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Synthesis of optically active tertiary silanes *via* Pd-catalyzed enantioselective arylation of secondary silanes[†]

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We herein describe the development of an efficient enantioselective catalytic system that promotes the arylation of secondary silanes. Our method involves treatment of secondary silanes and aryl iodides with a $Pd_2(dba)_3$ -asymmetric phosphoramidite ligand system to afford optically active tertiary silanes with good enantioselectivities.

Optically active organosilicon compounds containing a stereogenic tetrahedral silicon atom are promising for use as chiral auxiliaries, reagents, resolving agents, and drug candidates.¹ Although considerable effort has been devoted to the preparation of optically active silanes, most studies have centered on optical resolution (Fig. 1a).² The development of an asymmetric catalytic process that yields stereogenic silanes is therefore expected to enhance the potential of the synthetic tool. Many reports have demonstrated transition metal-catalyzed Si–H functionalization as a direct and effective method for the preparation of optically active organosilicon compounds through carbenoid insertion,³ hydrosilylation,⁴ reduction,⁵ and so on.⁶ However, most of them are on the construction of the chirality on backbone carbon, and there are a limited number of reports on the construction of chiral silicon centers using a catalyst.⁷

Hydrosilanes are useful reducing agents in the presence of transition metals. In particular, the reduction of aryl halides with hydrosilanes has been widely investigated.⁸ We and other groups have shown that hydrosilanes do not always act as reducing agents; *i.e.* we demonstrated that aryl iodides induced arylation of hydrosilanes with the aid of transition metal complexes.^{9,10} In the present study, we describe the enantioselective arylation of prochiral secondary silanes using an asymmetric Pd complex (Fig. 1b). This versatile enantioselective arylation reaction of secondary silanes is a valuable addition to existing methodologies for the preparation of optically active tertiary silanes.

To tune product enantioselectivity through ligand design, we first examined the reaction of methylphenylsilane and 2-iodoanisole in the presence of various phosphine ligands and $Pd_2(dba)_3$ catalyst. Initially, axially asymmetric MeO–MOP

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Fig. 1 Preparation of optically active tertiary silanes. (i) Optical resolution.(ii) Reduction with LiAlH₄. (iii) Asymmetric transition metal catalyst.

((2-diphenylphosphino)-2'-methoxy-1,1'-biphenyl) did not demonstrate reactivity and enantioselectivity (4% yield, 3% ee).¹¹ In contrast, TADDOL-based phosphoramidite (R,R)-1 afforded products in high yield with moderate enantioselectivity (Table 1, entry 1).^{12–15} Not only can TADDOL-based phosphoramidites be readily synthesized by published methods, but such compounds also possess modular properties that allow for fine-tuning of their steric and electronic characteristics. The results of ligand modification are provided in Table 1. The steric bulk of amine evidently has a significant impact on enantioselectivity (entries 1-4). The effect of varying the aromatic group of the TADDOL moiety was also subsequently examined (entries 1 and 5-8). The electron-rich 3,5-diethylphenyl TADDOLbased phosphoramidite (R,R)-6 ligand displayed the best performance for this transformation. These results show that the steric and electronic effects of the aromatic group on the TADDOL moiety play a significant role in determining enantioselectivity. The low yield of this reaction is attributed to the undesired reaction of the aryl iodide by the secondary silane. By decreasing the reaction temperature, however, such decompositions or reductions could be suppressed and the enantioselectivity slightly improved. The reaction did though require longer time to reach completion at reduced temperature (entries 9 and 10).

Under the optimized reaction conditions, a wide range of substrates was tested in order to determine the scope of this reaction. As depicted in Table 2, Pd-catalyzed arylation of secondary silanes proceeds in an enantioselective fashion.

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Table	1 Optin	nization of the r	reaction	conditio	ns ^a	
		¹ Pd ₂ (dba) ₃ / L*			L* : Ar	→ Ar O
		Et ₃ N, THF	Si 9	CH3	Ar	→P−X →O Ar
Entry	Ar	Х	Temp/	°C Time	e/d Yield	$(\%) ee^{b} (\%)$
1	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	₹—N (<i>R</i> , <i>R</i>)-1	20	2	92	36
2		$\sum_{(R,R)-2}^{\xi-N}$	20	2	43	21
3		ξ—Ν (<i>R</i> , <i>R</i>)- 3	20	2	53	20
4	ş.	$\left \begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$	20	2	14	4
5	¥{	(<i>R</i> , <i>R</i>)-5	20	2	53	51
6	ţ-{	(<i>R</i> , <i>R</i>)-6	20	2	35	54
7	ş—	0	20	2	65	39
8	ş{	CF ₃ CF ₃ (<i>R</i> , <i>R</i>)-8	20	2	28	<1
9 10	(<i>R</i> , <i>R</i>)-6 (<i>R</i> , <i>R</i>)-6		0 - 40	2 3	64 57	57 61

^{*a*} The reaction was carried out with methylphenylsilane (1.5 mmol), 2-iodoanisole (1.0 mmol), triethylamine (3.0 mmol), $Pd_2(dba)_3$ (0.025 mmol), and L* (0.075 mmol) in THF (2.0 mL). ^{*b*} Determined by chiral HPLC analysis employing a chiral stationary phase.

These results indicate that the substitution pattern of the substituent on the phenyl ring of aryl iodides has a major effect on the enantioselectivity. Low asymmetric yields were achieved with m- and p-substituted aryl iodides (entries 2 and 3). However, alkylarylsilanes with o-substituted aryl iodides afforded useful chemical and asymmetric yields (entries 4–11). In contrast, the corresponding monoarylated products of diarylsilane and dialkylsilane could only be synthesized in moderate

 Table 2
 Catalytic enantioselective arylation of secondary silanes^a

R ¹ -	H Si-H R ²	+	I—Ar –	Pd ₂ (dl (<i>R,R</i>) Et ₃ N, ⁻	0a) ₃)- 6 ⊤HF		Ar R ¹ -Si [*] -H R ²
Entry	R^1	R^2	Ar	°C	Product	Yield (%)	$ee^{b,c}$ (%)
1	Ph	Me	2-MeOC ₆ H ₄	-40	9	57	$61(+,S)^d$
2	Ph	Me	3-MeOC ₆ H ₄	-40	10	29	23 (-)
3	Ph	Me	4-MeOC ₆ H ₄	-40	11	16	8 (-)
4	Ph	Me	2-MeC ₆ H ₆ H ₄	-40	12	44	$58 (-, S)^d$
5	Ph	Me	$2,3-Me_2C_6H_4$	-40	13	36	67(-)
6	Ph	Me	$2,4-Me_2C_6H_4$	-40	14	47	53 (-)
7	Ph	Me		-40	15	29	77(-)
8	Ph	Me	1-Np	20	16	58	51 $(-, S)^d$
9	Ph	nPr	2-MeOC ₆ H ₄	-40	17	73	70(+)
10	Ph	iPr	2-MeOC ₆ H ₄	-40	18	73	76(+)
11	1-Np	Me	2-MeOC ₆ H ₄	-40	19	54	73(+, S)
12	1-Np	Ph	2-MeOC ₆ H ₄	20	20	36	$11(ND)^{e}$
13	<i>t</i> Bu ¹	Me	2-MeOC ₆ H ₄	20	21	34	28 (-)
^a Unle	ss other	wise	noted all reaction	ons were	conducted	1 at 0 f	5 M in THE

^a Unless otherwise noted, all reactions were conducted at 0.5 M in THF with 2.5 mol% of Pd₂(dba)₃ and 7.5 mol% of ligand (*R*,*R*)-6. ^b Determined by HPLC analysis. ^c Signs in the parentheses are those of $[\alpha]_D$ in CH₂Cl₂. ^d The absolute stereo configurations were determined by the comparison of $[\alpha]_D$ of enantiomer-rich (or enantiopure) tertiary silanes or *via* chiral HPLC analysis. ^e $[\alpha]_D$ value was approximately 0.

quantities with low asymmetric yields (entries 12 and 13). The absolute stereo configurations of several products were determined by optical rotation or chiral HPLC analysis (entries 1, 4 and 8).^{8,16,17}

To further investigate the stereochemistry of this reaction, the absolute configuration of **19** was confirmed by singlecrystal X-ray analysis following a couple of recrystallization steps of enantiomer-rich **19**.¹⁸ HPLC analysis determined the optical purity after recrystallization to be >99%ee. As shown in Fig. 2, the absolute configuration of **19** was assigned as the (*S*) enantiomer. These results reveal that *ortho*-substituted aryl iodides react with pro-(*S*) at the hydrogen of secondary silanes when (*R*,*R*)-**6** is used as the chiral source.



Fig. 2 X-ray structure analysis of enantiopure (S)-19. Purity > 99%ee.

On the basis of the obtained results, a tentative transition state, dominated by a repulsion among the ethyl group of (R,R)-6, the *o*-substituent of the aryl iodide, and the alkyl group of the secondary silane, was proposed.⁷ The reduced enantioselectivities of *m*- and *p*-substituted aryl iodides as compared with the *o*-substituted one can be attributed to the lack of steric effects with the phosphoramidite ligand and secondary silanes.

In conclusion, we have described the first enantioselective arylation of secondary silanes. TADDOL-based phosphoramidite (R,R)-6 was found to be highly effective for palladiumcatalyzed asymmetric arylation of secondary silanes (up to 77%ee). Investigations evaluating the full scope of this reaction are currently in progress.

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