JOC*Article*

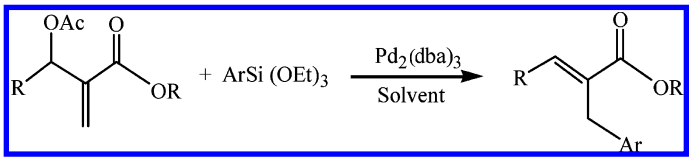
Palladium-Catalyzed Cross-Coupling of Baylis−Hillman Acetate Adducts with Organosilanes

George W. Kabalka,* Gang Dong, Bollu Venkataiah, and Chunlan Chen

Departments of Chemistry and Radiology, The University of Tennessee, Knoxville, Tennessee 37996-1600

kabalka@utk.edu

Received June 10, 2005



A cross-coupling reaction between acetates of Baylis−Hillman adducts and organosilanes is described. A nonconventional solvent poly(ethylene glycol) (PEG) is used as the reaction medium.

Introduction

Palladium-catalyzed carbon−carbon bond formation has become one of the most important reactions in organic synthesis.[1] It provides a highly effective method for preparing a variety of natural products,[2] supramolecules,[3] and liquid crystals.[4] Grignard,[5] organotin,[6] organozinc,[7] and organoboron reagents[8] have all been used as organometallic reactants in palladium-mediated coupling reactions.

Since Hiyama demonstrated that arylfluorosilanes undergo palladium-catalyzed cross-coupling reactions with aryl iodides,[9] the use of silicon-derived compounds as transmetalation reagents has attracted attention because of their low cost, ready availability, low toxicity, and chemical stability.[10] Lee and Wolf reported efficient coupling reactions of aryl chlorides and bromides with organotrimethoxysilanes.[11] DeShong coupled vinyl and aryl halides, aryl triflates, and allylic benzoates with hypervalent silanes.[12] Denmark and others have developed Lewis base-promoted reactions using hypervalent silicates,[13] and the use of alkenyl- and arylsilanols as efficient coupling partners under fluoride-free conditions.[14]

The Baylis−Hillman reaction provides molecules possessing hydroxyl, alkene, and electron-withdrawing groups

(1) (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (b) Miyaura, N., Ed. *Cross-Coupling Reactions*; Springer: Berlin, Germany, 2002. (c) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (d) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (e) Tsuji, J. *Palladium Reagents and Catalysts. Innovations in Organic Synthesis*; John Wiley & Sons: New York, 1995.

(2) (a) Schmitd, U.; Meyer, R.; Leitenberger, V.; Lieberknecht, A. *Angew. Chem., Int. Ed. Engl*. **1989**, *28*, 929. (b) Tamao, K.; Kodama, S.; Nakajima, I.; Kumada, M.; Minato, A.; Suzuki, K. *Tetrahedron* **1982**, *38*, 3347. (c) Muller, D.; Fleury, J. *Tetrahedron Lett*. **1991**, *32*, 2229. (d) Tius, M. A.; Gomez-Galeno, J.; Gu, X.; Zaidi, J. H. *J. Am. Chem. Soc*. **1991**, *113*, 5775.

(3) (a) Rehahn, M.; Schlüter, A. D.; Wegner, G. *Makromol. Chem*. **1990**, *191*, 1991. (b) Wallow, T. I.; Novak, B. M. *J. Am. Chem. Soc*. **1991**, *113*, 7411. (c) Bochmann, M.; Kelly, K. *J. Chem. Soc., Chem. Commun*. **1989**, 532.

(4) Poetsch, E.; Meyer, V.; Böttcher, H. German Patent *DE*3736489, 1987; *Chem. Abstr*. **1990**, *112*, 88951a.

(5) (a) Yamamura, M.; Moritani, I.; Murahashi, S. *J. Organomet. Chem*. **1975**, *91*, C39. (b) Tamao, K.; Kiso, Y.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc*. **1972**, *94*, 9268. (c) Sekiya, A.; Ishikawa, N. *J. Organomet. Chem*. **1976**, *118*, 349. (d) Widdowson D. A.; Zhang, Y.-Z. *Tetrahedron* **1986**, *42*, 2111. (e) Minato, A.; Tamao, K.; Hayashi, T.; Suzuki, K.; Kumada, M. *Tetrahedron Lett*. **1981**, *22*, 5319. (f) Hayashi, T.; Konishi, M.; Fukushima, M.; Mise, T.; Kagotani, M.; Tajika, M.; Kumada, M. *J. Am. Chem. Soc*. **1982**, *104*, 180. (g) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc*. **1984**, *106*, 158. (h) Sofia, A.; Karlstrom, E.; Itami, K.; Backvall, J.-E. *J. Org. Chem*. **1999**, *64*, 1745.

(6) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl*. **1986**, *25*, 508. (b) Farina, V.; Krishnamurthy, V.; Scott, W. *J. Org. React*. **1998**, *50*, 1. (c) Mitchell, T. N. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinhein, Germany, 1998; pp 167−202.

(7) (a) Hayashi, T. *Handbook of Organopalladium Chemistry for Organic Synthesis* **2002**, *1*, 791. (b) Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. *Org. React*. **2001**, *58*, 417. (c) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed*. **2000**, *39*, 4415. (d) Negishi, E. *Organozinc Reagents* **1999**, 213.

(8) (a) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457. (b) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinhein, Germany, 1998; pp 49. (c) Suzuki, A. *J. Organomet. Chem*. **1999**, *576*, 147. (d) Suzuki, A. *Pure Appl. Chem*. **1994**, *66*, 213. (e) Suzuki, A. *Pure Appl. Chem*. **1985**, *57*, 1749.

(9) Hatanaka, Y.; Hiyama, T. *J. Org. Chem*. **1988**, *53*, 918.

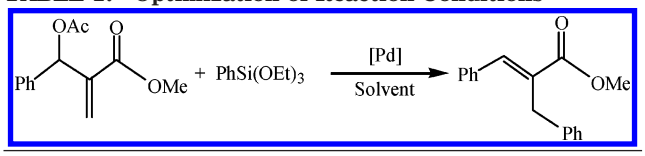
(10) (a) Hiyama, T. In *Metal Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinhein, Germany, 1998; Chapter 10. (b) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res*. **2002**, *35*, 835. (c) Hiyama, T. *J. Organomet. Chem*. **2002**, *653*, 58.

(11) (a) Wolf, C.; Lerebours, R. *Org. Lett*. **2004**, *6*, 1147. (b) Lee, H. M.; Nolan, S. P. *Org. Lett*. **2000**, *2*, 2053.

(12) (a) Brescia, M.-R.; DeShong, P. *J. Org. Chem*. **1998**, *63*, 3156. (b) Mowery, M. E.; DeShong, P. *J. Org. Chem*. **1999**, *64*, 1684. (c) Mowery, M. E.; DeShong, P. *Org. Lett*. **1999**, *1*, 2137. (d) DeShong, P.; Handy, C. J.; Mowery, M. E. *Pure Appl. Chem*. **2000**, *72*, 1655. (e) Riggleman, S.; DeShong, P. *J. Org. Chem*. **2003**, *68*, 8106. (f) Correia, R.; DeShong, P. *J. Org. Chem*. **2001**, *66*, 7159−7165. (g) Hoke, M., E.; Brescia, M.-R.; Bogaczyk, S.; DeShong, P.; King, B. W.; Crimmins, M. T. *J. Org. Chem*. **2002**, *67*, 327. (h) McElroy, W. T.; Deshong, P. *Org. Lett*. **2003**, *5*, 4779.

10.1021/jo051177k CCC: $30.25
Published on Web 10/12/2005

TABLE 1. Optimization of Reaction Conditions



entry	catalyst[a]	base[b]	solvent	temp (°C)	time (h)	yield (%)[d]
1	$Pd_2(dba)_3$	KF	THF/H_2O[c]	50	5	35
2	$Pd(OAc)_2$	KF	THF/H_2O[c]	50	5	trace
3	$Pd_2(dba)_3$	*n*-Bu_4NF	THF	50	2	45
4	$Pd_2(dba)_3$	*n*-Bu_4NF	toluene	50	2	49
5	$Pd_2(dba)_3$	*n*-Bu_4NF	$BmimBF_4$	50	6	0
6	$Pd_2(dba)_3$	*n*-Bu_4NF	PEG	rt	3	92
7	$Pd_2(dba)_3$	*n*-Bu_4NF[e]	PEG	rt	3	80
8	$Pd(OAc)_2$	*n*-Bu_4NF	PEG	rt	3	85

[a] 3 mol % of $Pd_2(dba)_3$ or 5 mol % of $Pd(OAc)_2$ (based on the adduct). [b] Two equivalents of base used. [c] The ratio of THF/H_2O was 20/1. [d] Isolated yields. [e] One equivalent of base used.

in close proximity, which makes them valuable in a number of stereoselective processes.[15] We recently demonstrated that potassium organotrifluoroborates can be employed in palladium-catalyzed cross-coupling reactions with Baylis−Hillman acetate adducts.[16] In view of the similarities between boron and silicon chemistry, the cross-coupling reactions of Baylis−Hillman acetate adducts with silicon reagents were explored with use of palladium catalysis. We wish to report the successful palladium-catalyzed coupling of organosilanes with Baylis−Hillman acetate adducts and related reagents.

Results and Discussion

Optimization of Reaction Conditions. The reaction of methyl 3-acetoxy-3-phenyl-2-methylenepropanoate with phenyltriethoxysilane was chosen as the model system to define the optimum reaction conditions (Table 1). When the coupling reaction was performed in THF/H_2O in the presence of 3 mol % of $Pd_2(dba)_3$ and 2 equiv of KF at 50 °C for 5 h, only a 35% yield of desired product was obtained. When the catalyst was changed to $Pd(OAc)_2$, the yield decreased. Better results were achieved when KF was replaced by tetrabutylammonium fluoride (TBAF) as the silane activator. Treatment of a Baylis−Hillman adduct (0.5 mmol) with phenyltriethoxysilane (0.65 mmol) in the presence of 3 mol % of $Pd_2(dba)_3$ and 2 equiv of TBAF produced 45% of the desired cross-coupled product, 27% of the regioisomer, and 2-benzhydrylacrylic acid methyl ester. To increase the yield of the desired product and suppress the formation of the regioisomer, additional solvents were evaluated. In toluene, 25% of the regioisomer formed along with 49% of the desired product. Due to recent interest in nonconventional solvents, reactions were carried out in an ionic liquid, butylmethylimidazolium tetrafluoroborate ($BmimBF_4$), but no reaction occurred. We then investigated poly(ethylene glycol) (PEG) as a reaction medium.[17] PEG has been shown to be an effective polar, nonprotic solvent for a number of organic reactions. When PEG-600 was used, the isomerization reaction was inhibited and an excellent yield of the coupled product was obtained at room temperature. The quantity of TBAF was also evaluated. One equivalent of TBAF afforded good yields (80%) but 2 equiv of TBAF led to the highest yields (92%). The reaction also proceeded in the presence of $Pd(OAc)_2$ when PEG was used as solvent, and 85% of desired product was formed.

On the basis of the results summarized in Table 1, the optimal reaction conditions for coupling phenyltriethoxysilane with Baylis−Hillman acetate adducts were found to be 3 mol % of $Pd_2(dba)_3$ and 2 equiv of TBAF in PEG-600 at room temperature.

Study of the Reaction Scope. With an optimal set of reaction conditions established, the versatility of the reaction was then surveyed. Baylis−Hillman acetate adducts derived from reactions of aryl aldehydes, heteroaryl aldehydes, and aliphatic aldehydes with methyl acrylate, acrylonitrile, or α,β-unsaturated cyclic ketones were subjected to the new coupling reaction process.

Coupling of Baylis−Hillman Adducts Derived from Methyl Acrylate and Acrylonitrile. The reactions of various Baylis−Hillman acetate adducts derived from methyl acrylate were investigated first. The results are summarized in Table 2 (entries 1−9). Aryl- and heteroarylsilanes readily participate in the reaction (entries 10−12). The reaction yields are very good in the absence of electron withdrawing groups on the aromatic moiety of the adduct (Table 2, entry 9). The reaction is highly stereoselective. The stereochemistry of the products was established by comparing NMR parameters for the olefinic and methylene protons for the products with literature values.[18] The ratio of *E*/*Z* isomers was determined by ^1H NMR analysis. The ratio was normally found to be exceed 90/10 even for aliphatic Baylis−Hillman adducts.

The protocol was then applied to reactions between two 3-acetoxy-2-methylenealkanenitriles **4** and *p*-tolyltriethoxysilane. The desired coupling did not occur at room temperature but the product was obtained after heating the reaction mixture to 50 °C (Figure 1). The reactions afforded products with excellent stereoselectivity. Interestingly, for Baylis−Hillman nitrile adducts, the *Z* isomer was the major product. This inversion in stereochemistry

(13) (a) Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *Chem. Rev.* **1993**, *93*, 1371. (b) Kobayashi, S.; Nishio, K. *J. Am. Chem. Soc.* **1995**, *117*, 6392. (c) Kobayashi, S.; Yasuda, M.; Hachiya, I. *Chem. Lett.* **1996**, 407. (d) Denmark, S. E.; Winter, S. B. D.; Su, X. P.; Wong, K. T. *J. Am. Chem. Soc.* **1996**, *118*, 7404. (e) Denmark, S. E.; Wong, K. T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333. (f) Denmark, S. E.; Winter, S. B. D. *Synlett* **1997**, 1087. (g) Denmark, S. E.; Stavenger, R. A.; Wong, K. T.; Su, X. P. *J. Am. Chem. Soc.* **1999**, *121*, 4982. (h) Denmark, S. E.; Stavenger, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 8837. (i) Denmark, S. E.; Fujimori, S. *Org. Lett.* **2002**, *4*, 3473. (j) Denmark, S. E.; Fujimori, S. *Org. Lett.* **2002**, *4*, 3477. (k) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835.

(14) (a) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2001**, *123*, 6439. (b) Denmark, S. E.; Ober, M. H. *Org. Lett.* **2003**, *5*, 1357.

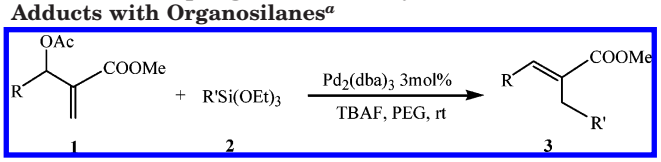
(15) (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Drewes, S. E.; Ross, G. H. P. *Tetrahedron* **1988**, *44*, 4653. (c) Basavaiah, D.; Dharmarao, P.; Suguna H. R. *Tetrahedron* **1996**, *52*, 8001.

(16) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Org. Lett.* **2003**, *5*, 3803.

(17) PEG is soluble in solvents, such as CH_2Cl_2, $CHCl_3$, tetrahydrofuran, CH_3OH, and H_2O at room temperature. It can be precipitated from these solutions by the addition of diethyl ether, hexane, or *tert*-butyl methyl ether. Physical properties of PEG-600: mp 20−25 °C, viscosity (210 F) = 10.5 cSt. See: (a) Zhao, X.; Metz, W. A.; Sieber, F.; Janda, K. D. *Tetrahedron Lett.* **1998**, *39*, 8433. (b) Fu, Y.; Etienne, M. A.; Hammer, R. P. *J. Org. Chem.* **2003**, *68*, 9854.

(18) (a) Basavaiah, D.; Muthukumaran, K.; Sreenivasulu, B. *Synthesis* **2000**, 545. (b) Mason, P. H.; Emsile, N. D. *Tetrahedron* **1994**, 50, 12001. (c) Shanmugam, P.; Singh, P. R. *Synlett* **2001**, 1314.

TABLE 2. Coupling of Various Baylis–Hillman Acetate Adducts with Organosilanes[a]



entry	R	R′	product	yield (%)[b]	*E*/*Z*
1	phenyl	phenyl	**3a**	92	93/7
2	*p*-chlorophenyl	phenyl	**3b**	91	99/1
3	*p*-tolyl	phenyl	**3c**	89	95/5
4	1-naphthyl	phenyl	**3d**	87	94/6
5	2-furyl	phenyl	**3e**	78	99/1
6	*p*-methoxyphenyl	phenyl	**3f**	94	99/1
7	2-chlorophenyl	phenyl	**3g**	86	92/8
8	*n*-octyl	phenyl	**3h**	85	90/10
9	*p*-nitrophenyl	phenyl	**3i**	62	96/4
10	phenyl	*p*-tolyl	**3j**	86	97/3
11	phenyl	*p*-chlorophenyl	**3k**	92	98/2
12	phenyl	2-thienyl	**3l**	70	93/7

[a] Reactions carried out at room temperature for 3 h with 2 equiv of Bu_4NF. [b] Isolated yield.

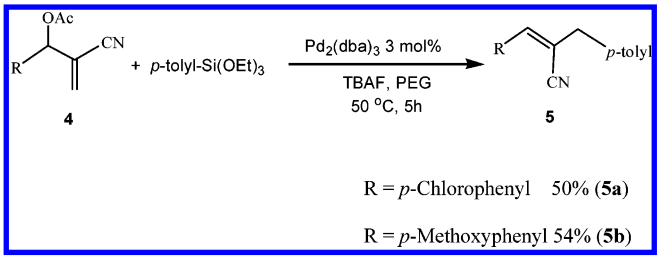


FIGURE 1. Coupling of Baylis–Hillman nitrile adducts.

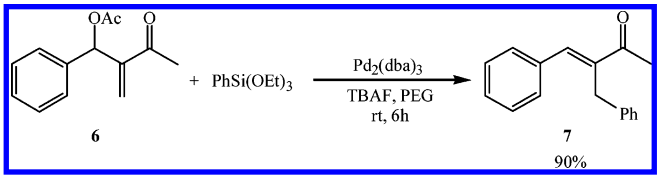


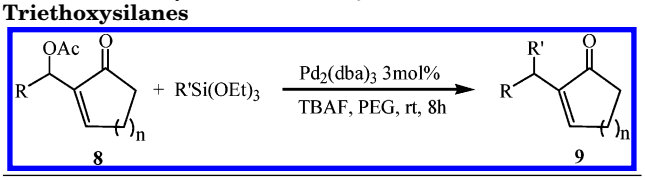
FIGURE 2. Coupling of Baylis–Hillman adduct derived from vinyl ketone.

was noted in an earlier trifluoroborate study that also resulted in slightly higher product yields.[16]

Coupling of Baylis–Hillman Adducts Derived from Acylic and Cyclic α,β-Unsaturated Ketones. The reaction of adduct **6** (derived from methyl vinyl ketone) with organosilanes was then investigated (Figure 2). The coupling reaction proceeded smoothly in excellent (90%) yield. No regioisomer formation was observed in the reaction, only the desired S_N2' product, **7**, was formed.

Having demonstrated that an acyclic vinyl ketone derived Baylis–Hillman adduct underwent coupling with phenyltriethoxysilane, reactions of Baylis–Hillman adducts **8** derived from α,β-unsaturated cycloalkenones were examined. The reaction of **8** with various aryltriethoxysilanes proceeded such that the aryl group of the aryltriethoxysilane replaced the acetoxy group at its original position (S_N2 coupling). This reaction has not been reported previously. Representative results of the cross-coupling reaction of a variety of cyclic ketone derived Baylis–Hillman adducts, **8**, are summarized in Table 3. Adducts derived from 2-cyclohexenone produced higher yields than those derived from 2-cyclopentenones.

TABLE 3. Coupling of Various Baylis–Hillman Adducts Derived from α,β-unsaturated Cycloalkenones with Triethoxysilanes



entry	R	*n*	R′	product	yield (%)
1	phenyl	1	phenyl	**9a**	51
2	phenyl	1	*p*-tolyl	**9b**	53
3	phenyl	2	phenyl	**9c**	70
4	phenyl	2	*p*-tolyl	**9d**	66
5	phenyl	2	*p*-chlorophenyl	**9e**	77
6	2-methoxyphenyl	2	phenyl	**9f**	61
7	2-methoxyphenyl	2	*p*-tolyl	**9g**	65

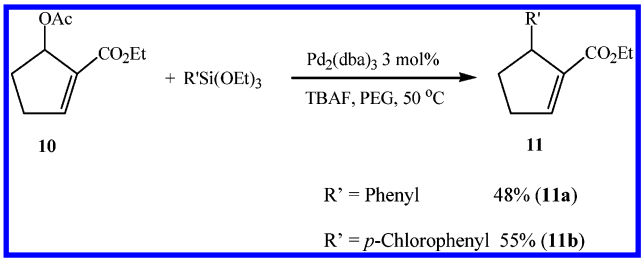


FIGURE 3. Coupling of 5-acetoxycyclopent-1-enecarboxylic acid ethyl ester.

The substituents on the aromatic ring of organosilane only slightly affected the reaction yields.

Coupling of Functionally Substituted Allylic Cycloalkenol Acetates with Organotriethoxysilanes. Allylic cycloalkenol acetates are important synthetic precursors in organic and medicinal chemistry. For example, Casara utilized them as key precursors in the synthesis of cyclopentanecarboxylic acid matrix metalloproteinase (MMP) inhibitors.[19] Amri converted allylic cycloalkenol acetates to alkylcarbethoxycycloalkenes as the key step in a short synthesis of (±)-mitsugashiwalactone.[20,21]

To extend the scope of the new reaction, the reaction of a 5-acetoxycyclopent-1-enecarboxylic acid ethyl ester (**10**) was investigated (Figure 3). The reaction proceeded at 50 °C to produce good yields of product **11**.

Conclusion

An efficient palladium-catalyzed coupling reaction of aryltrialkoxysilanes with various Baylis–Hillman acetate adducts has been developed. PEG is the most effective solvent in that it suppresses the formation of regioisomers. The coupling reaction of Baylis–Hillman adducts

(19) Le Diguarher, T.; Chollet, A.-M.; Bertrand, M.; Hennig, P.; Raimbaud, E.; Sabatini, M.; Guilbaud, N.; Pierre, A.; Tucker, G. C.; Casara, P. *J. Med. Chem.* **2003**, *46*, 3840.
(20) Amri, H.; Rambaud, M.; Villieras, J. *Tetrahedron* **1990**, *46*, 3535.
(21) Amri, H.; Villieras, J. *Tetrahedron Lett.* **1987**, *28*, 5521.
(22) (a) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311. (b) Aggarwal, V. K.; Emme, I.; Fulford, S. Y. *J. Org. Chem.* **2003**, *68*, 692. (c) Reddy, M. V. R.; Rudd, M. T.; Ramachandran, P. V. *J. Org. Chem.* **2002**, *67*, 5382. (d) Takano, S.; Yamane, T.; Takahashi, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1992**, *3*, 837. (e) Luo, S.; Zhang, B.; He, J.; Janczuk, A.; Wang, P. G.; Cheng, J.-P. *Tetrahedron Lett.* **2002**, *43*, 7369.

derived from unsaturated cyclic ketones with silanes was also studied. Adducts derived from methyl acrylate, acrylonitrile, and vinyl ketones couple with organosilanes to give allylic rearranged (S_N2') products whereas adducts derived from unsaturated cyclic ketones gave S_N2 products. The observed results for the acyclic adducts are comparable to those obtained utilizing the organotrifluoroborate reagents.[16] Interestingly, reactions involving the unsaturated cyclic ketones are only successful utilizing silane reagents. Application of this chemistry to asymmetric reactions is currently under investigation.

Experimental Section

Preparation of 2-Benzyl-3-phenylacrylic Acid Methyl Ester (3a): Representative Procedure. To a solution of 3-acetoxy-3-phenyl-2-methylenepropanoate (117 mg, 0.50 mmol), phenyltriethoxysilane (156 mg, 0.65 mmol), and 3 mol % of $Pd_2(dba)_3$ (16 mg, 0.015 mmol) in PEG-600 (3 mL) contained in a 25 mL round-bottomed flask fitted with a rubber septum was added tetrabutylammonium fluoride in THF (1.0 mL, 1.0 M, 1.0 mmol) via syringe. The flask was purged with nitrogen and then stirred at room temperature for 3 h. The mixture was extracted with ether (4 × 5 mL) and the combined organic layers were dried over anhydrous $MgSO_4$. After removal of the solvent under reduced pressure, purification of the residue by flash chromatography over silica gel with 5% ethyl acetate in hexanes gave the desired product **3a** (116 mg, 92%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.94 (s, 1H), 7. 34−7.18 (m, 10H), 3.95 (s, 2H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.5, 140.9, 139.3, 135.2, 130.5, 129.1, 128.7, 128.5, 128.4, 127.8, 126.0, 52.0, 33.1. Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.87; H, 6.40.

Acknowledgment. We wish to thank the U.S. Department of Energy and the Robert H. Cole Foundation for support of this research.

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra along with the general synthetic procedure for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051177K