).[3] However, more extensive studies dealing with

$$Me_3Si \overset{}{\underset{Pd^+}{\diagup\!\!\diagdown}} R \quad \xrightarrow[EWG]{\overset{EWG}{\diagdown}(-)} \quad Me_3Si \diagdown\!\diagup\!\diagdown^R \underset{EWG \quad EWG}{} \qquad (1)$$

nucleophiles other than active methylenes or the optically active starting materials have not appeared even though such precedents will be very helpful in construction of complex molecules. Considering the synthetic versatility of vinylsilanes, we wish to disclose here that substitution of the hydroxy group of optically active γ-trimethylsilylallyl alcohols **1** with a few nitrogen nucleophiles proceeds in a highly regioselective manner to give γ-silylallylamines and their derivatives with virtually complete retention of configuration (eq 2).[4]

Optically active γ-trimethylsilylallyl alcohols **1**[5] were prepared by the kinetic resolution in the Sharpless epoxidation[6] and were converted to carbonates **2** in a standard manner. These carbonates were treated with a few nitrogen nucleophiles such as benzylamine (BnNH2), *p*-toluenesulfonamide (TsNH2), and azide in the presence of a palladium catalyst as shown in eq 2.[7] The results are summarized in Table 1.[8] Of a few palladium catalysts and solvents examined, Pd2(dba)3·CHCl3-PBu3 in CH3CN was critical for the

Table 1. Preparation of γ-Silylallylamines and Their Derivatives.[a]

$$Me_3Si\diagdown\diagup\diagdown^R_{OX} \quad \xrightarrow[\text{Pd catalyst}]{\text{[N]H or [N]}^-} \quad Me_3Si\overset{\gamma}{\diagdown}\diagup\diagdown^{\alpha}_{[N]}R \quad (2)$$

1 X = H	a(R) R = C_5H_{11}	3 [N] = BnNH
2 CO_2Me	b(R) ^iBu	4 TsNH
(>99%ee)	c(S) c-C_6H_{11}	5 N_3
	d(R) Ph	

Entry	[N]H or [N]$^-$	2	Conditions	Product	Yield (%)[b]	α : γ[c]	Ee (%)[d]
1	$BnNH_2$	a	55 °C; 17 h	3a	82-99	>99 : <1	>98(R)
2		b	65 °C; 26 h	3b	53-83	>99 : <1	>98(R)
3		c	65 °C; 48 h	3c	32[e]	>97 : <3	90[f]
4		d	55 °C; 17 h	3d	78	>95 : <5	98[g](R)
5	$TsNH_2$	a	75 °C; 12 h	4a	76-84	97 : 3	>98(R)
6		b	80 °C; 18 h	4b	43-61	83 : 17[h]	>98[f]
7	NaN_3	a	r.t.; 24 h	5a	63[i]	>95 : <5	>98(R)
8	Me_3Si⌒⌒⌒⌒ MeOCOO NHBoc **6**		55 °C; 5 h	Me_3Si⌒⌒⌒⌒ BocN—⌒ **7**	85	--	87[f]

[a]A mixture of 2, [N]H or [N]$^-$ (3-5 equiv), $Pd_2(dba)_3$·$CHCl_3$ (2 mol%) and PBu_3 (16 mol%) was heated in CH_3CN unless otherwise noted. See ref 8 for a typical procedure. [b]Isolated, combined yield of the regioisomers. [c]Determined by ^{1}H nmr analysis of a crude sample (entries 1, 5, and 6) or an isolated product (others). In the latter case there was no evidence that the regioisomers were separated during the isolation. [d]Ee of the major isomer determined by ^{1}H nmr (3: derivatization to mandelic acid salt (ref 9); 4 and 7: chiral shift study with Eu(hfc)$_3$; or 5: derivatization to 4 (i. PPh$_3$ (ref 10); ii. TsCl) followed by chiral shift study as above) and absolute configuration shown in parentheses. [e]The Pd catalyst (4 mol%) and PBu$_3$ (32 mol%) were used. The formation of (3-trimethylsilylpropenylidene)cyclohexane (11%) was also detected. [f]Absolute configuration should be consistent with the overall retention of configuration based on analogy. [g]This value refers to optical purity after derivatization to known (R)-methyl N-benzoyl-N-benzylphenylglycinate (ref 11). [h]One recrystallization from hexane increased the α/γ ratio to be 95:5. [i]Reaction performed with the Pd catalyst (2 mol%) and PBu$_3$ (8 mol%) in THF-H_2O (2:1).

satisfactory results. Under these conditions, allylic carbonates 2a and b afforded allylic amines 3 in excellent yields. However, the carbonate 1c with a bulkier substituent R was found to become less reactive to show decrease in the product yield even under the forcing conditions (cf. entries 1-3). In the latter case (entry 3), the high optical purity of the starting material was no longer retained in the product 3c. Carbonate 2d which is prone to afford the product having the olefin conjugated with the phenyl group did selectively give the unconjugated product 3d, showing the prevailing effect of the silyl group over phenyl as a regiocontrolling element. The absolute stereochemistries of 3a, b, and d correlated to those of authentic samples by

appropriate derivatizations are consistent with the prediction based on the known reaction mechanism.[4] The same tendency has been seen in the reactions of *p*-toluenesulfonamide in place of benzylamine (entries 5 and 6). The olefinic moieties in the products were fixed exclusively in *trans* and the desilylative substitution as reported in the reactions with active methylene compounds[3a,c] was not observed. In contrast to the above two nucleophiles low reactivities were encountered with NaN_3 or $BocNH_2$, though the yield of the reaction with the former still fell within an acceptable range when the reaction was carried out in aqueous THF (entry 7). Although $BocNH_2$ did not participate in the intermolecular reaction at all, it did in an intramolecular version to afford 5-membered heterocyclic compound in good yield (entry 8) without the formation of the diene via β-elimination (cf. entry 3).

The γ-trimethylsilylallylamine derivatives are versatile precursors of substituted allylamines as illustrated in Scheme 1. For instance, epoxidation of **4a** with m-CPBA afforded a 3:1 isomeric mixture of the epoxysilanes **6**[12] which was converted to *trans*-γ-cyano- (**7**), *trans*-γ-tributylstannyl- (**8**), or *trans*-γ-alkyl-allyl sulfonamide (**9**) in good yields, while bromination of **4a** followed by elimination of Me_3SiBr with Bu_4NF gave *cis*-γ-bromoallyl sulfonamide (**10**).[13] The high ee's (>98%) retained in the products **7-10** have been verified in each case. These allylamine derivatives having reactive functional groups should find wide use in organic synthesis.[14]
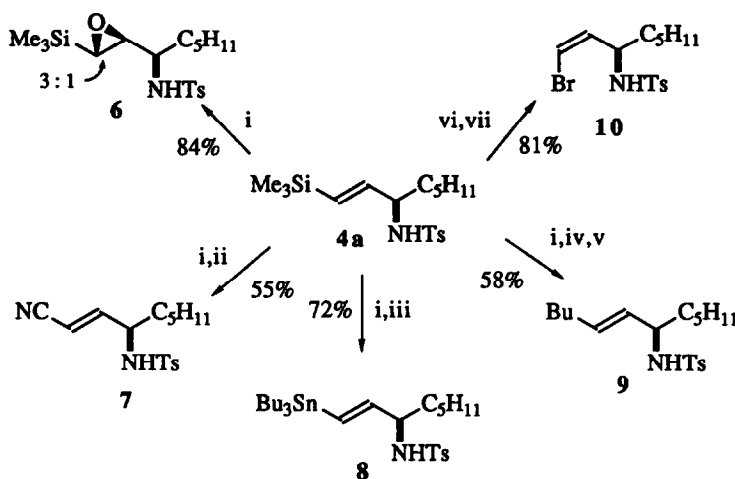
Scheme 1[a]

[a]i. m-CPBA, CH_2Cl_2, r.t.; ii. Et_2AlCN, THF, 0 °C→r.t.; iii. Bu_3SnLi, THF, -78

In summary, a preparation of highly optically active γ-trimethylsilylallylamines and their equivalents (**3-5**) has been reported, in which the silyl group plays a triple role: i. to effect the highly efficient kinetic resolution of the starting alcohol **1**; ii. to allow the regioselective introduction of the amine functionalities, and iii. to enable facile conversions to a variety of γ-functionalized derivatives (**6-10**).

REFERENCES AND NOTES

1. Review: Magid, R.M. *Tetrahedron* **1980**, *36*, 1901.
2. Reviews: Trost, B.M. *Tetrahedron* **1977**, *33*, 2615; Trost, B.M. *Acc. Chem. Res.* **1980**, *13*, 385; Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer Verlag: Berlin, 1980; Trost, B.M.; Verhoeven, T.R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F.G.A.; Abel, E.W., Eds.; Pergamon Press: Oxford, 1982; Vol. 8, p 799; Trost, B.M. *Angew. Chem. Int. Ed. Engl.* **1988**, *28*, 1173; Frost, C.G.; Howarth, J.; Williams, J.M.J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089.
3. (a) Tsuji, J.; Yuhara, M.; Minato, M.; Yamada, H; Sato, F.; Kobayashi, Y. *Tetrahedron Lett.* **1988**, *29*, 343; see also (b) Hirao, T.; Enda, J.; Ohshiro, Y.; Agawa, T. *Tetrahedron Lett.* **1981**, *22*, 3079; (c) Trost, B.M.; Self, C.R. *J. Am. Chem. Soc.* **1983**, *105*, 5942; (d) Kang, J.; Cho, W.; Lee, W.K. *J. Org. Chem.* **1984**, *49*, 1838.
4. For stereochemical outcome in the reaction of π-allylpalladium species: see ref 2 and the following. Review: Consiglio, G.; Waymouth, R.M. *Chem. Rev.* **1989**, *89*, 257; Hayashi, T.; Yamamoto, A.; Hagihara, T. *J. Org. Chem.* **1986**, *51*, 723; Uemura, M.; Minami, T.; Hayashi, Y. *Tetrahedron Lett.* **1988**, *29*, 6271; Zhou, B.; Xu, Y. *J. Org. Chem.* **1988**, *53*, 4419; Tanikaga, R.; Jun, T.X.; Kaji, A. *J. Chem. Soc., Perkin Trans 1* **1990**, 1185.
5. Kitano, Y.; Matsumoto, T.; Sato, F. *Tetrahedron* **1988**, *44*, 4073. Both enantiomers of 1 are readily available.
6. Reviews: Finn, M.G.; Sharpless, K.B. In *Asymmetric Synthesis*; Morrison, J.D., Ed.; Academic Press: New York, 1985; Vol. 5, p 247; Pfenninger, A. *Synthesis* **1986**, 89; Jonson, R.A.; Sharpless K.B. In *Comprehensive Organic Synthesis*; Trost, B.M., Ed.; Pergamon Press: Oxford, 1991; Vol. 7, Chapter 3-2.
7. Reaction of π-allylpalladium intermediates with nitrogen nucleophiles: (a) amine: Trost, B.M.; Keinan, E. *J. Org. Chem.* **1979**, *44*, 3451; (b) sulfonamide: Byström, S.E.; Aslanian, R.; Bäckvall, J.-E. *Tetrahedron Lett.* **1985**, *26*, 1749; (c) azide: Murahashi, S.-I.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54*, 3292; (d) amide: Takagi, M.; Yamamoto, K. *Chem. Lett.* **1989**, 2123; Inoue, Y.; Taguchi, M.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2721; (e) imide: Inoue, Y.; Taguchi, M.; Toyohuku, M.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3021; Connell, R.D.; Rein, T.; Åkermark, B.; Helquist, P. *J. Org. Chem.* **1988**, *53*, 3845; (f) hydroxylamine: Murahashi, S.-I.; Imada, Y.; Taniguchi, Y.; Kodera, Y. *Tetrahedron Lett.* **1988**, *29*, 2973.
8. Preparation of 3a is typical. To a solution of Pd2(dba)3·CHCl3 (4.1 mg, 0.0039 mmol) in CH3CN (1.5 mL) under nitrogen was added PBu3 (0.0078 mL, 0.031 mmol) at r.t. The mixture was stirred at r.t. for 30 min during which period the color of the solution turned from dark violet to light yellow. Carbonate 2a (50 mg, 0.193 mmol) in 0.5 mL of CH3CN was then added, followed by benzylamine (0.064 mL, 0.580 mmol) after a 10-min interval. After stirred at r.t. for 10 min, the mixture was heated in an oil bath maintained at 55 °C for 17 h. The solution was diluted with ether, washed successively with saturated NaHCO3 solution and brine, dried (Na2SO4), and concentrated to give a crude oil, ^{1}H nmr analysis of which showed the absence of another regioisomer, confirming α/γ ratio to be >99:<1. Purification of the crude product on silica gel (ether-hexane) afforded the title compound 3a (55.3 mg, 99%) as an oil. [1]H nmr analysis of this sample in the presence of mandelic acid (2 equiv)[9] in CDCl3 determined its ee to be >98% and the absolute configuration by comparison with an authentic sample.
9. Benson, S.C.; Cai, P.; Colon, M.; Haiza, M.A.; Tokles, M.; Snyder, J.K. *J. Org. Chem.* **1988**, *53*, 5335.
10. Knouzi, N.; Vaultier, M.; Carrie, R. *Bull. Soc. Chim. Fr.* **1985**, 815.
11. Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301.
12. The *syn* structure is tentatively assigned to the major isomer based on analogous cases. See: Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1984**, *25*, 1587; Luly, J.R.; Dellaria, J.F.; Plattner, J.J.; Soderquist, J.L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487.
13. Review: Sato, F.; Kobayashi, Y. *Synlett* **1992**, 849.
14. Hauske, J.R.; Dorff, P.; Julin, S.; Martinelli, G.; Bussolari, J. *Tetrahedron Lett.* **1992**, *33*, 3715 and references cited therein.