

Palladium-Catalyzed Conjugate Addition of Organosiloxanes to α,β -Unsaturated Carbonyl Compounds and Nitroalkenes

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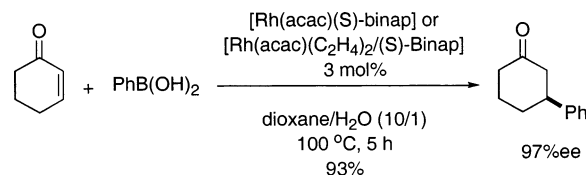
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The addition of aryltrialkoxysilanes to α,β -unsaturated carbonyl compounds (ketones, aldehydes) and nitroalkenes in the presence of SbCl_3 , TBAF, AcOH, and a catalytic amount of $\text{Pd}(\text{OAc})_2$, in CH_3CN at 60°C , provides the corresponding conjugate addition products in moderate to good yields. The addition of equimolar amounts of SbCl_3 and TBAF is necessary for this reaction to proceed smoothly. The arylpalladium complex, which is generated by the transmetalation from a putative hypercoordinate silicon compound, is considered to be the catalytically active species.

Introduction

The 1,4-conjugate addition of organometallic reagents to α,β -unsaturated carbonyl compounds is an important process for carbon–carbon bond formation.^{1,2} Recently, Hayashi and Miyaura have described a general and selective rhodium-catalyzed, asymmetric 1,4-addition of organoboron reagents to α,β -unsaturated ketones (Scheme 1), esters, amides, phosphonates and nitroalkenes.³ Furthermore, Inoue and Oi have reported the rhodium-catalyzed conjugate addition of organostannanes^{4a} and organosiloxanes^{4b,c} to α,β -unsaturated carbonyl compounds. In these catalytic reactions, the aryl- or alkenyl-rhodium complex, which is generated by the transmet-

SCHEME 1



alation from the organometallic precursors, is considered to be the catalytically active species.

In 1995, Uemura reported the palladium-catalyzed conjugate addition of organoboron reagents to α,β -unsaturated ketones and aldehydes (Scheme 2).^{5a} In this reaction, the addition of a catalytic amount of SbCl_3 resulted in the formation of the corresponding conjugate addition products in high yield from enones and enals with a variety of arylboron compounds. The key step of this reaction is believed to be the formation of an antimony enolate derived from the initial coordination of SbCl_3 to the carbonyl oxygen of an organopalladium intermediate. Furthermore, these authors reported a palladium-catalyzed conjugate addition of organostannanes^{5b} and organoantimony reagents^{5c} to α,β -unsaturated carbonyl compounds and Pd-catalyzed Michael-type hydroarylation of nitroalkenes with aryltin compounds.^{5d}

The palladium-catalyzed cross-coupling reactions of organosilicon reagents with organic halides in the pres-

(1) For reviews on 1,4-addition reactions, see: (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. (b) Schmalz, H.-G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 1.5. (c) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.

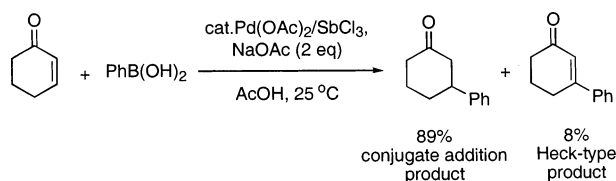
(2) For reviews on enantioselective 1,4-addition reactions, see: (a) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (b) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, Chapter 31.1. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley and Sons: New York, 1994; pp 207–212. (d) Nógrádi, M. *Stereoselective Synthesis*; VCH Publishers: New York, 1995; pp 213–224. (e) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley and Sons: New York, 1995. (f) Feringa, B. *Acc. Chem. Res.* **2000**, *35*, 346.

(3) (a) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1998**, *39*, 8479. (c) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1999**, *40*, 6957. (d) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591. (e) Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047. (f) Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 5951. (g) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Chirality* **2000**, *12*, 469. (h) Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716. (i) Kuriyama, M.; Tomioka, K. *Tetrahedron Lett.* **2001**, *42*, 921. (j) Reetz, M. T.; Moulin, D.; Gosberg, A. *Org. Lett.* **2001**, *3*, 4083. (k) Sakuma, S.; Miyaura, N. *J. Org. Chem.* **2001**, *66*, 8944. (l) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052. (m) Hayashi, T. *Synlett* **2001**, 879. (n) Kuriyama, M.; Nagai, K.; Yamada, K.; Miwa, Y.; Taga, T.; Tomioka, K. *J. Am. Chem. Soc.* **2002**, *124*, 8932. (o) Boiteau, J.-G.; Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 681.

(4) (a) Oi, S.; Moro, M.; Ito, H.; Honma, Y.; Miyano, S.; Inoue, Y. *Tetrahedron* **2002**, *58*, 91. (b) Oi, S.; Honma, Y.; Inoue, Y. *Org. Lett.* **2002**, *4*, 667. (c) Oi, S.; Taira, A.; Honma, Y.; Inoue, Y. *Org. Lett.* **2003**, *5*, 97. For other examples of Rh-catalyzed conjugated addition, see: (d) Venkatraman, S.; Li, C.-J. *Tetrahedron Lett.* **2001**, *42*, 781. (e) Venkatraman, S.; Meng, Y.; Li, C.-J. *Tetrahedron Lett.* **2001**, *42*, 4459. (f) Huang, T.-S.; Li, C.-J. *Chem. Commun.* **2001**, 2348. (g) Kabalka, G. W.; Das, B. C.; Das, S. *Tetrahedron Lett.* **2002**, *43*, 2323. (h) Amengual, R.; Michelet, V.; Genet, J.-P. *Tetrahedron Lett.* **2002**, *43*, 5905. (i) Murata, M.; Shimazaki, R.; Ishikura, M.; Watanabe, S.; Masuda, Y. *Synthesis* **2002**, 717.

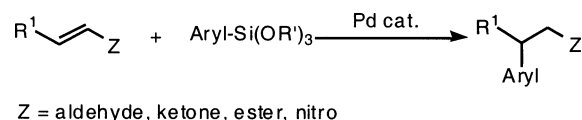
(5) (a) Cho, C. S.; Motofusa, S.; Ohe, K.; Uemura, S.; Shim, S. C. *J. Org. Chem.* **1995**, *60*, 883. (b) Ohe, T.; Wakita, T.; Motofusa, S.; Cho, C. S.; Ohe, K.; Uemura, S. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2149. (c) Cho, C. S.; Motofusa, S.; Ohe, K.; Uemura, S. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2341. (d) Ohe, T.; Uemura, S. *Tetrahedron Lett.* **2002**, *43*, 1269.

SCHEME 2



ence of fluoride ion (pioneered by Hiyama) has emerged as a viable and powerful alternative to the conventional boron and tin-based reagents.⁶ Recent reports from these and other laboratories have demonstrated that simple organosilicon compounds bearing a single oxygen substituent can serve effectively as the donor in palladium-catalyzed cross-coupling reactions.^{7–9} Compared to the other organometallic reagents, silicon compounds have the advantages of (1) low molecular weight, (2) higher stability, (3) ease of activation, and (4) conversion to harmless byproducts. In view of the strong similarities between boron and silicon chemistry, we naturally considered the possibility of effecting the Hayashi/Miyaura addition with silicon reagents under palladium catalysis. Herein, we report the palladium-catalyzed conjugate addition of organosiloxanes to α,β -unsaturated carbonyl compounds and nitroalkenes (Scheme 3).

SCHEME 3

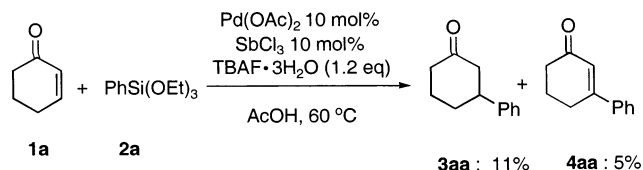


Results

1. Application of Uemura's Method. First, the conditions described by Uemura^{5a} for the conjugate addition of phenyltriethoxysilane were tested. Treatment of 2-cyclohexenone (**1a**, 0.5 mmol) with phenyltriethoxysilane (**2a**, 0.6 mmol) in the presence of $\text{TBAF}\cdot 3\text{H}_2\text{O}$ (0.6 mmol) and catalytic amounts of Pd(OAc)_2 and SbCl_3 in AcOH at $60\text{ }^\circ\text{C}$ afforded 3-phenylcyclohexanone (**3aa**) in 11% yield (GC yield) along with 3-phenylcyclohexenone (**4aa**) in 5% yield (GC yield) (Scheme 4). The formation of the Heck-type product **4aa** indicated the intervention of an undesirable oxidative pathway.

Although the desired product could be obtained, the yield of **3aa** was low and formation of the Heck-type product **4aa** remained problematic. To suppress the formation of the **4aa** and to obtain the addition product

SCHEME 4



in high yield, we undertook an extensive optimization study by GC analysis using naphthalene as an internal standard.

2. Optimization Experiments. 2.1. Survey of Fluoride Sources in the Reaction without SbCl_3 . At first, several fluoride sources were surveyed in this reaction in absence of SbCl_3 (Table 1). These reactions were carried out in AcOH as the solvent at room temperature for 2 h. Of the fluoride sources tested, tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF) provided the best result (entry 4). However, all of the reactions did not proceed to completion and often gave a black precipitate, most likely Pd(0) from reduction of the Pd(II) catalyst. To establish the nature of the reducing agent, pairwise combinations of the reagents (2-cyclohexenone (**1a**), phenyltriethoxysilane (**2a**), $\text{TBAF}\cdot 3\text{H}_2\text{O}$) were added to Pd(OAc)_2 in AcOH . When **2a** and TBAF were added to the reaction together in the absence of **1a**, the reaction became a black heterogeneous suspension, presumably from formation of Pd(0) . Subsequently, we found that TASF was not the best promoter, but that under conditions that suppressed the formation of Pd(0) , TBAF was superior (vide infra).

TABLE 1. Survey of Fluoride Sources in the Reaction without SbCl_3 ^a

entry	fluoride source	time, h	GC yield, ^b %		
			1a	3aa	4aa
1	$\text{TBAF}\cdot 3\text{H}_2\text{O}$	2	75	12	2
2	KF	2	75	0	0
3	CsF	2	43	8	trace
4	TASF	2	30	30	4

^a Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), fluoride source (3.0 mmol), Pd(OAc)_2 (0.05 mmol), AcOH (1 mL), rt, Ar atmosphere. ^b Determined by GC analysis using naphthalene as an internal standard.

2.2. Optimization of the $\text{PhSi(OEt)}_3/\text{TBAF}/\text{SbCl}_3/\text{AcOH}$ Ratio. The next optimization studies focused on identification of the appropriate ratio of the arylsilicon agent, TBAF , SbCl_3 , and AcOH (Table 2). Preliminary results indicated that the reaction could be run in CH_3CN without adverse effects on the rate or yield. Therefore, in this study, all of the reactions were conducted in CH_3CN . The reaction without SbCl_3 quickly stalled and gave a black precipitate (entry 1). However, the reactions with SbCl_3 did not give the black precipitate. In the reaction with equimolar amounts of SbCl_3 and TBAF , **3aa** was formed in 42% yield (entry 2). Treatment of the silane **2a** with 2 equiv each of TBAF and

(6) (a) Hiyama, T. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P., J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 10. (b) Hiyama, T.; Hatanaka, Y. *Pure Appl. Chem.* **1994**, *66*, 1471.

(7) (a) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835. (b) Denmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull.* **2002**, *50*, 1531. (c) Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2002**, *124*, 2102. (d) Denmark, S. E.; Sweis, R. F. *Org. Lett.* **2002**, *4*, 3771.

(8) (a) Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Org. Lett.* **1999**, *1*, 299. (b) Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 5342. (c) Chang, S.; Yang, S. H.; Lee, P. H. *Tetrahedron Lett.* **2001**, *42*, 4833.

(9) Polyalkoxysilanes have also been reported as viable agents for fluoride-activated cross-coupling reactions: (a) Tamao, K.; Kobayashi, K.; Ito, Y. *Tetrahedron Lett.* **1989**, *30*, 6051. (b) Mowery, M. E.; DeShong, P. *Org. Lett.* **1999**, *1*, 2137. (c) Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053. (d) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684. (e) Shibata, K.; Miyazawa, K.; Goto, Y. *Chem. Commun.* **1997**, 1309.

TABLE 2. Optimization of the PhSi(OEt)₃/TBAF/SbCl₃/AcOH Ratio^a

$$1\mathbf{a} + 2\mathbf{a} \xrightarrow[\text{CH}_3\text{CN}, 60\text{ }^\circ\text{C}]{\text{Pd(OAc)}_2, \text{SbCl}_3, \text{TBAF}\cdot 3\text{H}_2\text{O}, \text{AcOH}} 3\mathbf{aa} + 4\mathbf{aa}$$

entry	ratio ^b of PhSi(OEt) ₃ /TBAF/SbCl ₃ /AcOH	time, h	GC yield, ^c %		
			1a	3aa	4aa
1	1.2/1.2/0/5.0	2	66	17	8
2	1.2/1.2/1.2/5.0	67	32	42	5
3	1.2/2.4/2.4/5.0	93	10	76	5
4	2.0/3.0/3.0/5.0	50	4	84	8
5	2.0/3.0/3.0/0	92	7	68	9
6	2.0/4.0/2.0/5.0	48	9	73	12
7	2.0/4.0/4.0/5.0	48	0	82	5
8	3.0/3.0/3.0/5.0	44	0	77	6
9	3.0/4.0/4.0/5.0	67	10	67	4

^a Reaction conditions: **1a** (0.5 mmol), Pd(OAc)₂ (0.05 mmol), CH₃CN (1 mL), 60 °C, Ar atmosphere. ^b Based on **1a**. ^c Determined by GC analysis using naphthalene as an internal standard.

TABLE 3. Survey of Lewis Acids^a

$$1\mathbf{a} + 2\mathbf{a} \xrightarrow[\text{CH}_3\text{CN}, 60\text{ }^\circ\text{C}]{\text{Pd(OAc)}_2, \text{Lewis acid}, \text{TBAF}\cdot 3\text{H}_2\text{O}, \text{AcOH}} 3\mathbf{aa} + 4\mathbf{aa}$$

entry	Lewis acid	time, h	GC yield, ^b %		
			1a	3aa	4aa
1	SbCl ₃	48	0	82	5
2	ZnCl ₂	45	82	5	5
3	BiCl ₃	45	32	45	6
4	AlCl ₃	43	57	0	0
5	FeCl ₃	43	94	3	0
6	SnCl ₄	21	65	0	0
7	BF ₃ ·Et ₂ O	19	83	0	0
8	CeCl ₃	20	55	0	0

^a Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), TBAF·3 H₂O (2.0 mmol), Lewis acid (2.0 mmol), AcOH (2.5 mmol), Pd(OAc)₂ (0.05 mmol), CH₃CN (1 mL), 60 °C, Ar atmosphere. ^b Determined by GC analysis using naphthalene as an internal standard.

SbCl₃ further increased the yield of **3aa** (entry 3). Moreover, the use of 2 equiv of silane **2a** per enone **1a**, produced **3aa** in still higher yield (entry 3 vs 4, 7).

If the ratio of SbCl₃ to TBAF was decreased to 0.5, the amount of the Heck-type product **4aa** increased (entry 6 vs 7). A reaction without AcOH led to a decrease in the yield of **3aa** and a slower reaction rate (entry 4 vs 5). Further increasing the loading of **2a** did not have a beneficial effect (entries 8, 9). From these studies, we concluded that the optimal ratio of **2a**/SbCl₃/TBAF/AcOH was 2.0/4.0/4.0/5.0 in CH₃CN solvent. Although TASF was examined instead of TBAF using these conditions, the reaction did not proceed as well.

2.3. Survey of Lewis Acids. The effect of a wide range of Lewis acids (other than SbCl₃) on the rate and yield of the conjugate addition was examined next (Table 3). Whereas almost all of the Lewis acids surveyed were ineffective for formation of **3aa**, SbCl₃ was clearly the Lewis acid of choice. BiCl₃ gave a modest yield of the desired product (entry 3) whereas ZnCl₂ and FeCl₃ (entries 2 and 5, respectively) afforded only a trace of the product. This is in sharp contrast to Uemura's studies with arylboronic acids,^{5a} wherein almost all of the Lewis

TABLE 4. Survey of Palladium Catalysts^a

$$1\mathbf{a} + 2\mathbf{a} \xrightarrow[\text{CH}_3\text{CN}, 60\text{ }^\circ\text{C}]{\text{Pd cat.}, \text{SbCl}_3, \text{TBAF}\cdot 3\text{H}_2\text{O}, \text{AcOH}} 3\mathbf{aa} + 4\mathbf{aa}$$

entry	Pd catalyst	time, h	GC yield, ^b %		
			1a	3aa	4aa
1	Pd(OAc) ₂	48	0	82	5
2	PdCl ₂	43	4	82	6
3	Pd(TFA) ₂	43	0	85	4
4	(CH ₃ CN) ₂ PdCl ₂	43	0	86	6
5	(PPh ₃) ₂ PdCl ₂	46	69	6	0
6	PdBr ₂	46	2	86	5

^a Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), TBAF·3 H₂O (2.0 mmol), SbCl₃ (2.0 mmol), AcOH (2.5 mmol), Pd cat. (0.05 mmol), CH₃CN (1 mL), 60 °C, Ar atmosphere. ^b Determined by GC analysis using naphthalene as an internal standard.

TABLE 5. Survey of Solvents^a

$$1\mathbf{a} + 2\mathbf{a} \xrightarrow[\text{solvent}, 60\text{ }^\circ\text{C}]{\text{Pd(OAc)}_2, \text{SbCl}_3, \text{TBAF}\cdot 3\text{H}_2\text{O}, \text{AcOH}} 3\mathbf{aa} + 4\mathbf{aa}$$

entry	solvent	time, h	GC yield, ^b %		
			1a	3aa	4aa
1	THF	26	6	78	7
2	toluene	26	0	79	6
3	MeOH	42	24	47	4
4	dioxane	29	0	78	8
5	DMF	23	24	51	11
6	CH ₃ CN	48	0	82	5
7	AcOH	67	2	79	6

^a Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), TBAF·3 H₂O (2.0 mmol), SbCl₃ (2.0 mmol), AcOH (2.5 mmol), Pd(OAc)₂ (0.05 mmol), solvent (1 mL), 60 °C, Ar atmosphere. ^b Determined by GC analysis using naphthalene as an internal standard.

acids afford moderate yields of the desired product. This suggested that the role of SbCl₃ in our studies may be different from its role in Uemura's work.

2.4. Survey of Pd(II) Catalysts. The conjugate addition reaction was examined using other Pd(II) catalysts such as PdCl₂, Pd(TFA)₂, (CH₃CN)₂PdCl₂, (PPh₃)₂PdCl₂, and PdBr₂ in place of Pd(OAc)₂ (Table 4). Remarkably, all Pd(II) catalysts except (PPh₃)₂PdCl₂ afforded similarly high yields as Pd(OAc)₂. Presumably, the presence of the phosphine in (PPh₃)₂PdCl₂ inhibited this reaction (entry 5).

2.5. Effect of the Solvent. The next stage in the optimization focused on the effect of the solvent (Table 5). The yield of **3aa** was found to be greater than 70% in THF, toluene, dioxane, and AcOH (entries 1, 2, 4, and 7). Although the reaction in AcOH gave **3aa** in 79% yield, the rate was slower than that in other solvents (entry 7). Thus, CH₃CN was selected to be optimal for this reaction.

2.6. Survey of Bronsted Acids and the Amount of the Palladium Catalyst. Several Bronsted acids were examined in addition to AcOH (Table 6). With trifluoroacetic acid, the most acidic additive in this study, **3aa** was obtained in 78% yield (entry 9). However, the reaction rate was lower than that with other acids. Several acids showed results similar to those with AcOH.

TABLE 6. Survey of Bronsted Acids and the Amount of the Palladium Catalyst^a

1a + 2a		Pd(OAc) ₂ , SbCl ₃ TBAF·3H ₂ O, acid			3aa + 4aa		
		CH ₃ CN, 60 °C					
entry	acid	pK _a ^b	Pd(OAc) ₂ , ^c mol %	time, h	GC yield, ^d %		
					1a	3aa	4aa
1	AcOH	4.76	10	30	5	80	5
2			5	30	6	83	5
3	MeOCH ₂ CO ₂ H	3.57	10	27	2	85	5
4			5	68	9	80	4
5	ClCH ₂ CO ₂ H	2.86	10	28	0	84	5
6			5	46	2	82	5
7	F ₂ HCO ₂ H	-	10	47	0	82	4
8	PhCO ₂ H	4.20	10	47	5	84	5
9	F ₃ CCO ₂ H	0.2	10	70	7	78	3
10	Cl ₃ CCO ₂ H	0.7	10	47	3	81	4
11	<i>t</i> -BuCO ₂ H	5.04	10	28	0	82	5

^a Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), TBAF·3H₂O (2.0 mmol), SbCl₃ (2.0 mmol), acid (2.5 mmol), Pd(OAc)₂, CH₃CN (1 mL), 60 °C, Ar atmosphere. ^b Reference 10. ^c Based on **1a**. ^d Determined by GC analysis using naphthalene as an internal standard.

The difference in pK_a of the acids did not seem to influence the yield of the reaction.

Next, the effect of lowering the Pd catalyst loading was examined (entries 2, 4, 6). Interestingly, the results were dependent on the nature of the acid additive. For example, with AcOH, lowering the catalyst loading to 5 mol % had no effect on the yield or rate of the reaction (entry 1 vs 2). However, with MeOCH₂CO₂H and ClCH₂CO₂H as the additives, the reaction rates were significantly lowered (entry 3 vs 4, 5 vs 6). From these studies, the conditions found in entry 2 were considered to be optimal.

3. Conjugate Addition of Phenyltriethoxysilane (2a) to α,β -Unsaturated Carbonyl Compounds and Nitroalkenes. With an optimal set of reaction conditions established, the scope of the reaction components could be surveyed. Various α,β -unsaturated carbonyl compounds (ketones, aldehydes, and ester) and nitroalkenes, were subjected to the conjugate addition process and the results are summarized in Table 7. These reactions were examined with both 5 and 10 mol % of the Pd catalyst (based on **1**), both of which showed good results. In all cases, biphenyl was formed in less than 5% yield as a side product.

First, both cyclic and acyclic enones were examined. With 2-cyclohexenone (**1a**) and 2-cyclopentenone (**1b**), the reaction was accompanied by the formation of an appreciable amount the Heck-type products, but in other cases the Heck-type product was scarcely formed. From various ketones, such as 2-cyclohexenone (**1a**), chalcone (**1e**), and 1-phenyl-2-buten-1-one (**1h**), the corresponding phenylation products were produced in good to excellent yield (entries 1, 5, 8). However, with other ketones (**1b**, **1c**, **1f**, **1g**, **1i**), the corresponding addition products were obtained in moderate yield (entries 2, 3, 6, 7, 9). The formation of phenylated products was not observed from 3-methyl-2-cyclohexenone (**1d**) (entry 4), even with 10 mol % of Pd, most likely due to the steric inhibition provided by the methyl group.

Next, several α,β -unsaturated aldehydes were surveyed. Gratifyingly, the conjugate addition product from (*E*)-cinnamaldehyde (**1k**) was obtained in excellent yield (93%) (entry 11). With α,β -unsaturated aldehydes bearing alkyl groups in the β -position (**1j**, **1m**, **1o**), the corresponding products were obtained in moderate to good yield (entries 10, 13, 15). Unfortunately, in reactions of 1-cyclohexene-1-carboxyaldehyde (**1l**) and 3-methyl-2-butenal (**1n**), the yields of the desired products were quite low. With methyl (*E*)-cinnamate (**1p**), the conjugate addition product was not obtained at all (entry 16).

Finally, to expand the scope of synthetically useful substrates, nitroalkenes were investigated. The addition of phenyltriethoxysilane was successful for linear nitroalkenes, 2-nitrostyrene (**1q**), 1-nitropropene (**1r**), 2-nitrovinylcyclohexane (**1s**), which gave the corresponding phenylation products with moderate to good yield (entries 17, 18, 19). In contrast, no reaction occurred in the case of cyclic nitroalkenes, such as 1-nitro-1-cyclohexene (**1t**) (entry 20).

4. Conjugate Addition of Various Aryltrialkoxysilanes to α,β -Unsaturated Carbonyl Compounds and Nitroalkenes. In addition to phenyltriethoxysilane, other aryltrialkoxysilanes could be used for this transformation under the same conditions. The aryltrialkoxysilanes investigated were 4-methoxyphenyltriethoxysilane (**2b**), 4-chlorophenyltriethoxysilane (**2c**) and 4-tolyltrimethoxysilane (**2d**). These silicon compounds were commercially available or easily prepared by Pd¹¹ or Rh-catalyzed¹² silylation of aryl halides.

Treatment of ketone **1i**, aldehyde **1k**, and nitroalkene **1q** with various aryltrialkoxysilanes (**2b–d**) under the optimized condition afforded the corresponding products in moderate to high yields, respectively (Table 8). In the case of 4-chlorophenyltriethoxysilane (**2c**), the yields of the desired products from substrates **1k** and **1q** were lower than those with 4-methoxyphenyltriethoxysilane (**2b**) and 4-tolyltrimethoxysilane (**2d**) (entries 2, 3, 8, 9 vs 5, 6). In entries 5 and 6, the conjugate addition reactions were not complete, and the starting material remained.

Discussion

The palladium-catalyzed conjugate addition of **2a** to ketones, aldehydes, and nitro compounds showed modest structural generality. Among the cyclic ketones examined, 2-cyclohexenone (**1a**) showed higher reactivity than 2-cyclopentenone (**1b**) and 2-cycloheptenone (**1c**) (Table 7, entry 1 vs 2 and 3). With linear ketones, aldehydes, and nitroalkenes, the reactivity of the substrates bearing a phenyl group at the R¹ position was higher than that of the substrates bearing an alkyl group at the R¹ position (Table 7, entry 5 vs 8, 9, entry 11 vs 10, 13, 15, entry 17 vs 18, 19).

Inspection of the results reported with a variety of α,β -unsaturated carbonyl compounds (Table 7, entries 5, 11,

(10) Wronski, M. *J. Chromatogr. A* **1997**, *772*, 19.

(11) (a) Murata, M.; Suzuki, K.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 8569. (b) Manoso, A. S.; DeShong, P. *J. Org. Chem.* **2001**, *66*, 7449.

(12) Murata, M.; Ishikura, M.; Nagata, M.; Watanabe, S.; Masuda, Y. *Org. Lett.* **2002**, *4*, 1843.

TABLE 7. Palladium-Catalyzed Conjugate Addition of Phenyltriethoxysilane to α,β -Unsaturated Carbonyl Compounds and Nitroalkenes^a

entry	1	Pd cat., mol %	time, h ^b	product	yield, % ^c	
1		(1a)	5	29	(3aa) (4aa)	73 (7) ^d
2		(1b)	10	28	(3ba) (4ba)	60 (10) ^d
3		(1c)	10	25	(3ca)	60
4		(1d)	10	49	-	0
5		(1e)	5	28		88
6		(1f)	10	30		47
7		(1g)	5	25		45
8		(1h)	5	41		78
9		(1i)	5	24		52
10		(1j)	5	29		70
11		(1k)	5	36		93
12		(1l)	10	29		12
13		(1m)	5	30		66
14		(1n)	10	48		trace
15		(1o)	10	25		64
16		(1p)	10	47	-	0
17		(1q)	5	26		70
18		(1r)	5	22		55
19		(1s)	10	29		44
20		(1t)	10	28	-	0

^a Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), TBAF·3H₂O (4.0 mmol), SbCl₃ (4.0 mmol), Pd(OAc)₂, AcOH (5.0 mmol), CH₃CN (2 mL), 60 °C, Ar atmosphere. ^b Reactions were stopped after the educt was no longer detected by GC analysis. ^c Yield of isolated, chromatographically homogeneous product. ^d Yield of the Heck-type product.

TABLE 8. Palladium-Catalyzed Conjugate Addition of Phenyltriethoxysilane to α,β -Unsaturated Carbonyl Compounds and Nitroalkenes^a

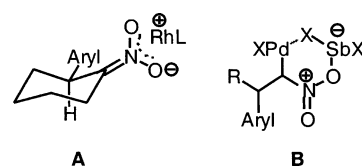
entry	1	2	Pd cat., ^b mol%	time, h	yield (3), % ^c
1		4-MeOC ₆ H ₄ Si(OEt) ₃ (2b)	10	34	55 (3hb)
2		(2b)	5	25	82 (3kb)
3		(2b)	5	24	53 (3qb)
4	(1h)	4-ClC ₆ H ₄ Si(OEt) ₃ (2c)	10	34	64 (3hc)
5	(1k)	(2c)	10	25	43 (3kc)
6	(1q)	(2c)	10	24	34 (3qc)
7	(1h)	4-MeC ₆ H ₄ Si(OMe) ₃ (2d)	10	34	47 (3hd)
8	(1k)	(2d)	5	24	85 (3kd)
9	(1q)	(2d)	5	25	54 (3qd)

^a Reaction conditions: **1** (1.0 mmol), **2** (2.0 mmol), TBAF·3H₂O (4.0 mmol), SbCl₃ (4.0 mmol), Pd(OAc)₂, AcOH (5.0 mmol), CH₃CN (2 mL), 60 °C, Ar atmosphere. ^b Based on **1**. ^c Yield of isolated chromatographically homogeneous product.

16) shows that increasing in the electron-withdrawing power of the Z group favors the formation of the conjugate addition product. This result is the same as that in other Pd(II)-catalyzed conjugate addition reactions^{13a} but is unlike the Rh-catalyzed process.³

In the Rh-catalyzed conjugate additions of organoboronic acids to nitroalkenes,^{3h} cyclic nitroalkenes give the desired product in higher yields than did linear nitroalkenes. In contrast, this reaction (Table 7, entry 20) as well as the Pd-catalyzed hydroarylation of nitroalkenes with aryltin compounds^{5d} was not successful with cyclic nitroalkenes such as 1-nitro-1-cyclohexene (**1t**). We surmise that this behavior arises from the difference between a rhodium nitronate intermediate (**A**) (Chart 1)^{3h,14} and an alkylpalladium species with coordination of Sb(III) to the oxygen of nitro group (**B**).^{5d} This difference might also explain why cyclic aldehydes such as 1-cyclohexene-1-carboxyaldehyde (**1l**) afforded the addition products in low yield (Table 7, entry 12).

Proper adjustment of the ratios of the reaction components was crucial to the success of this reaction. If SbCl₃ was not added, the reaction stopped quickly and a black precipitate was immediately observed (Table 1, entries 1–4; Table 2, entry 1). This black precipitate,

CHART 1

most likely Pd(0) from reduction of the Pd(II) catalyst, occurred upon mixing the arylsiloxane **2a** and TBAF with the Pd(II) catalyst. Because the precipitation of Pd(0) did not occur in the presence of SbCl₃ alone, SbCl₃ may serve as a fluoride scavenger. Thus, one of the roles of SbCl₃ may be to inhibit the reduction of the Pd(II). Although the use of SbCl₃ in this capacity is critical, it also detrimental because it attenuates the activation of **2a** by fluoride ion. Accordingly, reactions with SbCl₃ were slower than those without SbCl₃ (Table 1, entry 1 vs Table 5, entry 7), which is consistent with the action of SbCl₃ as a fluoride scavenger.

On the other hand, Pd-catalyzed conjugate additions using SbCl₃^{5a} or arylantimony compounds,^{5c} increasing the amount of SbCl₃ or organoantimony(III) compounds increases the yield of the conjugate addition product. The organoantimony(III) compounds, present in excess in the reaction system, may coordinate to the palladium to prevent a β -hydride elimination process, thus suppressing the formation of the Heck-type coupling product. In

(13) Bordwell, F. G.; Yee, K. C. *J. Am. Chem. Soc.* **1970**, *92*, 5939.

(14) Cacchi, S.; Misiti, D.; Palmieri, G. *Tetrahedron* **1981**, *37*, 2941.

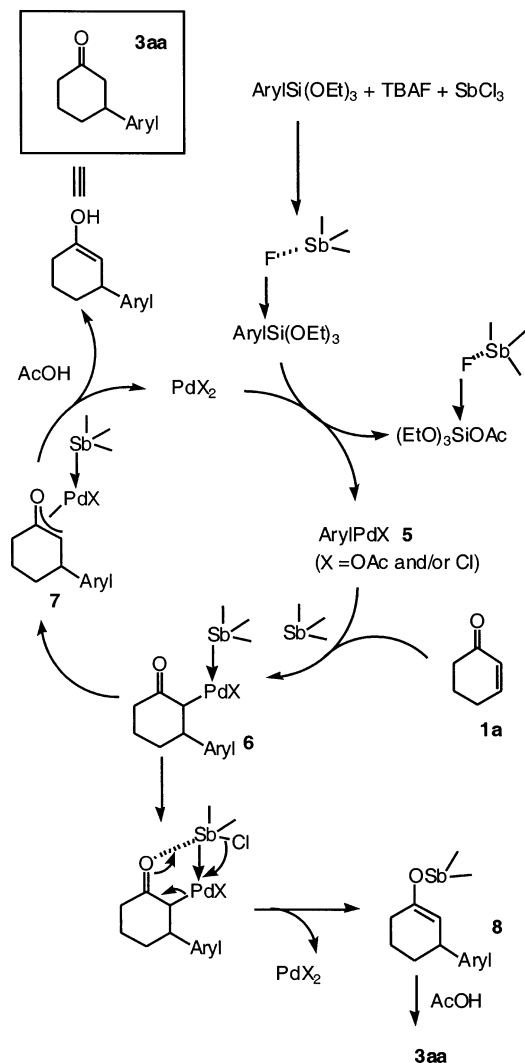


FIGURE 1. Proposed catalytic cycle for palladium-catalyzed conjugate addition.

this conjugate addition reaction, excess SbCl_3 is considered to have the same effect.

We found that several Pd(II) catalysts could be employed (Table 4). However, reaction in the presence of a phosphine ligand did not proceed as well as other Pd(II)-catalyzed conjugate addition reactions using organotin,^{5b} organoantimony,^{5c} and organomercury¹⁵ compounds. In Pd(0)-catalyzed conjugate addition of aryl halides with α,β -unsaturated carbonyl compounds,¹⁵ the use of phosphine ligands does not inhibit the reaction. From these results, it is concluded that addition of ArylPd(II)X (X = OAc or Cl) and ArylPd(II)XL₂ (X = OAc or Cl, L = ligand) to the α,β -unsaturated carbonyl compounds can take place. Thus, in the reactions studied herein, the phosphine ligands must inhibit another part

of catalytic cycle, possibly the transmetalation of the arylsiloxane to Pd(II).

Carrying out the reaction in the absence of AcOH (Table 2, entry 5) led to a decrease in the formation of the desired product and the rate was slowed. The role of AcOH is proposed to be the protonolysis of the Pd- or Sb-enolate which leads to the desired product with regeneration of the Pd(II) catalyst. The pK_a of acid did not strongly influence the rate, yield, or product distribution of the reaction (Table 6). This is most likely due to the buffering action of the fluoride ion. Protonolysis may be turnover limiting, so that any acid below a given pK_a value can effect the release of the Pd(II) salt.

In other Pd-catalyzed conjugate additions of organometallic compounds (B, Sn, Sb),⁵ AcOH is the only effective solvent. In contrast, the reaction described herein gave the desired product in good yield in several other solvents (Table 5, entries 1, 2, 4, 6, 7) using AcOH as an additive.

A plausible catalytic cycle for the conjugate addition reaction based on the original proposal by Uemura^{5c} is presented in Figure 1. An arylpalladium species **5**, generated by the transmetalation between a hypercoordinate silicon compound and the palladium(II) complex, is assumed to be the active intermediate. Addition of **5** to the α,β -unsaturated carbonyl compound **1a** leads to an alkylpalladium species **6**. This species may be converted to an η^3 -type palladium enolate **7**, followed by protonolysis to give the conjugate addition product **3aa**.

On the other hand, SbCl_3 , as a weak Lewis acid, may coordinate to the carbonyl oxygen of species **6**. Concerted elimination of PdX_2 gives an antimony enolate **8**. The protonolysis of the enolate then leads to the conjugate addition product **3aa**.

Conclusion

An efficient palladium-catalyzed conjugate addition of aryltrialkoxysilanes to α,β -unsaturated carbonyl compounds (ketones, aldehydes) and nitroalkenes has been developed. It was shown that an equal molar ratio of SbCl_3 and TBAF was necessary for high yields and to suppress formation of oxidative byproducts. The arylpalladium complex, generated by the transmetalation from a putative hypercoordinate silicon compound, is considered to be the active nucleophilic species. Further application of this process to an asymmetric version of the reaction is currently under investigation.

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Supporting Information Available: Preparation and characterization of all conjugate addition products and a representative procedure for the conjugate addition reaction. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(15) (a) Cacchi, S.; Arcadi, A. *J. Org. Chem.* **1983**, *48*, 4236. (b) Cacchi, S.; Torre, F. L.; Palmieri, G. *J. Organomet. Chem.* **1984**, *268*, C48. (c) Amorese, A.; Arcadi, A.; Bernocchi, E.; Cacchi, S.; Cerrini, S.; Fedeli, W.; Ortar, G. *Tetrahedron* **1989**, *45*, 813.