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Tandem Intramolecular Silylformylation and Silicon-Assisted Cross-Coupling Reactions. Synthesis of Geometrically Defined α,β-Unsaturated Aldehydes

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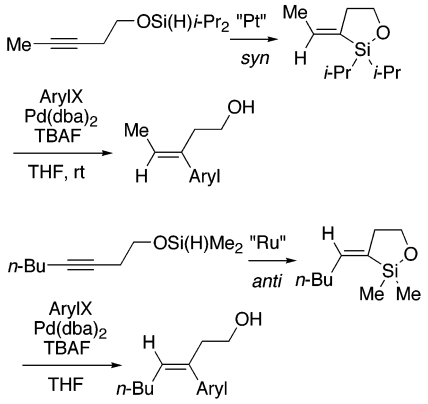
The palladium- and copper-catalyzed cross-coupling reactions of cyclic silyl ethers with aryl iodides are reported. Silyl ethers **3** were readily prepared by intramolecular silylformylation of homopropargyl silyl ethers **2** under a carbon monoxide atmosphere. The reaction of cyclic silyl ethers **3** with various aryl iodides **7** in the presence of $[(allyl)PdCl]_2$, CuI, a hydrosilane, and $KF{\cdot}2H_2O$ in DMF at room temperature provided the α,β-unsaturated aldehyde coupling products **8** in high yields. The need for copper in this process suggested that transmetalation from silicon to copper is an important step in the mechanism. Although siloxane **3** and the product **8** are not stable under basic conditions, $KF{\cdot}2H_2O$ provided the appropriate balance of reactivity toward silicon and reduced basicity. The addition of a hydrosilane to $[(allyl)PdCl]_2$ was needed to reduce the palladium(II) to the active palladium(0) form.

Introduction and Background

The formation of carbon−carbon bonds by palladium- or nickel-catalyzed cross-coupling reactions of organometallic reagents is one of the most powerful carbon−carbon bond-forming reactions in organic chemistry.[1] Although the Suzuki, Stille, and Negishi couplings are well-known as very useful reactions, they each have distinct drawbacks such as the requirement of forcing conditions, the involvement of toxic reagents and byproducts, as well as oxygen and moisture sensitivity.[1a,2] Recently, the cross-coupling reactions of organosilicon compounds have been extensively developed as an alternative method which can provide practical solutions to these problems.[3]

In the past few years, reports from these laboratories have described new variants of organosilicon cross-coupling reactions for the stereospecific construction of bonds between unsaturated carbon functions.[4] For example, the synthesis of trisubstituted homoallylic alcohols by means of either a syn (platinum)[5a] and an anti (ruthenium)[5b] selective hydrosilylation reaction of alkynylhydrosilanes followed by palladium-catalyzed cross-coupling has recently been reported (Scheme 1). The intramolecular hydrosilylation of alkynylsilyl ethers affords cyclic siloxanes having a stereodefined alkenyl moiety. Thus, subsequent stereospecific cross-coupling

SCHEME 1



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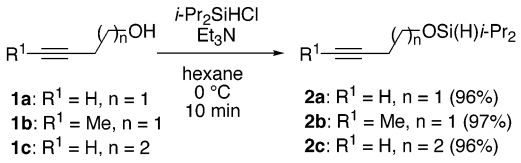
reactions afford geometrically homogeneous trisubstituted alkenes. The geometry of the alkene moiety is predictable and depends on the stereoselectivity of the hydrosilylation.

Introduction of both a carbon−carbon bond and a carbon−silicon bond, as for example in intramolecular silylformylation of an alkynylsilane, is a well-studied and powerful synthetic method for introduction of an aldehyde function into organic molecules with concomitant formation of a defined alkenyl unit.[6] Recently, novel tandem processes employing the intramolecular silylformylation have been reported.[6b,c] To expand the scope of organosilicon couplings, we envisioned the use of intramolecular silylformylation for the preparation of unsaturated silicon substrates that could provide access to a diverse family of α,β-unsaturated aldehydes bearing hydroxyalkyl groups. Herein, we report the development and application of a novel method for the preparation of stereodefined, functionalized α,β-unsaturated aldehydes in three steps starting from alkynyl alcohols.

Results

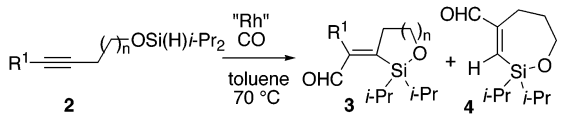
1. Intramolecular Silylformylation of Alkynyl Hydrosilanes. The substrates for intramolecular silylformylation, alkynyloxy hydrosilanes **2**, were easily prepared in excellent yield from alkynyl alcohols **1** (Scheme 2). The intramolecular silylformylation was initially carried out following a procedure described by Ojima.[7]

SCHEME 2



Two catalysts, $Rh(acac)(CO)_2$ (**5**) and $[Rh(CNt\text{-}Bu)_4][Co(CO)_4]$ (**6**), were tested for the silylformylation of **2a**. These rhodium complexes are reported to be effective catalysts that can provide aldehydes in high yield.[7] The intramolecular silylformylation of **2a** was performed in the presence of a rhodium catalyst under a carbon monoxide atmosphere (150 psi) in toluene at 70 °C. Although the commercially available rhodium catalyst **5** gave the cyclic silyl ether **3a** only in 26% yield, the rhodium−cobalt catalyst **6** afforded the same product in 72% yield (Table 1, entries 1 and 2). The ^1H NMR spectrum of **3a** displayed a doublet at δ 9.46 ppm for the aldehyde group and doublet of triplets at δ 6.82 ppm for the olefinic proton. The olefin geometry in **3a** was determined by a NOE experiment. A measurable (5%) NOE was observed between the olefinic proton (δ 6.82 ppm) next to the aldehyde and allylic methylene protons (δ 2.81 ppm). The reaction of alkynyloxy hydrosilane **2b** with the bimetallic catalyst **6** also proceeded smoothly to give the cyclic silyl ether **3b** bearing a methyl group on the alkene in 72% yield (entry 3). However, under similar reaction conditions, the reaction of **2c** gave only 8% of the six-membered cyclic silyl ether **3c**. Employing higher pressures (i.e., 750 psi) led to no improvement in the yield (entries 4 and 5). The geometries of the double bonds in **3b** and **3c** were also established by NOE experiments.

TABLE 1. Silylformylation of Alkynylhydrosilane 2

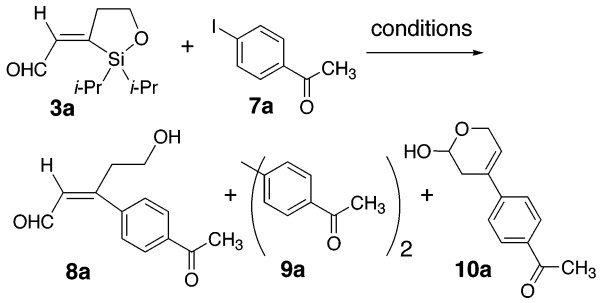


entry	substrate (*n*)	catalyst	CO, psi	time, h	products (yield, %)
1	**2a** (1)	**5**[a]	150	9	**3a** (26)
2	**2a** (1)	**6**[b]	150	9	**3a** (72)
3	**2b** (1)	**6**	150	9	**3b** (72)
4	**2c** (2)	**6**	150	20	**3c** (8) + **4c** [c]
5	**2c** (2)	**6**	750	20	**3c** (18) + **4c** (2)

[a] $Rh(acac)(CO)_2$. [b] $[Rh(CNt\text{-}Bu)_4][Co(CO)_4]$. [c] Observed on TLC but not isolated.

2. Cross-Coupling Reaction of the Cyclic Silyl Ether. Initial studies on the cross-coupling reactions of **3a** revealed that it possessed reactivity distinct from that of other alkenylsilanes. The reaction conditions commonly used for organosilicon cross-coupling reactions ($Pd_2(dba)_3 \cdot CHCl_3$, TBAF, THF) failed, presumably because the silyl ether is unstable. For example, the reaction of cyclic silyl ether **3a** with 4-iodoacetophenone (**7a**) in the presence of $Pd_2(dba)_3 \cdot CHCl_3$ and TBAF in THF did not yield the desired product (Table 2, entry 1) but rather the homocoupling product, **9a**.[8] Formation of the homocoupling product is often observed in transition-metal-catalyzed cross-coupling reactions.[9] Even at elevated temperatures,

TABLE 2. Cross-Coupling Reaction of 3a



entry	conditions	products (yield,[a] %) 8a	9a	10a
1	$Pd_2(dba)_3 \cdot CHCl_3$ TBAF, THF, rt, 24 h	0	28	0
2	$Pd_2(dba)_3 \cdot CHCl_3$ TBAF, THF, 50 °C, 2 h	0	46	0
3	$Pd_2(dba)_3 \cdot CHCl_3$ TBAF, THF, 50 °C, 3 h[b]	0	40	0
4	APC,[c] CsF, DMF, CuI (5 mol %), rt, 30 min	55	13	9

[a] Yield of isolated product. [b] Aryl iodide was added in three portions every 20 min. [c] APC = $[(allyl)PdCl]_2$.

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(9) Denmark, S. E.; Wu, Z. *Org. Lett.* **1999**, *1*, 1495 and references therein.

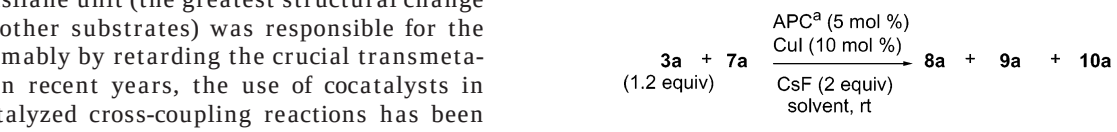
the desired product could not be obtained (entry 2). Because the maintenance of low aryl iodide concentration often suppresses a formation of homocoupling products,[5a] the aryl iodide **7a** was added in three portions every 20 min. Unfortunately, even this modification did not work and again only homocoupling product **9a** was isolated in 40% yield (entry 3). $[(Allyl)PdCl]_2$, which is soluble in THF (unlike $Pd_2(dba)_3{\cdot}CHCl_3$), was employed as the palladium catalyst, but the desired product was not obtained at all. Because the silyl ether seemed to be unstable to TBAF, a weaker fluoride activator CsF was employed in DMF (to increase the solubility of CsF), but again no desired product was observed.

Clearly, the problem with this coupling process was more fundamental, as variation in the common reaction components did not give even a hint of the desired products. We surmised that the electron-deficient nature of the alkenylsilane unit (the greatest structural change compared to other substrates) was responsible for the failure, presumably by retarding the crucial transmetalation step. In recent years, the use of cocatalysts in palladium-catalyzed cross-coupling reactions has been effective in improving reaction rates and product yields.[10] In particular, copper cocatalysts have been used successfully in Stille cross-coupling reactions of electronic-deficient alkenylstannanes.[10a,b] Organosilicon cross-coupling reactions also benefit from the use of copper cocatalysts.[11] Among many readily available copper salts, CuI is frequently employed as the cocatalyst and often gives better results than other copper salts.[10b,11d,g] To our delight, the use of CuI in the present cross-coupling reaction showed a remarkable effect. Thus, reaction of **3a** with **7a** in the presence of both $[(allyl)PdCl]_2$ and CuI with CsF as the activator in DMF at room temperature gave the desired product **8a** in 55% yield along with homocoupling product **9a** and hemiacetal **10a** in 13 and 9% yields, respectively (Table 2, entry 4).

At this point, although the desired product could be obtained, formation of the homocoupling product **9a** and the hemiacetal **10a** remained problematic. To suppress the formation of these side products and to obtain the products in higher yields, we undertook further optimization studies by HPLC analysis using biphenyl as an internal standard. The ratio of copper to palladium as well as the sources of copper and palladium catalysts, the fluoride activator, addition of water and ligands, and use of hydrosilane as additives were systematically surveyed as described below.

2.1. Effect of the Solvent. To identify a suitable solvent for the cross-coupling reaction, 1.2 equiv of **3a** with respect to **7a** was used at room temperature under an argon atmosphere. The reaction in DMF afforded a rapid reaction, and HPLC analysis after 5 min showed 73% of **8a** and 15% of **9a**. No hemiacetal **10a** was observed (Table 3, entry 1). Although the reaction in acetonitrile gave the product **8a**, the reaction was slower than that in DMF (entry 2). Use of THF and 1,4-dioxane afforded little desired product even after 10 h (entries 3 and 4). Thus, DMF was selected as the appropriate solvent for both rapid conversion and high yield.

TABLE 3. Optimization of the Solvent



entry	solvent	time, min	HPLC yield,[b] % 7a	8a	9a	10a
1	DMF	5	4	73	15	<1
		10	2	53	19	10
2	CH_3CN	5	54	3	5	<1
		60	<1	53	17	8
3	THF	600	67	11	3	6
4	1,4-dioxane	600	73	1	2	<1

[a] APC = $[(allyl)PdCl]_2$. [b] Determined by HPLC analysis using biphenyl as an internal standard.

2.2. Effect of Cu and Pd Sources and Their Ratio. Next, optimization studies focused on identification of the appropriate ratio of copper to palladium in DMF as a solvent (Table 4). The initial reaction conditions that employed 5 mol % of $[(allyl)PdCl]_2$ and 10 mol % of CuI (Pd/Cu = 1.0) proved to be optimal (Table 4, entry 3). Decreasing in the amount of CuI tended to slow the reaction (entries 1 and 2). For example, with 5 mol % of $[(allyl)PdCl]_2$ and 5 mol % of CuI (Pd/Cu = 2.0), the reaction was not complete within 30 min. Increasing the amount of CuI increased the rate of formation of the homocoupling product **9a** (entries 4 and 5). Further

TABLE 4. Optimization of the Cu/Pd Ratio

entry	catalysts (mol %)	Cu/Pd	time, min	HPLC yield,[b] % 7a	8a	9a	10a
1	APC[a] (5)	0.25	5	53	23	8	<1
	CuI (2.5)		30	39	23	15	7
2	APC (5)	0.5	5	24	46	17	4
	CuI (5)		30	18	24	23	27
3	APC (5)	1	5	4	73	15	<1
	CuI (10)		10	2	53	19	10
4	APC (5)	2	5	<1	55	23	2
	CuI (20)		10	<1	56	27	8
5	APC (5)	4	5	<1	72	26	<1
	CuI (40)		10	<1	72	25	4

[a] APC = $[(allyl)PdCl]_2$. [b] Determined by HPLC analysis using biphenyl as an internal standard.

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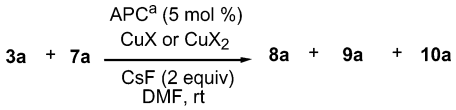
TABLE 5. Survey of Cu Cocatalysts in Combination with [(allyl)PdCl]$_2$



entry	Cu (mol %)	time, min	HPLC yield,[b] % 7a	8a	9a	10a
1	CuI (10)	5	4	73	15	<1
2	CuBr (10)	5	5	56	19	<1
		10	2	56	27	5
3	CuCl (10)	10	51	9	17	<1
		30	43	8	23	3
4	CuCN (10)	10	62	10	10	12
		30	51	3	10	18
5	CuOTf·toluene (10)	5	9	71	18	<1
		10	<1	57	19	11
6	$CuCl_2$ (10)	10	10	49	16	6
		30	<1	21	21	26
7	CuF_2 (10)	10	40	8	25	<1
		30	29	5	42	9
8	$Cu(OTf)_2$ (10)	10	37	19	17	9
		30	18	9	27	14
9	$Cu(BF_4)_2·6H_2O$ (10)	10	50	18	12	<1
		30	26	31	22	4
10	$CuSO_4·5H_2O$ (10)	10	38	32	22	<1
		30	21	19	36	8

[a] APC = [(allyl)PdCl]$_2$. [b] Determined by HPLC analysis using biphenyl as an internal standard.

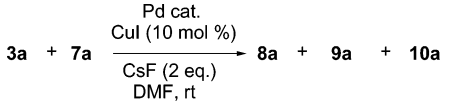
optimization focused on identifying superior sources of the copper and palladium catalysts. In the absence of an understanding of the reaction mechanism, it was unclear which oxidation states of the copper and palladium agents were active in the carbon−carbon bond-formatting process. A survey of copper and palladium sources was undertaken that maintained a 1/1 ratio of the two metals as was shown above.

Other Cu(I) cocatalysts in combination with [(allyl)-PdCl]$_2$ were generally inferior to CuI (Table 5, entries 2−4). However, Cu(I)OTf−toluene complex gave results comparable to CuI (entry 5). Interestingly, Cu(II) catalysts such as $CuCl_2$, $Cu(OTf)_2$, $Cu(BF_4)_2$, and $CuSO_4$ also gave the desired coupling product, but in each case, HPLC analysis showed a significant amount of the homocoupling product as well (entries 6−10). Thus, CuI seemed to be the best cocatalyst in combination with [(allyl)PdCl]$_2$.

Several palladium sources were surveyed in the presence of CuI (10 mol %) as the cocatalyst (Table 6). Palladium(II) catalysts such as $PdCl_2$, $Pd(PPh_3)_2Cl_2$, and $Pd(OAc)_2$ were tested, but all these Pd(II) catalysts were inferior to [(allyl)PdCl]$_2$ (Table 6, entries 1−4). Next, a survey of Pd(0) sources was conducted. Most palladium cross-coupling reactions proceed through a Pd(0) to Pd-(II) cycle because Pd(0) is required for the oxidative addition step.[1] Hence, Pd(0) sources may allow for faster and more efficient reactions. Surprisingly, the use of a Pd(0) catalyst such as $Pd(dba)_2$ or $Pd(PPh_3)_4$ with CuI slowly afforded the product **8a** in poor yield (entries 5 and 6) as did the coupling reaction in the presence of Pd-$(dba)_2$ and $CuCl_2$ (entry 7). As a result, it was concluded that the combination of [(allyl)PdCl]$_2$ and CuI was optimal (Table 6, entry 1).

2.3. Survey of Fluoride Source. As shown in Table 4, entry 3, the reaction of cyclic silyl ether **3a** and

TABLE 6. Survey of Pd Catalysts in Combination with CuI



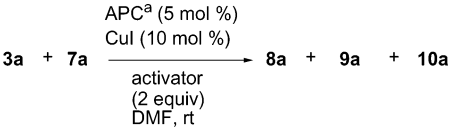
entry	Pd (mol %)	time, min	HPLC yield,[b] % 7a	8a	9a	10a
1	APC[a](5)	5	4	73	15	<1
2	$PdCl_2$ (10)	5	14	43	32	<1
		10	5	39	33	7
3	$Pd(PPh_3)_2Cl_2$ (10)	10	10	50	12	13
		30	5	24	12	30
4	$Pd(OAc)_2$ (10)	5	14	30	30	7
		10	8	25	35	15
5	$Pd(dba)_2$ (10)	10	60	3	8	7
		30	54	2	9	6
6	$Pd(PPh_3)_4$ (10)	10	46	4	3	6
		30	43	<1	4	13
7[c]	$Pd(PPh_3)_4$ (10)	5	41	29	17	<1
		10	27	24	18	7

[a] APC = [(allyl)PdCl]$_2$. [b] Determined by HPLC analysis using biphenyl as an internal standard. [c] $CuCl_2$ (10 mol %) was used.

4-iodoacetophenone (**7a**) in the presence of CsF was almost complete within 5 min. However, longer reaction times yielded larger amounts of the rearranged hemiacetal compound. Thus, the hemiacetal **10a** is apparently derived from the cross-coupling product **8a** (See Discussion). Thus, slower reacting aryl halides would likely lead to a greater proportion of this side reaction. Accordingly, the search for a milder activator became a priority.

Potassium fluoride also has been used as an activator for organosilicon cross-coupling reactions.[12] Thus, commercially available, spray-dried KF was employed (Table 7, entry 2). Although the reaction required a considerably longer time (>15 h) as compared to CsF, HPLC analysis showed a higher yield of the coupling product **8a** and smaller amounts of the homocoupling product **9a**.

TABLE 7. Survey of Fluoride Sources for Cross-Coupling



entry	3a (equiv)	activator	time, min	HPLC yield,[b] % 7a	8a	9a	10a
1	1.2	CsF	5	4	73	15	<1
2	1.2	KF[c]	300	33	57	7	<1
			900	14	78	10	<1
3	1.2	$KF·2H_2O$	300	6	81	9	<1
			600	5	80	9	3
4	1.3	$KF·2H_2O$	60	19	71	7	<1
			120	<1	90	9	<1

[a] APC = [(allyl)PdCl]$_2$. [b] Determined by HPLC analysis using biphenyl as an internal standard. [c] Spray-dried KF purchased from Aldrich was used.

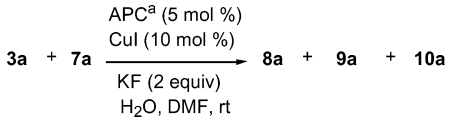
Previous studies of these laboratories have shown that water strongly effects the nucleophilicity and/or basicity of the fluoride activator to reduce the formation of

(12) Hatanaka, Y.; Goda, K.; Okahara, Y.; Hiyama, T. *Tetrahedron* **1994**, *50*, 8301.

byproducts.[4c] Thus, commercially available $KF\cdot 2H_2O$ was tested as an activator. The reaction with $KF\cdot 2H_2O$ proceeded at a considerably faster rate; after 5 h, 81% of **8a** and 9% of **9a** were observed by HPLC (Table 7, entry 3). However, the reaction was not complete even after 10 h. For the complete consumption of iodide, 1.3 equiv of **3a** was used. This additional 0.1 equiv of **3a** had a dramatic effect. The reaction was complete within 2 h, and HPLC analysis showed the formation of **8a** and **9a** in 90 and 9% yields, respectively (entry 4). It is noteworthy that even after an extended reaction time, almost no hemiacetal product **10a** was observed.

The obvious dependence on water content in the fluoride source motivated a search for the appropriate amount of water in this reaction. In these experiments, water was added to a suspension of anhydrous KF in DMF. Although the reaction rates relative to anhydrous KF increased by the addition of water (up to 40 equiv), the reactions were still slower than with $KF\cdot 2H_2O$ (Table 8). High rates and yields are specific to use of $KF\cdot 2H_2O$, presumably because of its solubility in DMF. From these studies, it is clear that $KF\cdot 2H_2O$ is the most suitable activator for suppressing hemiacetal formation and decreasing the amount of the homocoupling product.

TABLE 8. Effect of the Amount of Water



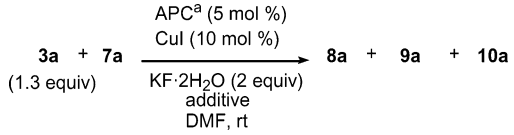
entry	water (equiv)	time, h	HPLC yield,[b] % 7a	8a	9a	10a
1	$KF\cdot 2H_2O$	2	<1	90	9	<1
2	0	2	83	2	<1	<1
		10	74	12	<1	<1
3	2	2	92	2	<1	<1
		10	75	12	<1	<1
4	4	2	69	10	<1	<1
		10	46	29	7	<1
5	10	2	37	38	2	<1
		10	15	67	10	<1
6	20	2	34	47	4	<1
		10	10	78	10	<1
7	40	2	20	62	6	<1
		10	6	74	9	<1
8	110	2	28	53	6	<1
		10	7	72	9	5

[a] APC = [(allyl)PdCl]$_2$. [b] Determined by HPLC analysis using biphenyl as an internal standard.

2.4. Survey of Ligands. Having addressed the problems of reaction rate (and indirectly hemiacetal byproduct formation), we turned our attention to the problem of homocoupling. Previous studies have revealed that the formation of homocoupling products can often be suppressed by addition of a phosphine or an arsine ligand.[9] The effect of the ligand was also tested in reactions employing KF as an activator. Chelating phosphines such as DPPF and DPPP, as well as triphenylphosphine and triphenylarsine, were tested, and in no case was any significant improvement observed (6−10% of **9a**).

2.5. In Situ Reduction of [(Allyl)PdCl]$_2$. A major concern at the outset of these studies was the purity of the cyclic silyl ethers **3**. Since **3** could not be purified by silica gel chromatography, distillation was employed.

TABLE 9. In Situ Reduction of [(allyl)PdCl]$_2$ with Various Hydrosilanes



entry	source of **3a**	additive	time, h	HPLC yield,[b] % 7a	8a	9a	10a
1	c	none	2	<1	90	9	<1
2	d	none	2	49	26	6	<1
			20	9	72	14	<1
3	d	$(i\text{-}Pr_2SiH)_2O$ (**11**)	2	1.5	87	9	<1
4	d	$i\text{-}Pr_2Si(H)OH$ (**12**)	2	<1	89	9	<1
5	d	$[-MeSi(H)O-]_4$ (**13**)	2	<1	89	9	<1
6	d	$[-MeSi(H)O-]_{3-5}$ (**14**)	2	1.5	89	9	<1
7	d	Et_3SiH (**15**)	2	1.8	90	8	<1
8	d	$PhSi(Me)_2H$ (**16**)	1	2	85	11	<1
9	d	$EtOSi(Me)_2H$ (**17**)	2	10	79	7	<1
			5	3	84	8	<1

[a] APC = [(allyl)PdCl]$_2$. [b] Determined by HPLC analysis using biphenyl as an internal standard. [c] Distilled material. [d] Chromatographed material.

However, simple fractional distillation did not provide analytically pure materials. The ^{1}H NMR analysis of the distilled material indicated approximately 95% purity, which was considered to be sufficient for use in subsequent cross-coupling reactions.

Although silica gel chromatography did cause the decomposition of the silyl ether (ca. 30−80% recovery), small amounts of pure **3a** could be obtained. Surprisingly, coupling reactions that employed chromatographed material proved to be considerably slower under the optimal conditions (Table 9, entry 2). This prompted further investigation of the trace impurities present in **3a** and their possible role in the catalytic cycle. However, further purification of the distillated material by chromatography was fairly difficult. Whereas aluminum oxide destroyed **3a**, it was found that **3a** was stable to Florisil. Chromatographic purification using Florisil and silica gel gave pure material without decomposition.[13] Two side products, $(i\text{-}Pr_2SiH)_2O$ (**11**) and an unknown hydrosilane were also found in some fractions.[14] Both hydrosilanes could be seen in the ^{1}H NMR spectra of the distilled material as trace impurities. These impurities could not be removed from **3a** by repeated or fractional distillation. However, use of the Florisil/silica gel chromatography did remove them. Apparently, the presence of these hydrosilanes was essential for initiating the catalytic cycle. This was proven by addition of 0.025 equiv of **11** to a mixture of pure **3a** and **7a** (under standard conditions), which led to a rapid reaction (Table 9, entry 3). HPLC analysis showed almost identical results compared to the reaction of **3a**, which contained hydrosilane impurities. The addition of **11** to the reaction mixture caused immediate formation of a black precipitate, presumably colloidal Pd(0). The precipitation was also observed in the reaction of **3a** contaminated with hydrosilane impurities.

Several hydrosilanes were next examined as additives (Table 9, entries 4−9). These reagents accelerated the

(13) Chromatography on Florisil did not give good separation.
(14) Tetraisopropyldisiloxane (**11**) and an unknown hydrosilane were obtained from the distilled material in about 1 and 3 w/w%, respectively.

reaction as did the hydrosilane **11** (entry 3). Among the hydrosilanes tested, methylhydrocyclosiloxane (**14**) was chosen as an additive because of its low cost and ready availability. The commercially available material is a mixture of three cyclosiloxanes {[−MeSi(H)O]$_{3-5}$} and is easy to handle.

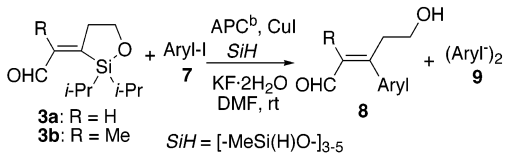
The foregoing extensive optimization revealed that use of [(allyl)PdCl]$_2$ and CuI in a 1 to 1 ratio is the optimal combination of catalysts. Although TBAF is commonly employed for organosilicon cross-coupling reactions, in this case, KF·2H$_2$O is a suitable activator in terms of the yield, reaction rate, and minimization of byproduct. Finally, in situ reduction of [(allyl)PdCl]$_2$ by the hydrosilane was necessary for rapid reaction.

3. Survey of Electrophiles in the Cross-Coupling Reaction. With optimal reaction conditions in hand, several electrophiles were examined. The reaction of **3a** with 4-iodoacetophenone (**7a**) under the optimal conditions proceeded smoothly to completion in 2 h. The desired product **8a** was isolated in 91% yield along with 7% of homocoupling product **9a** (Table 10, entry 1). The ^{1}H NMR spectrum of **8a** showed a doublet at δ 9.43 ppm for the aldehyde and two broad doublets at δ 8.01 and 7.42 ppm for the aromatic protons. The olefin geometry was determined as before by NOE experiments. Reaction of **3a** with ethyl 4-iodobenzoate (**7b**) also proceeded cleanly, and the ester functionality was compatible under these conditions. The desired product **8b** could be obtained in 92% yield (entry 2). 4-Iodonitrobenzene (**7c**) reacted with **3a** rapidly, and the reaction was complete within 1 h to afford **8c** in 83% yield (entry 3). In this case, however, a larger amount (13%) of homocoupling product **9c** was also obtained. Iodobenzene (**7d**) gave a cleaner reaction, and the product **8d** was isolated in 93% yield (entry 4). Electrophiles such as 4-iodoanisole (**7e**) bearing electron-donating groups often react more slowly than those bearing electron-withdrawing groups. Under the optimal conditions, the reaction of **7e** with **3a** was also complete within 2 h to give **8e** in 87% yield (entry 5). Steric hindrance near the coupling center such as in 2-iodotoluene (**7f**) gave the product **8f** in 57% yield; even after extended time, the reaction did not go to completion. However, the use of 1.5 equiv of **3a** and 4.0 equiv of KF·2H$_2$O gave **8f** in 79% yield (entries 6 and 7). Although the reaction with ethyl 2-iodobenzoate was also tested, ^{1}H NMR analysis showed only small amounts of the product (∼5%). Heteroaromatic iodides **7g** and **7h** also gave the products **8g** and **8h** in 78 and 88% yields, respectively (entries 8 and 9).

The reaction of cyclic silyl ether **3b** (bearing a methyl group on the alkene) with 4-iodoacetophenone (**7a**) was slower than the reaction of **3a** with **7a**. Even after 24 h, the reaction did not go to completion under the optimal conditions. However, higher catalyst and hydrosilane loadings gave the desired product **8i** in 83% yield, after 7 h (entry 11). The geometries of the olefinic moiety of all the products **8b**−**i** were also established by NOE experiments (see Supporting Information).

Finally, the reaction of the six-membered cyclic silyl ether **3c** with **7a** was also investigated. Although several conditions were examined, the coupling product could not be obtained.

TABLE 10. Cross-Coupling Reaction with Various Aromatic Iodides[a]



entry	silyl ether	aryl iodide	time, h	yield,[c]% **8**	**9**
1	**3a**	4-(CH$_3$CO)C$_6$H$_4$I (**7a**)	2	91	7
2	**3a**	4-(EtO$_2$C)C$_6$H$_4$I (**7b**)	2	92	5
3	**3a**	4-O$_2$NC$_6$H$_4$I (**7c**)	1	83	13
4	**3a**	C$_6$H$_5$I (**7d**)	2	93	(4)[f]
5	**3a**	4-MeOC$_6$H$_4$I (**7e**)	2	87	5
6	**3a**	2-MeC$_6$H$_4$I (**7f**)	2	57	(11)[f]
7[d]	**3a**	2-MeC$_6$H$_4$I (**7f**)	4	79	(18)[f]
8	**3a**	2-iodothiophene (**7g**)	3	78	(7)[f]
9	**3a**	5-iodo-1-phenylsulfonyl-indole (**7h**)	2	88	(8)[f]
10	**3b**	4-(CH$_3$CO)C$_6$H$_4$I (**7a**)	24	(36)[f]	(10)[f]
11[e]	**3b**	4-(CH$_3$CO)C$_6$H$_4$I (**7a**)	7	83	(14)[f]

[a] Reaction was conducted using silyl ether (1.3 equiv), [(allyl)PdCl]$_2$ (5 mol %), CuI (10 mol %), and [−MeSi(H)O−]$_{3-5}$ (2.5 mol %) unless otherwise mentioned. [b] APC = [(allyl)PdCl]$_2$. [c] Yield of isolated purified material. [d] Silyl ether (1.5 equiv) and KF·2H$_2$O (4.0 equiv) were added. [e] [(Allyl)PdCl]$_2$ (10 mol %), CuI (20 mol %), and [−MeSi(H)O−]$_{3-5}$ (5 mol %) were employed. [f] Expected yield from ^{1}H NMR analysis of crude mixture.

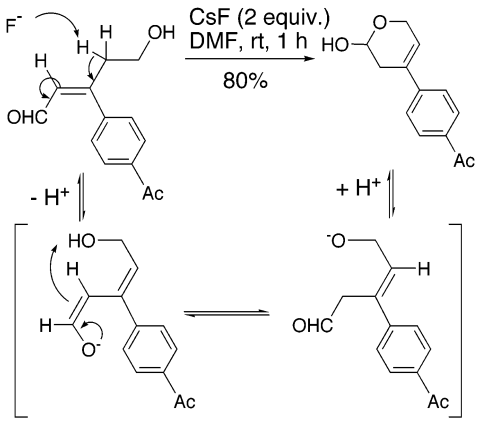
Discussion

The intramolecular silylformylation of alkynes **2a** and **2b** proceeded as expected from the literature precedent and occasions no special comment. However, unlike the five-membered ring siloxanes prepared previously by intramolecular hydrosilylation, compounds **3a** and **3b** behaved very differently in the cross-coupling process. Clearly, the electron-withdrawing formyl group greatly attenuated the reactivity of the siloxane under the conventional reaction conditions. Fortunately, the addition of catalytic amounts of copper iodide reinstated the desired reactivity and cross-coupling could then proceed rapidly at room temperature with a range of aryl iodides. The beneficial effect of copper in cross-coupling reactions is precedented,[11] and there are some reports suggesting that transmetalation from silicon to copper may be the source of the observed effects.[11a−d,15] The mechanism of transmetalation from silicon to palladium in any cross-coupling process has not been elucidated, but may reasonably be viewed as involving the silicon moiety as a nucleophile and the palladium moiety as an electrophile. Thus, electron-deficient silanes are expected to react very slowly, if at all. The use of a shuttle such as CuI that behaves as a strong alkenophile and still maintains nucleophilic reactivity toward palladium could mediate the formation of the diorganopalladium complex.

In organosilicon cross-couplings, TBAF is frequently employed for activation of the silicon−carbon bond.[3] In initial attempts for the cross-coupling reaction of **3a** with **7a**, TBAF was not suitable, presumably due to its high basicity. Further experiments revealed that the cross-coupling product **8a** decomposed in the presence of TBAF.

(15) (a) Trost, B. M.; Ball, Z. T.; Joge, T. *J. Am. Chem. Soc.* **2002**, *124*, 7922. (b) Nishihara, Y.; Ikegashira, K.; Toriyama, F.; Mori, A.; Hiyama, T.; *Bull Chem. Soc. Jpn.* **2000**, *73*, 985. See also ref 8 and references therein.

SCHEME 3



Accordingly, the use of a milder activator was required. Although the reaction employing CsF did afford the cross-coupling product **8a**, hemiacetal **10a** was also obtained from the reaction via the coupling product **8a**. Indeed, treatment of **8a** with 2.0 equiv of CsF yielded hemiacetal **10a** in 80% yield. The mechanism of hemiacetal formation may involve deprotonation by CsF at the γ-position of **8a** followed by tautomerization and pyran ring formation (Scheme 3).

To suppress the formation of hemiacetal **10a**, the use of a much milder activator that possessed weaker basicity yet maintained sufficient affinity for the silicon atom was sought. It was found that KF·2H_2O fulfilled these requirements and afforded a clean and rapid reaction. The addition of water to the reaction mixture employing anhydrous KF revealed that higher reaction rates and yields were unique to the preformed dihydrate. This hydration state helped solubilize KF in DMF without attenuating its silicophilicity.

Another interesting discovery was the need for trace amounts of a hydrosilane to initiate and promote completion of the reaction. Hydrosilane **11**, which was isolated as an impurity from **3a**, was probably formed from diisopropylchlorohydrosilane used in the silylation of 3-butyn-1-ol by hydrolysis followed by dehydration. The role of the hydrosilane in this reaction is believed to be reduction of the Pd(II) source to Pd(0).[16] Indeed, addition of the hydrosilanes such as **11**−**17** to a solution of [(allyl)-$PdCl]_2$ in DMF immediately formed a black precipitate. Hence, it is believed that the addition of hydrosilane for in situ reduction of $[(allyl)PdCl]_2$ is necessary for the rapid reaction and high yields. Interestingly, the in situ reduction of $[(allyl)PdCl]_2$ seemed to be the most effective way to generate Pd(0) for the reaction, as external Pd(0) sources failed to promote the reaction.

Although, the cross-coupling reactions of **3a** and **3b** with various aromatic iodides gave products **8** in excellent yield, the reaction of **3c** with **7a** did not proceed at all. Apparently, the conversion of the silicon unit to a reactive state for transmetalation under these conditions requires the added assistance of ring strain. The nature of that intermediate and the involvement of copper species is under active study.

Conclusion

The cross-coupling reaction of cyclic siloxanes derived from a silylformylation reaction has been demonstrated. The intramolecular silylformylation was found to be an operationally simple, high-yielding, and highly reproducible process for the preparation of cyclic silyl ethers. Because the intramolecular silylformylation proceeds in a stereoselective manner, the cyclic silyl ethers obtained possess a stereodefined olefin moiety. Extensive optimization of the cross-coupling reaction identified conditions to make the reaction efficient and high yielding. The addition of CuI as a cocatalyst was crucial. Although the role of the copper is not clear, the mechanism might involve transmetalation from silicon to copper prior to transmetalation to palladium. Also, this study showed that KF·2H_2O is an effective activator for the base-sensitive organosilane substrate and the product. Finally, it was found that the in situ reduction of $[(allyl)PdCl]_2$ by a hydrosilane is critical for rapid completion of the desired coupling process. The reaction of cyclic silyl ethers such as **3a** and **3b** with various aromatic iodides gave the cross-coupling products in good to excellent yield.

Mechanistic studies on the role of the copper cocatalyst and further application of the present reaction conditions to a more diverse group of coupling partners are currently under investigation.

Acknowledgment. We are grateful to the National Institutes of Health for generous financial support (R01 GM63167).

Supporting Information Available: Procedures for the preparation and characterization of cyclic silyl ethers and all new coupling products, as well as representative procedures for coupling reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034064E

(16) Boukherroub, R.; Chatgilialoglu, C.; Manuel, G. *Organometallics* **1996**, *15*, 1508.