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Direct and Selective Arylation of Tertiary Silanes with Rhodium Catalyst

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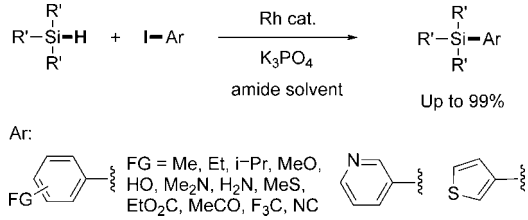
Received April 16, 2008



We have developed a convenient and efficient approach to the arylation of tertiary silanes under mild conditions. A variety of arylsilanes were synthesized in a one-step process with good to excellent yields in the presence of a rhodium catalyst with a base. The reaction was highly solvent dependent, and amides were the most effective of the various solvents used. This common catalyst system is highly tolerant of the various sensitive functional groups on the substrates, which might be difficult to extract by other methods. The rhodium-promoted silylation of aryl halides with electron-donating groups occurred more efficiently than the silylation of aryl halides substituted with electron-withdrawing groups. Heteroaromatic halides were also found to be readily silylated with tertiary silanes. The successful application of this reaction to the synthesis of a TAC-101 analogue, which is a trialkylsilyl-containing synthetic retinoid benzoic acid derivative with selective binding affinity for retinoic acid receptor-α, is also described.

Introduction

Arylsilanes and their derivatives have been widely studied in material science for their unique properties. Recently, these compounds have been discussed as potential candidates as intermediates for Hiyama coupling,[1] organic phosphorescent materials,[2] and medicinal products.[3] For this reason, the efficient synthesis and functionalization of arylsilane derivatives have attracted the interest of many synthetic chemists. Although arylsilanes have been classically prepared by the reaction of Grignard or with organolithium reagents with silicon electrophiles,[4] these protocols lack wide applicability; however, an efficient synthesis of functionally substituted arylsilanes has been elusive.

Transition metal-catalyzed C−C coupling reactions have been recognized as powerful tools in multiple organic transformations.[5] Transition metal-catalyzed C−Si bond-forming reactions are also potent methods for the preparation of arylsilanes, and

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(1) For reviews of Hiyama coupling, see: (a) Hiyama, T. In *Metal-Catalyzed Cross Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; p 421. (b) Hiyama, T.; Shirakawa, E. In *Topics in Current Chemistry*; Miyaura, N., Ed.; Springer-Verlag: Heidelberg, Germany, 2002; Vol. 219, p 61. (c) Horn, K. A. *Chem. Rev.* **1995**, *95*, 1317. (d) Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845. (e) Denmark, S. E.; Baird, J. D. *Chem. Eur. J.* **2006**, *12*, 4954. (f) Nakao, Y.; Sahoo, A. K.; Imanaka, H.; Yada, A.; Hiyama, T. *Pure Appl. Chem.* **2006**, *78*, 435. (g) Handy, C. J.; Manoso, A. S.; McElroy, W. T.; Seganish, M.; DeShong, P. *Tetrahedron* **2005**, *61*, 12201.

(2) For example, see: (a) You, Y.; An, C.-G.; Kim, J.-J.; Park, S. Y. *J. Org. Chem.* **2007**, *72*, 6241. (b) Liu, X.-M.; He, C.; Haung, J.; Xu, J. *Chem. Mater.* **2005**, *17*, 434.

(3) For example, see: (a) Bains, W.; Tacke, R. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 526. (b) Showwell, G. A.; Mills, J. S. *Drug Discovery Today* **2003**, *8*, 551. (c) Daiss, J. O.; Burschka, C.; Mills, J. S.; Montana, J. G.; Showell, G. A.; Fleming, I.; Gaudon, C.; Ivanova, D.; Gronemeyer, H.; Tacke, R. *Organometallics* **2005**, *24*, 3192.

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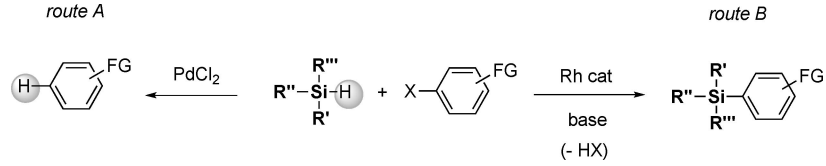
10.1021/jo8008148 CCC: $40.75
Published on Web 08/06/2008

SCHEME 1. Direct Arylation of Tertiary Silanes



several examples of synthesis with transition metal catalysts have been reported. The silylation of aromatic C−H bonds is the most straightforward and atom-economical route to arylsilane derivatives.[6] However, only limited protocols have been reported in the literature. The reaction usually requires a long reaction time and high temperatures (often above 150 °C), has a low yield, and is limited by the small range of potential starting materials.

Generally, hydrosilanes have been widely used as mild reducing reagents for fine organic syntheses.[7] Since the pioneering work of Murata et al., Manoso and DeShong, Denmark and Kallemyn, Komuro et al., and Ito, transition metal-catalyzed cross-coupling reactions of aryl halides with trialkoxysilane have emerged as an alternative and promising method for Si−C bond formation.[8] This method has received much attention because it can produce important synthetic building blocks that are difficult to prepare with other technologies. However, in most cases trialkylsilanes were not suitable silylating reagents because of their strong reducing power toward aryl halides in the presence of catalyst.[9] For example, Chatgilialoglu et al. reported that the addition of a catalytic amount of palladium dichloride to a mixture of 4-iodoanisole and triethylsilane in ether at room temperature exclusively produced the corresponding reduction product, anisole (Scheme 1, route A).[10] In the course of our study of the synthetic use of trialkylsilanes, we recently reported the palladium- and rhodium-catalyzed cross coupling of trialkylsilanes with aryl iodides under mild conditions with good to high yields.[11,12] In the present work, the scope and limitations of this silylation are evaluated by testing a wide variety of aryl halides and tertiary silanes reacted with a rhodium catalyst (Scheme 1, route B). The application of silylation to the total synthesis of a TAC-101 analogue,[13] a synthetic retinobenzoic acid with selective binding affinity for retinoic acid receptor (RAR)-α,[14] is also demonstrated.

Results and Discussion

Rhodium-Catalyzed Arylation of Tertiary Silane. To demonstrate the feasibility of rhodium-catalyzed arylation of a tertiary silane, we examined the triethylsilylation of 2-iodoanisole (**1a**) using a series of catalysts, bases, and solvents, as summarized in Table 1. As we reported previously, the palladium-catalyzed reaction of a sterically hindered ortho-substituted aryl iodide gave a trace amount of silylated product **2** and a much larger quantity of **3**. In short, $[Rh(cod)_2]BF_4$ and $RhCl(CO)(PPh_3)_2$ appear to be the best catalysts for producing the silylated product **2**, with almost complete conversion at room temperature in amide solvent (entries 7 and 8).[15] The yield of silylated product **2** was slightly reduced at 50 °C, although the reaction time became shorter with lower catalyst loading (entries 9 and 10). In addition to K_3PO_4,[16] several other bases (K_2CO_3, KOAc, and Et_3N) were tested in the protocol, but none of these yielded better results than K_3PO_4 (entries 12−14).

Next, we focused our attention on a range of possible leaving groups on the aromatic ring. As outlined in Table 2, iodide, bromide, chloride, and triflate[17] were tested as leaving groups. The iodide substrates exhibited much higher reactivity than their bromide, triflate, or chloride analogues. When we examined the reaction of 2-bromoanisole with triethylsilane in the presence of an additional equal amount of tetraethylammonium iodide, the yield of silylated product was slightly increased. These results clearly indicate that the iodide anion plays a key role in suppressing the undesired reduction reaction. For further comparison, we note that our attempt to use hexamethyldisilane ($Me_3SiSiMe_3$) or iodotrimethylsilane (I-$SiMe_3$) instead of hy-

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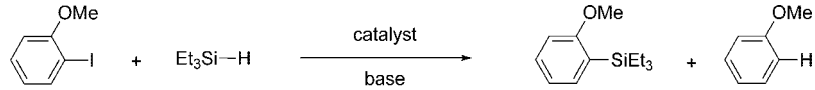
(15) $RhCl(CO)(PPh_3)_2$ and $[Rh(cod)_2]BF_4$ are commercially available from Strem Chemicals.

(16) K_3PO_4 was dried at 100 °C for 2 h under vacuum before use.

(17) 2-Methoxyphenyl trifluoromethanesulfonate was prepared by Ritter's method. See: Ritter, K. *Synthesis* **1993**, 735.

TABLE 1. Reaction of 2-Iodoanisole with Triethylsilane under Various Conditions[a]

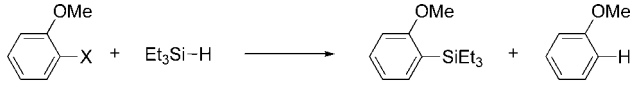


1a 2 3

						ratio[b]			
entry	catalyst	base	solvent	temp	time/h	**1a**	**2**	**3**	yield of **2** (%)
1[c]	$Pd(P(t\text{-}Bu)_3)_2$	K_3PO_4	NMP[d]	rt	5	*e*	<1	99	*f*
2	$PdCl_2(dppf)$	K_3PO_4	NMP	rt	96	52	2	46	*f*
3	$Pd(PCy_3)$	K_3PO_4	NMP	rt	96	57	<1	43	*f*
4	$IrCl(CO)(PPh_3)_2$	K_3PO_4	NMP	rt	96	75	*e*	25	*f*
5	$RhCl(PPh_3)_3$	K_3PO_4	NMP	rt	96	1	2	97	*f*
6	$[RhCl(nbd)]_2$	K_3PO_4	NMP	rt	96	*e*	41	59	32
7	**$RhCl(CO)(PPh_3)_2$**	**K_3PO_4**	**NMP**	**rt**	**96**	***e***	**96**	**4**	**88**
8	**$[Rh(cod)_2]BF_4$**	**K_3PO_4**	**NMP**	**rt**	**96**	***e***	**96**	**4**	**91**
9[c]	$RhCl(CO)(PPh_3)_2$	K_3PO_4	NMP	50 °C	10	<1	89	11	83
10[c]	$[Rh(cod)_2]BF_4$	K_3PO_4	NMP	50 °C	10	*e*	84	16	81
11	$[Rh(cod)_2]BF_4$	none	NMP	rt	96	28	*e*	72	*f*
12	$[Rh(cod)_2]BF_4$	K_2CO_3	NMP	rt	96	36	59	5	40
13	$[Rh(cod)_2]BF_4$	Et_3N	NMP	rt	96	25	60	15	49
14	$[Rh(cod)_2]BF_4$	KOAc	NMP	rt	96	2	94	4	82
15	$RhCl(CO)(PPh_3)_2$	K_3PO_4	DMF	rt	96	*e*	53	47	50
16	$[Rh(cod)_2]BF_4$	K_3PO_4	THF	rt	96	3	60	37	54
17	$[Rh(cod)_2]BF_4$	K_3PO_4	toluene	rt	96	61	4	35	*f*

[a] Reaction conditions: 2-iodoanisole (0.5 mmol), triethylsilane (1.0 mmol), catalyst (0.025 mmol), base (1.5 mmol), and solvent (1.0 mL). [b] The ratio was determined by GC analysis of the crude reaction mixture. [c] The reaction was carried out in the presence of 1 mol % of catalyst. [d] NMP: *N*-methylpyrrolidinone. [e] No detection. [f] The silylated product could not be isolated by column chromatography.

TABLE 2. Electrophile Compatibility[a]



1a-d 2 3

				ratio[b]			
entry	X	additive	time/d	**1a−d**	**2**	**3**	yield of **2** (%)
1	I (**1a**)	[c]	4	[d]	96	4	91
2	Br (**1b**)	[c]	20	<1	51	49	48
3	Br (**1b**)	Et_4NI	20	[d]	60	40	60
4	Cl (**1c**)	[c]	20	88	[d]	12	[e]
5	OTf (**1d**)	[c]	20	54	[d]	46	[e]

[a] Reaction conditions: aryl (pseudo)halide (0.5 mmol), triethylsilane (1.0 mmol), $[Rh(cod)_2]BF_4$ (0.025 mmol), K_3PO_4 (1.5 mmol), and NMP (1.0 mL) at rt. [b] The ratio was determined by GC analysis. [c] No additive. [d] No detection. [e] The silylated product could not be isolated.

drosilane in the coupling reaction under similar conditions resulted in failure, giving complete recovery of aryl iodide, demonstrated by GC-MS measurements.[18]

As summarized in Table 3, various aryl halides substituted with electron-donating or electron-withdrawing groups were converted to the corresponding arylsilanes with good to high yields when the reactions were performed under optimized conditions. In all cases, the reduction of the Ar−I bonds occurred as a side reaction to produce volatile aromatic compounds, as revealed by GC-MS analysis.

In the reactions of aryl iodides containing electron-donating groups on the aromatic ring, the desired silanes were successfully obtained with good to high yields (entries 1−26).[19,20] Conversely, the presence of an electron-withdrawing group bound to an arene ring slightly reduced the yield of the silylated product (entries 32, 33, 35, 36, 38, 39, 41, and 42). The presence of amino ($-NH_2$), hydroxy ($-OH$), ester ($-CO_2Et$),[21,22] cyano ($-CN$),[22] or acetyl ($-COCH_3$)[22] functionalities on the aromatic ring was tolerated in this reaction (entries 18−23, 32, 33, 35, 36, 41, and 42). In the traditional methods of Grignard or with organolithium reagents, the protection of these functional groups is frequently required. Thus, our protocol is particularly useful for the preparation of functionalized arylsilanes. Furthermore, sterically hindered ortho-substituted aryl iodides were also effectively coupled with hydrosilanes without difficulty, in sharp contrast to palladium-catalyzed silylation (entries 1−3, 9, 12, 14, 17, 18, 21, 24−26, and 29), although the larger alkyl group resulted in a reduced yield of the silylated product (*t*-Bu,[23] 0% > *i*-Pr, 68% > Et, 79% > Me, 99%). Unfortunately, attempts at the silylation of ortho-substituted electron-deficient aryl iodides were unsuccessful (entries 28, 31, 34, 37, and 40).[24] We also examined the effects of other hydrosilanes under similar

(18) Transition metal-catalyzed silylations of aryl halides with disilanes in the presence of fluoride anion as activator or at high temperature have been reported. For example, see: (a) McNeill, E.; Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 3785. (b) Goossen, L. J.; Ferwanah, A.-R. S. *Synlett* **2000**, 1801. (c) Shirakawa, E.; Kurahashi, T.; Yoshida, H.; Hiyama, T. *Chem. Commun.* **2000**, 1895. (d) Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1987**, *28*, 4715. (e) Eaborn, C.; Griffiths, R. W.; Pidcock, A. *J. Organomet. Chem.* **1982**, *225*, 331. (f) Babin, P.; Bennetau, B.; Theurig, M.; Dunogues, J. *J. Organomet. Chem.* **1993**, *446*, 135. (g) Matsumoto, H.; Nagashima, S.; Yoshihiro, K.; Nagai, Y. *J. Organomet. Chem.* **1975**, *85*, C1. (h) Azarian, D.; Dua, S. S.; Eaborn, C.; Walton, D. R. M. *J. Organomet. Chem.* **1976**, *117*, C55.

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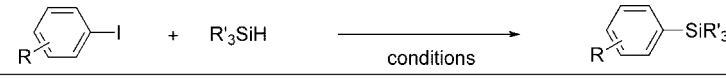
(20) 2-Iodo-*N*,*N*-dimethylaniline was prepared from 2-iodoaniline by methylation with iodomethane in the presence of K_2CO_3. Bunnett, J. F.; Mitchel, E.; Galli, C. *Tetrahedron* **1985**, *41*, 4119.

(21) Murata et al. reported the reaction of ethyl 4-iodobenzoate with triethylsilane in DMF at 80 °C in the presence of $[Rh(cod)(MeCN)_2]BF_4$ to produce the corresponding silylated product with a 53% GLC yield. See ref 8a.

(22) Quite recently, Iizuka and Kondo reported the triethylsilylation of 4-iodobenzonitrile, 4-iodoacetophenone, and methyl 4-iodobenzoate using triethylsilane in the presence of $Pd(OAc)_2$ as catalyst. The yields of the triethylsilylated products were 46%, 38%, and 35%, respectively. See 12d.

TABLE 3. Scope of Rhodium-Catalyzed Silylation with Aryl Iodides with Hydrosilanes[a]



entry	R	R_3'	catalyst[b]	solvent[c]	time/d	product	yield (%)
1	2-MeO	Et_3	A	NMP	4	2-$MeOC_6H_4SiEt_3$ (**2**)	91
2	2-MeO	Ph_3	A	NMP	4	2-$MeOC_6H_4SiPh_3$ (**4**)	99
3	2-MeO	$PhMe_2$	A	NMP	7	2-$MeOC_6H_4SiMe_2Ph$ (**5**)	69
4	3-MeO	Et_3	A	NMP	4	3-$MeOC_6H_4SiEt_3$ (**6**)	78
5	4-MeO	Et_3	A	NMP	4	4-$MeOC_6H_4SiEt_3$ (**7**)	99
6	4-MeO	*i*-Pr_3	A	NMP	4	4-$MeOC_6H_4Si$*i*-Pr_3 (**8**)	83
7	4-MeO	*t*-$BuMe_2$	A	NMP	4	4-$MeOC_6H_4Si$*t*-$BuMe_2$ (**9**)	99
8	4-MeO	Ph_2Me	A	NMP	4	4-$MeOC_6H_4SiPh_2Me$ (**10**)	98
9	2-Me_2N	Et_3	B	DMI	30	2-$Me_2NC_6H_4SiEt_3$ (**11**)	37
10	3-Me_2N	Et_3	B	NMP	4	3-$Me_2NC_6H_4SiEt_3$ (**12**)	81
11	4-Me_2N	Et_3	A	NMP	4	4-$Me_2NC_6H_4SiEt_3$ (**13**)	69
12	2-MeS	Et_3	A	NMP	7	2-$MeSC_6H_4SiEt_3$ (**14**)	99
13	4-MeS	Et_3	B	TMU	4	4-$MeSC_6H_4SiEt_3$ (**15**)	75
14	2-Me	Et_3	A	NMP	4	2-$MeC_6H_4SiEt_3$ (**16**)	99
15	3-Me	Et_3	A	NMP	4	3-$MeC_6H_4SiEt_3$ (**17**)	74
16	4-Me	Et_3	A	NMP	4	4-$MeC_6H_4SiEt_3$ (**18**)	91
17	2,4-Me_2	Et_3	A	NMP	4	4-$MeC_6H_4SiEt_3$ (**19**)	76
18	2-HO	Et_3	A	NMP	4	2-$HOC_6H_4SiEt_3$ (**20**)	99
19	3-HO	Et_3	A	NMP	4	3-$HOC_6H_4SiEt_3$ (**21**)	99
20	4-HO	Et_3	A	NMP	4	4-$HOC_6H_4SiEt_3$ (**22**)	80
21	2-H_2N	Et_3	A	NMP	4	2-$H_2NC_6H_4SiEt_3$ (**23**)	99
22	3-H_2N	Et_3	A	NMP	4	3-$H_2NC_6H_4SiEt_3$ (**24**)	98
23	4-H_2N	Et_3	A	NMP	4	4-$H_2NC_6H_4SiEt_3$ (**25**)	99
24	2-Et	Et_3	A	NMP	7	2-$EtC_6H_4SiEt_3$ (**26**)	79
25	2-Et	Ph_3	A	NMP	7	2-$EtC_6H_4SiPh_3$ (**27**)	93
26	2-*i*-Pr	Et_3	B	DMA	7	2-*i*-$PrC_6H_4SiEt_3$ (**28**)	68
27	2-*t*-Bu	Et_3	A	NMP	10	-	*d*
28	2-Ph	Et_3	A	NMP	10	-	*d*
29	1-$C_{10}H_7$	Et_3	B	DMA	7	1-$C_{10}H_7SiEt_3$ (**29**)	89
30	2,4,6-Me_3	Et_3	A	NMP	10	-	*d*
31	2-EtO_2C	Et_3	A	NMP	10	-	*d*
32	3-EtO_2C	Et_3	A	NMP	4	3-$EtO_2CC_6H_4SiEt_3$ (**30**)	77[e]
33	4-EtO_2C	Et_3	B	NMP	4	4-$EtO_2CC_6H_4SiEt_3$ (**31**)	68[e]
34	2-MeCO	Et_3	A	NMP	10	-	*d*
35	3-MeCO	Et_3	A	NMP	4	3-$MeCOC_6H_4SiEt_3$ (**32**)	83[e]
36	4-MeCO	Et_3	A	NMP	4	4-$MeCOC_6H_4SiEt_3$ (**33**)	57[e]
37	2-CF_3	Et_3	A	NMP	10	-	*d*
38	3-CF_3	Et_3	B	NMP	4	3-$CF_3C_6H_4SiEt_3$ (**34**)	72[e]
39	4-CF_3	Et_3	B	NMP	4	4-$CF_3C_6H_4SiEt_3$ (**35**)	51[e]
40	2-NC	Et_3	A	NMP	10	-	*d*
41	3-NC	Et_3	A	NMP	4	3-$NCC_6H_4SiEt_3$ (**36**)	72[e]
42	4-NC	Et_3	B	NMP	4	4-$NCC_6H_4SiEt_3$ (**37**)	53[e]
43	H	*n*-Pr_3	A	NMP	4	C_6H_5Si*n*-Pr_3 (**38**)	89

[a] Reaction was performed with aryl iodide (0.5 mmol), hydrosilane (1.0 mmol), K_3PO_4 (1.5 mmol), and rhodium catalyst (5 mol %) in solvent (1.0 mL) at rt. [b] A: $[Rh(cod)_2]BF_4$, B: $RhCl(CO)(PPh_3)_2$. [c] NMP: *N*-methylpyrolidinone; DMI: *N*,*N*-dimethylimidazolidinone; TMU: *N*,*N*,*N*′,*N*′-tetramethylurea; DMA: *N*,*N*-dimethylacetamide. [d] No detection. [e] Aryl iodide (0.5 mmol), hydrosilane (0.6 mmol), K_3PO_4 (1.5 mmol), and rhodium catalyst (5 mol %) in solvent (1.0 mL).

reaction conditions (entries 2, 3, 6−8, 25, and 43). This rhodium-catalyzed silylation was also practical at a 20 mmol scale, without deleterious effects.[25]

We continued our investigation by exploring the reaction of tertiary silanes with heteroaryl iodides. The scope of the silylation was explored by using heteroaryl iodides, as outlined in Table 4. Different heteroaryl iodides, such as thiophene and pyridine derivatives, were successfully coupled to triethylsilane under the same reaction conditions to produce the desired compounds with good yields (entries 1 and 2). It should also be noted that coupling diiodo- and triiodobenzene to triphenylsilane produced the oligoarylsilanes with good yields in this catalytic system (entries 4−6). Thus, the present reactions offer a convenient method for directly synthesizing oligoarylsilanes, which have wide applications in material science, from di- and triiodoaromatics. As another application of this work, we found that it is possible to efficiently couple vinyl and alkynyl iodide to hydrosilane under conditions similar to those used for the corresponding aryl compounds (entries 7 and 8).[26] This type of compound has been the focus of considerable interest, notably

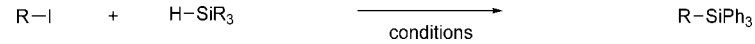
(23) 2-Iodo-*tert*-butylbenzene was prepared according with a modified method based on the literature. (a) Fey, N.; Howell, J. A. S.; Lovatt, J. D.; Yates, P. C.; Cunningham, D.; McArdle, P.; Gottlieb, H. E.; Coles, S. J. *Dalton Trans.* **2006**, 5464. (b) Åkermark, B.; Ljungqvist, A. *J. Organomet. Chem.* **1978**, *149*, 97.

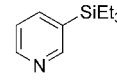
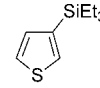
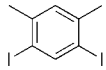
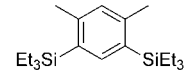
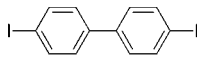
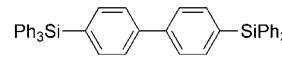
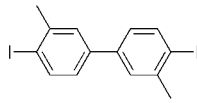
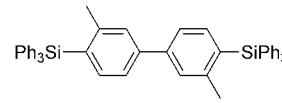
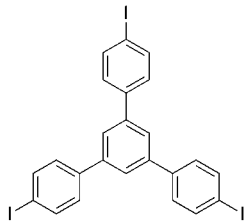
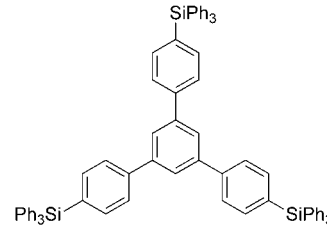
(24) The silylation reactions with aryl iodides containing a formyl group gave unsatisfactory results because complex mixtures were obtained, resulting from the high reactivity of the aldehyde moiety. Although the silylated products could not be isolated in a pure form, the yields were estimated to be less than 10% based on GC-MS analysis of the reaction mixture.

(25) In a 20 mmol scale experiment under the reaction conditions described, the silylation shown in Table 1 entry 1 proceeded to an 85% yield.

(26) For earlier work on the palladium-catalyzed coupling of alkenyl iodides with tertiary silanes, see: Murata, M.; Watanabe, S.; Masuda, Y. *Tetrahedron Lett.* **1999**, *40*, 9255.

TABLE 4. Rhodium-Catalyzed Silylation of Heteroaryl Iodides, Di- or Triiodo Aromatic Compounds, and Alkynyl-, Alkenyl-, Allyl-, and Alkyl Iodides



entry	R−I	R_3	conditions[a]	product	yield (%)
1		Et_3	A	 **39**	71
2		Et_3	B	 **40**	88
3		Et_3	B	 **41**	73
4		Ph_3	B	 **42**	86
5		Ph_3	B	 **43**	54
6		Ph_3	B	 **44**	55
7		Ph_3	C	**45**	38[b]
8		Ph_3	D	 **46**	49[b]
9		Ph_3	D	—	*C*
10		Ph_3	A	—	*C*

[a] Conditions: (A) R-I (0.5 mmol), $HSiR_3$ (2.0 equiv), K_3PO_4 (3.0 equiv), $RhCl(CO)(PPh_3)_2$ (5 mol %), NMP (1.0 mL), rt, 4 d. (B) R-I (0.5 mmol), $HSiR_3$ (2.0 equiv), $[Rh(cod)_2]BF_4$ (5 mol %), NMP (1.0 mL), rt, 6 d. (C) Ph_3SiH (1.0 mmol), R-I (3.0 equiv), K_3PO_4 (3.0 equiv), rt, 4 d. (D) Ph_3SiH (1.0 mmol), R-I (3.0 equiv), K_3PO_4 (3.0 equiv), 0 °C, 6 d. [b] The yield was based on the amount of triphenylsilane. No silylated product was obtained.

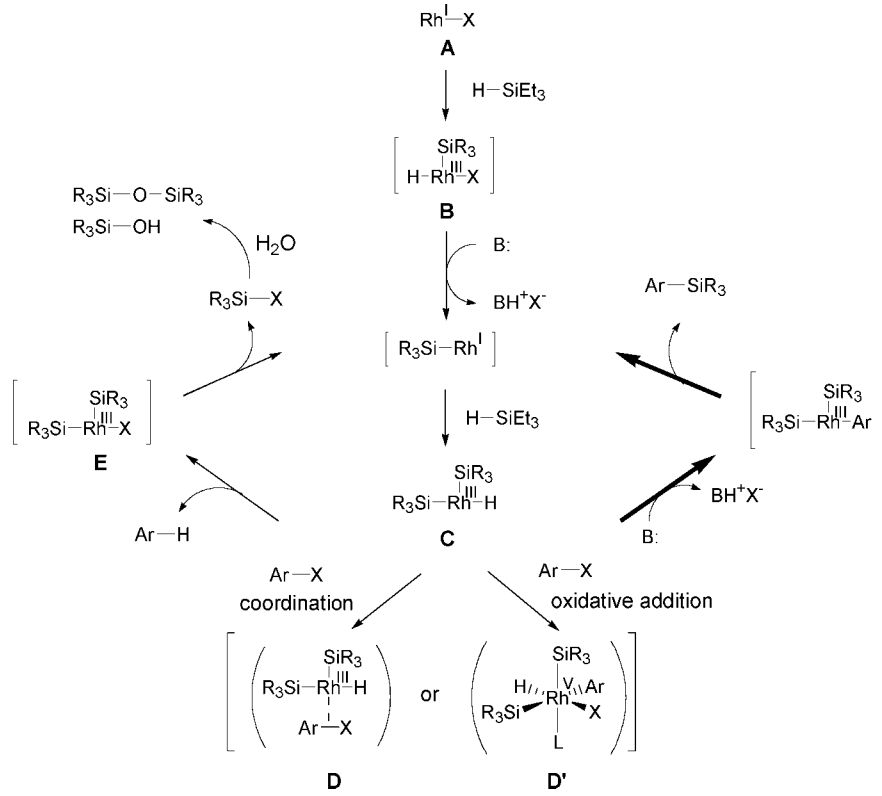
as a precursor to polyarylsilanes.[27] Disappointingly, allyl and alkyl iodides did not produce even trace amounts of the corresponding organosilane compounds (entries 9 and 10).

Reaction Mechanism. Rh complexes exhibit Si−H bond activation chemistry because these metals can support mononuclear silyl complexes in a variety of oxidation states.[28] Although several mechanisms may be considered for the silylation reaction, we have formulated a possible mechanism for the Rh-catalyzed arylation of hydrosilane, as described in Scheme 2, based on ^1H and ^{29}Si NMR analyses during the course of the stoichiometric reaction (Rh catalyst, $RhCl(CO)(PPh_3)_2$); aryl halide, 4-iodoanisole; hydrosilane, H-$SiEt_3$ [ratio 1:1:1] in

(27) For reviews, see: (a) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375. (b) Fleming, I.; Dunogues, J.; Smithers, R. H. *Org. React.* **1989**, *37*, 57. (c) Colvin, E. W. *Silicon Reagents in Organic Synthesis*; Academic Press: London, UK, 1988.

(28) For representative reports on the organosilane complexes of rhodium(V), see: (a) Fernandez, M.-J.; Maitlis, P. M. *J. Chem. Soc., Chem. Commun.* **1982**, 310. (b) Cook, K. S.; Incarvito, C. D.; Webster, C. E.; Fan, Y.; Hall, M. B.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 5474. (c) Fernandez, M.-J.; Bailey, P. M.; Bentz, P. O.; Ricci, J. C.; Koetzle, T. F.; Maitilis, P. M. *J. Am. Chem. Soc.* **1984**, *106*, 5458. (d) Nagashima, H.; Tatebe, K.; Ishibashi, T.; Nakaoka, A.; Sakakibara, J.; Itoh, K. *Organometallics* **1995**, *14*, 2868.

SCHEME 2. Plausible Mechanism for Rhodium-Catalyzed Silylation



DMF-d_7, at room temperature).[29]The catalytic cycle of the reaction is initiated by the reaction of the rhodium catalyst **A** with hydrosilane to produce a silyl metal hydride complex **B**. Although a hydrosilane as well as an aryl halide can be added oxidatively to Rh(I) complexes, the NMR studies indicated that the oxidative addition of hydrosilane occurred predominantly under the conditions used. Consequently, a mechanism involving the initial oxidative addition of an aryl halide can effectively be ruled out in the present reaction. The elimination of HX with the aid of a base, followed by the further oxidative addition of H-SiR_3, would produce the intermediate formulated as Rh(H)(SiR_3)$_2$ **C**,[30] which is the key intermediate in this transformation and has peaks at 1.00 (t) and 0.73 ppm (q) in the triethyl moiety, and −9.69 (br s) and −10.64 ppm (br s) in the hydride region. The integral ratio of the triethylsilyl moiety to the hydride region supports the structure of the intermediate.[31,32] Only one peak at 22.0 ppm was observed by the measurement of ^{29}Si NMR,[33] which supports the existence of a stable intermediate during the catalysis. K_3PO_4 is essential for the formation of intermediate **C**. As the reaction progresses, the coordination or oxidative addition of aryl halide to intermediate **C** takes place to produce the Rh(III) intermediate **D** or the Rh(V) intermediate **D′**. In the presence of base, the rapid base-promoted reductive elimination of HX, the subsequent reductive elimination of Ar-SiR_3, and the oxidative addition of H-SiR_3 dominates, to generate intermediate **C**. In this case, another cycle that produces the reduced product is competitive with this route, producing catalyst **C** through intermediate **E**, and steric and electronic factors have a significant effect on this step.[34–36] The signals of 9.1 and 13.4 ppm in the ^{29}Si NMR spectra, corresponding to the $Et_3SiOSiEt_3$ and Et_3SiOH, appeared as the reaction proceeded, and we believe that $Et_3SiOSiEt_3$ and Et_3SiOH are the compounds most likely to have been formed via the hydrolysis

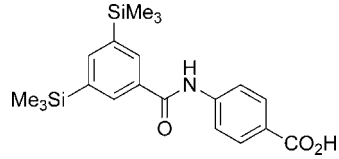


FIGURE 1. Structure of TAC-101.

(29) For ^{1}H and ^{29}Si NMR spectra, see the Supporting Information.

(30) (a) Sun et al. reported the intermediate "$(Ph_3P)_2Rh(H)(SiEt_3)_2$" in the hydrosilylation of cyclopropyl ketones, see: Sun, C.; Tu, A.; Slough, G. A. *J. Organomet. Chem.* **1999**, *582*, 235. (b) Osakada et al. reported "cyclic *fac*-[Rh($SiMe_2CH_2CH_2SiMe_2$)H(PMe_3)$_3$]" prepared in situ from RhCl(PMe_3)$_n$ and NaSPh with $Me_2HSiCH_2CH_2SiHMe_2$, see: Osakada, K.; Hataya, K.; Nakamura, Y.; Tanaka, M.; Yamamoto, T. *J. Chem. Soc. Chem. Commun.* **1993**, 576.

(31) The integral ratio of δ 1.00 ($-CH_3$)/hydride region (Rh-H) was 18/1. Because of the overlapping peaks, the integration of the methylene group could not be determined.

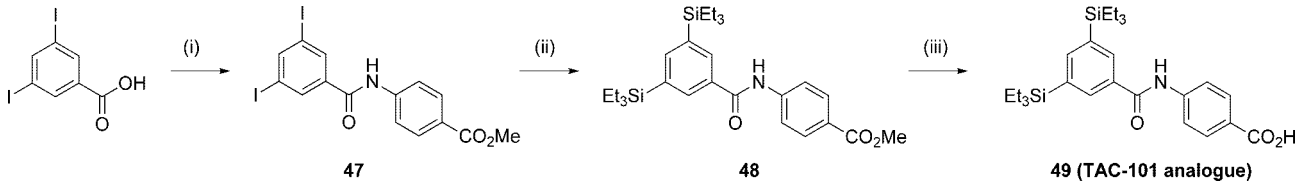
(32) 4-Iodoanisole was not completely reacted under the stoichiometric conditions. To complete the reaction, more than 2 equiv of triethylsilane for rhodium catalyst was necessary from the NMR studies. This result also provides some support for the existence of Rh(H)($SiEt_3$)$_2$ as a key intermediate.

(33) For representative ^{29}Si NMR data of rhodium(III) silyl complexes, see: (a) CpRh(C_2H_4)($SiEt_3$)(H) 41.6 ppm: Duckett, S. B.; Haddleton, D. M.; Jackson, S. A.; Perutz, R. N.; Paliakoff, M.; Upmacis, R. K. *Organometallics* **1988**, *7*, 1526. (b) CpRh(Si(*i*-Pr)$_3$)(C_2H_4)(H) 49.3 ppm: Duckett, S. B.; Perutz, R. N. *Organometallics* **1992**, *11*, 90. (c) *mer*-RhCl(H)($SiHPh_2$)(PMe_3)$_3$ 14.9 ppm: Osakada, K.; Sarai, S.; Koizumi, T.; Yamamoto, T. *Organometallics* **1997**, *16*, 3973. (d) RhCl(H)(Si(OEt)$_2$Me)(PPh_3)$_3$ 15.4 ppm: Nishihara, Y.; Takemura, M.; Osakada, K. *Organometallics* **2002**, *21*, 825. (e) *fac*-Tris[(8-quinolyl)dimethylsilyl]rhodium(III) 23.6 ppm: Djurovich, P. I.; Safir, A. L.; Keder, N. L.; Watts, R. J. *Inorg. Chem.* **1992**, *31*, 3195.

(34) Recently, Tilley and co-workers studied the reaction of chlorobenzene with triethylsilane in the presence of a rhodium complex bearing chelating nitrogen-based ligands. They pointed out the Rh(V) intermediates in the catalytic process. See ref 12e.

(35) Okazaki et al. reported that the reaction of the (2-phosphinoethyl)silyl rhodium(I) complex with excess $PhMe_2SiH$ proceeded spontaneously at rt to give the dihydrido rhodium(III) complex and ($PhMe_2Si$)$_2$ through a rhodium(V) intermediate. See: Okazaki, M.; Ohshitani, S.; Tobita, H.; Ogino, H. *Chem. Lett.* **2001**, 952.

SCHEME 3. Application of the Rh-Catalyzed Si−C Bond Formation to the Synthesis of TAC-101 Analogue[a]



47 **48** **49 (TAC-101 analogue)**

[a] Reagents and conditions: (i) 4-$H_2NC_6H_4CO_2Me$, EDC-HCl, Et_3N, HOBt, DMF, 50 °C, 2 d, 81%; (ii) $[Rh(cod)_2]BF_4$ (5 mol%), Et_3SiH, DMPU, rt, 4 d, 68%; (iii) aqueous NaOH/EtOH, rt, 1 d, 99%.

of Et_3SiX.[37–39] Although there was a possibility of the generation of hexaethyldisilane as a side product, the peak derived from disilane compound (−20 ppm) was not observed by ^{29}Si NMR during the catalysis.

Application. To demonstrate the utility of these reactions, we undertook the short-step synthesis of a TAC-101 (4-[[[3,5-bis(trimethylsilyl)phenyl]carbonyl]amino]benzoic acid) analogue, which is a synthetic retinobenzoic acid with selective binding affinity for RAR-α (Figure 1).[13] Kagechika and Shudo et al. have reported a synthetic process for the preparation of TAC-101 in five steps using 1,3,5-tribromobenzene as the staring material (total 3.4% yield). We have now developed a new synthetic route for the TAC-101 derivative in three steps, using the present Rh-catalyzed arylation of hydrosilane as a key step, starting from 3,5-diiodobenzoic acid. The synthesis is outlined in Scheme 3. Thus, 3,5-diiodobenzoic acid and methyl 4-aminobenzoate were treated with 1-ethyl-3-(3-dimethylaminoproyl)-carbodiimide hydrochloride (EDC-HCl) at 50 °C to produce the corresponding amide product **47** with an 81% yield. The introduction of trialkylsilyl groups with triethylsilane to the aromatic ring using the rhodium catalyst proceeded smoothly in DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) at room temperature to produce the corresponding bistriethylsilylated product **48** with a 68% yield.[40] The hydrolysis of the ester group was performed with NaOH to produce the TAC-101 derivative **49** with an almost quantitative yield. This new arylation reaction is a straightforward method for the preparation of an RAR-α-selective agonist for use in the treatment of liver cancer.

Conclusion

In summary, we have developed a general method for the silylation of aryl halides using tertiary silanes as the silylating reagent. A variety of substrates with different functional groups (electron-withdrawing and electron-donating groups) in para, meta, and ortho positions were successfully coupled in the presence of K_3PO_4 and a rhodium catalyst. The scope of the potential substrates is broader than those of palladium-catalyzed silylation, which we reported previously. The reactivity order of aryl halides was Ar−I > Ar−Br > Ar−Cl, Ar−OTf, and the effects of the substituent groups on the aromatic rings of the aryl halides were electron-donating > electron-withdrawing. In the case of aryl bromide, the yield of silylated product was slightly increased by treatment with an additional equal amount of tetraethylammonium iodide. By using this reaction as the key step, a concise synthesis of a pharmaceutical was achieved. The importance of $Rh(H)(SiR_3)_2$ as the key catalytic species and the reaction mechanism were discussed based on the results of ^1H and ^{29}Si NMR measurements during the catalysis. It is anticipated that these new reactions will begin to replace the use of aryl organometallics in the synthesis of tetraorganosilanes and that this new reactivity will facilitate the design of other catalytic Si−H bond functionalities. Further applications of this method to the preparation of other useful organosilane products are currently under investigation.

Experimental Section

All the experiments were carried out under an argon atmosphere in oven-dried glassware. Unless otherwise noted, the tertiary silanes and aryl halides were purchased from commercial sources and used without purification.

Typical Procedure for the Rhodium-Catalyzed Silylations of Aryl (Pseudo)halides with Trialkylsilane. An oven-dried Schlenk flask with a magnetic stirring bar was charged with $RhCl(CO)(PPh_3)_2$ or $[Rh(cod)_2]BF_4$ (0.025 mmol) and K_3PO_4 (1.5 mmol) in air. Aryl (pseudo)halides (0.5 mmol) and tertiary silanes (1.0 mmol) were also added at this time if the solid form of these reagents was used. The flask was capped with a rubber septum, evacuated, and then flushed with argon. Solvent (1 mL), aryl (pseudo)halides (if a liquid, 0.5 mmol), and tertiary silanes (if a liquid, 1.0 mmol) were then added successively with a syringe, and the reaction mixture was stirred at room temperature for several days. The reaction was quenched with water when the starting material was not detected on thin-layer chromatography (TLC). The aqueous layer was extracted three times with CH_2Cl_2 and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and column chromatography on silica gel produced the pure silylated product.

(2-Methoxyphenyl)triethylsilane (2).[11b] Colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.32 (m, 2H), 6.94 (t, 2H, J = 7.2 Hz), 6.82 (d, 1H, J = 8.1 Hz), 3.77 (s, 3H), 0.93 (t, 9H, J = 7.8 Hz), 0.78 (q, 6H, J = 8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5 (C_q), 136.0 (CH), 130.5 (CH), 125.1 (C_q), 120.3 (CH), 109.3 (CH), 54.8 (CH_3), 7.6 (CH_3), 3.5 (CH_2); EI-MS m/z 222 (M^+).

(3-Methoxyphenyl)triethylsilane (4). Colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, 1H, J = 7.7 Hz), 7.07 (d, 1H, J = 7.1 Hz), 7.03 (d, 1H, J = 2.7 Hz), 6.89 (ddd, 1H, J = 8.3, 2.8, 0.9 Hz), 3.82 (s, 3H), 0.96 (t, 9H, J = 7.8 Hz), 0.81−0.76 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8 (C_q), 139.2 (C_q), 128.8 (CH), 126.5 (CH), 119.9 (CH), 113.6 (CH), 55.0 (CH_3), 7.4 (CH_3), 3.3 (CH_2); EI-MS m/z 222 (M^+). Anal. Calcd for $C_{13}H_{22}OSi$: C, 70.21; H, 9.97. Found: C, 70.11; H, 10.01.

(36) For reviews of Rh(V) complexes as reaction intermediates, see: (a) Marciniec, B. *Appl. Organomet. Chem.* **2000**, *14*, 527. (b) Corey, J. Y.; Braddock-Wilking, J. *Chem. Rev.* **1999**, *99*, 175.

(37) The formation of $Et_3SiOSiEt_3$ and Et_3SiOH was also identified by GC-MS analysis of the reaction mixture and by comparing the data with those of authentic samples.

(38) Kunai et al. reported that the reaction of trialkylsilane and alkyl or aryl iodide in the presence of palladium dichloride gave corresponding iodosilane with a good to high yield, see: Kunai, A.; Sakurai, T.; Toyoda, E.; Ishikawa, M.; Yamamoto, Y. *Organometallics* **1994**, *13*, 3233.

(39) As one of the referees pointed out, when we reacted Ph_3SiH in K_3PO_4 with $RhCl(CO)(PPh_3)_2$ in NMP (in the absence of Ar-I), Ph_3Si-O-$SiPh_3$ was obtained with ca. 50% conversion because of the reduction of amide to amine. The presence of *N*-methylpyrrolidine has been confirmed by GC-MS. Igarashi and Fuchikami have reported the transition-metal-complex-catalyzed reduction of amides with hydrosilanes, see: Igarashi, M.; Fuchikami, T. *Tetrahedron Lett.* **2001**, *42*, 1945.

Synthetic Procedure for TAC-101 Derivative 49. (i) To a solution of 3,5-diiodobenzoic acid[41] (0.32 g, 0.86 mmol), methyl 4-aminobenzoate (0.19 g, 1.26 mmol), EDC-HCl (0.33 g, 1.72 mmol), and HOBt (0.21 g, 0.91 mmol) in DMF (4 mL) was added Et_3N (0.3 mL, 2.15 mmol) at rt under an argon atmosphere, and the mixture was stirred at 50 °C for 2 d. The reaction was quenched with sat. $NaHCO_3$ aqueous solution and the organic layer was separated. The aqueous layer was extracted five times with CH_2Cl_2. The combined extracts were washed with 1 M HCl and dried over Na_2SO_4, then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (eluent: hexane/EtOAc = 8/1) to produce **47** as a colorless solid (0.35 g, 81%). (ii) To a mixture of **47** (109 mg, 0.21 mmol), K_3PO_4 (365 mg, 1.72 mmol), and $[Rh(cod)_2]BF_4$ (11 mg, 0.025 mmol) in DMPU (1.0 mL) was added Et_3SiH (0.12 mL, 0.75 mmol) at rt under Ar. After being stirred for 4 d, the reaction was quenched with H_2O and the products were extracted five times with CH_2Cl_2. The solvent was removed under reduced pressure. Purification was by column chromatography on silica gel (eluent: hexane/EtOAc = 5/1) to give **48** (71 mg, 68%). (iii) To a solution of **48** (281 mg, 0.58 mmol) in EtOH (10 mL) was added 1 M NaOH solution (1.2 mL) and the reaction was monitored by TLC. The reaction was quenched with 1 M HCl to pH 3, as indicated by pH paper. The quenched reaction was extracted with CH_2Cl_2 five times and the combined extracts were dried over Na_2SO_4. The solvent was removed under reduced pressure to produce the TAC-101 analogue **49** (267 mg, 99%).

4-[[[3,5-Bis(triethylsilyl)phenyl]carbonyl]amino]benzoic acid (49). Colorless cubes (recrystallized from hexane−CH_2Cl_2); Mp 222.5−225.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, 2H, J = 8.8 Hz), 7.91 (br s, 1H), 7.81 (d, 2H, J = 1.0 Hz), 7.81−7.78 (m, 3H), 0.99 (t, 18H, J = 7.8 Hz), 0.87−0.82 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5 (C═O), 167.1 (C═O), 144.0 (C_q), 143.0 (C_q), 137.5 (CH), 133.1 (C_q), 132.9 (CH), 131.6 (CH), 124.9 (C_q), 119.3 (CH), 7.4 (CH_3), 3.3 (CH_2); EI-MS m/z 469 (M^+). Anal. Calcd for $C_{26}H_{39}NO_3Si_2$: C, 66.48; H, 8.37; N, 2.98. Found: C, 66.30; H, 8.33; N, 2.98.

Acknowledgment. We thank Ms. Kimiyo Saeki of the Elemental Analysis Center of the University of Tokyo for the elemental analyses. This work was financially supported by CREST from JST, by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and by the Global COE Program for Chemistry Innovation, Japan.

Supporting Information Available: Compound characterization data, copies of the ^{1}H and ^{13}C NMR spectra, and the ^{1}H and ^{29}Si NMR spectra used to monitor the reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8008148

(40) Because trimethylsilane is a volatile compound (bp 6.7 °C), triethylsilylated retinoid benzoic acid **49** was prepared instead of TAC-101.

(41) 3,5-Diiodobenzoic acid is commercially available from Tyger Scientific Inc. (Princeton, NJ, USA).