steps from commercially available starting materials, constitutes a formal total synthesis of the title alkaloid.

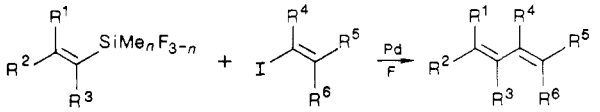
Acknowledgment. We thank the National Institutes of Health (CA 37929) and the Robert A. Welch Foundation for generous financial support of this research. We are also grateful to the NSF (CHE 8305785) and the NIH (RR 01912) for NMR facilities.

Stephen F. Martin,*[1] Wei Li[2]
Department of Chemistry
The University of Texas
Austin, Texas 78712
Received September 12, 1988

Alkenylfluorosilanes as Widely Applicable Substrates for the Palladium-Catalyzed Coupling of Alkenylsilane/F^- Reagents with Alkenyl Iodides

Summary: Introduction of fluorine(s) to the silyl groups of alkenylsilanes accelerated the rate of the coupling reaction with alkenyl iodides mediated by fluoride ion and palladium catalyst. The new version of the silicon-based coupling reaction has provided a general and highly stereospecific route to 1,3-dienes as well as alkenylarenes.

Sir: Organosilicon compounds are versatile synthetic reagents in that they are stable under normal conditions but activated to undergo nucleophilic reactions only in the presence of nucleophiles like fluoride ion.[1] The organic parts of organosilicons were recently found to be successfully transferred to a palladium complex in the presence of tris(diethylamino)sulfonium difluorotrimethylsilicate (TASF) to establish a catalytic cycle of the coupling reaction of the organosilanes with organic halides.[2] However, the scope of the reported reactions is severely limited mainly due to low reactivity of trimethylsilyl-substituted organosilanes compared with other organometallics.[3] For example, 1-(trimethylsilyl)-1-alkenes failed the coupling reaction under the standard conditions. We report that introduction of fluorine atom(s) into the silicon substituent extremely accelerates the cross-coupling reaction, and thus the silicon-based coupling reaction has now grown to be a powerful synthetic tool for carbon–carbon bond formation.



We first studied the substituent effect of the reaction of (*E*)-1-silyl-1-octenes with 1-iodonaphthalene in the presence of TASF[4] and $(\eta^3\text{-}C_3H_5PdCl)_2$[5] as a catalyst (50 °C). Results are given in the order of silyl group, reaction time, yield (%) of 1-[1(*E*)-octenyl]naphthalene: Me_3Si, 24 h, 0%; FMe_2Si, 10 h, 81%; F_2MeSi, 48 h, 74%; F_3Si, 24 h, 0%. Thus, (*E*)-1-(dimethylfluorosilyl)-1-octene (**1**) exhibited the highest reactivity, the reaction was complete within 10 h, and the coupled product was obtained in a yield of synthetic use. (E)-1-(Methyldifluorosilyl)-1-octene (**2**) was slightly less reactive and required a longer reaction time. To our surprise, trifluorosilyl in addition to the trimethylsilyl group was totally useless. The success of the reactions when **1** or **2** is used may be explained in terms of fluoride ion attacking the silicon atom of **1** or **2** to readily produce a pentacoordinate silicon species which is assumed to be the key intermediate of the coupling reaction.[6] Introduction of more fluorine might have strengthened the C–Si bond to prevent the transmetalation of alkenylsilanes with palladium complex or facilitated the formation of a hexacoordinated silicon species which presumably is unreactive toward the coupling reaction under the mild conditions.[7]

Using dimethylfluorosilyl-substituted alkenes as the substrate, we applied the reaction conditions to various iodoalkenes and iodoarenes. Results summarized in Table I clearly show the following salient features. Since the reaction proceeds with retention of the configuration of both the starting alkenylsilanes and the iodoalkenes, the method disclosed now is highly effective for the stereospecific syntheses of conjugated (*E*,*E*)-, (*E*,*Z*)-, and even (*Z*,*Z*)-dienes. In addition, a wide variety of carbonyl functionalities like ester and ketone tolerate the reaction conditions (entries 4, 5, 8, 9, and 13). It is worth noting that the conditions A [$(\eta^3\text{-}C_3H_5PdCl)_2$ catalyst and tetrahydrofuran (THF) solvent] employed for the coupling of (*E*)-1-(dimethylfluorosilyl)-1-decene, when applied to the reaction of (*Z*)-1-(dimethylfluorosilyl)-1-decene with (*E*)-1-iodo-1-octene, afforded a fair amount of (7*E*,9*E*)-7,9-octadecadiene, which is derived from $Z \rightarrow E$ isomerization of the desired (*E*,*Z*)-diene. The problem was soon cleared up by using $Pd(PPh_3)_4$ catalyst and dimethylformamide (DMF) solvent (conditions B), which reduced the extent of isomerization. Furthermore, when the reaction was monitored carefully, the isomerization was completely suppressed (entries 6–8).

TASF could be replaced by tetrabutylammonium fluoride (TBAF) (conditions C), especially in the reaction of 2-(dimethylfluorosilyl)-1-hexene (entries 9 and 10), wherein TASF caused methylation of iodoarenes to a fair extent.[8]

(1) (a) Furin, G. G.; Vyazankina, O. A.; Gostevsky, B. A.; Vyazankin, N. S. *Tetrahedron* **1988**, *44*, 2675. (b) Corriu, R. J. P.; Perz, R.; Reye, C. *Ibid.* **1983**, *39*, 999.

(2) (a) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918. (b) Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1988**, *29*, 97.

(3) For other examples of palladium-catalyzed cross-coupling reactions using organometallic compounds of main group elements, see footnote 1a of ref 2a.

(4) Middleton, W. J. U.S. Patent 3940402, 1976; *Chem. Abstr.* **1976**, *85*, P6388j. Cf.: *Org. Synth.* **1985**, *64*, 221.

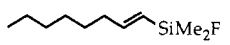
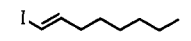
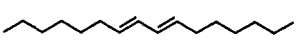
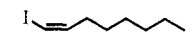
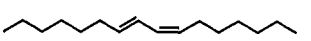
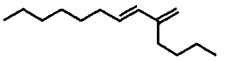
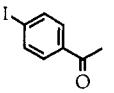
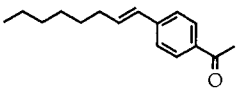
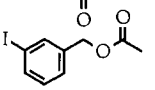
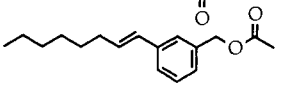
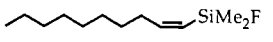
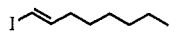
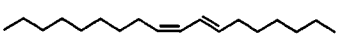
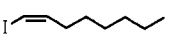
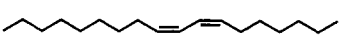
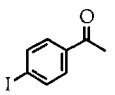
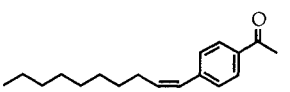
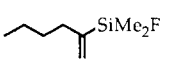
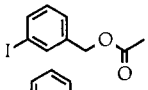
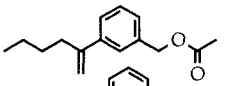
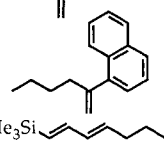
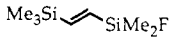
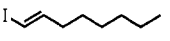
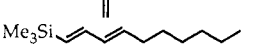
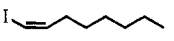
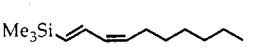
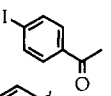
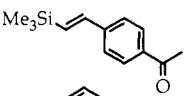
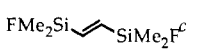
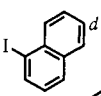
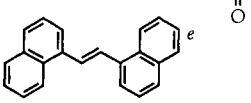
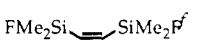
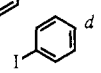
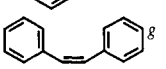
(5) Allylpalladium chloride dimer was purchased from Kanto Chemical Co., Inc., Japan.

(6) Many isolable pentacoordinate anionic silicon compounds possess more than two fluorine substituents on silicon, and double or more alkyl substitution reduces the stability of the pentacoordinate silicon species: Damrauer, R.; Danahey, S. E. *Organometallics* **1986**, *5*, 1490.

(7) Coordinative unsaturation of pentacoordinate anionic siliconates is essential for a smooth transmetalation reaction with palladium catalyst: Negishi, E. *Pure Appl. Chem.* **1981**, *53*, 2333. It was reported that coordinatively saturated hexacoordinate dianionic silicon species showed rather low reactivity in the palladium-catalyzed cross-coupling reaction with organic halides: Yoshida, J.; Tamao, K.; Yamamoto, H.; Kakui, T.; Uchida, T.; Kumada, M. *Organometallics* **1982**, *1*, 542. Indeed, a large excess of TASF (6 equiv) over the alkenylsilanes completely suppressed the reaction of (*E*)-1-(dimethylfluorosilyl)-1-octene with 1-iodonaphthalene catalyzed by $(\eta^3\text{-}C_3H_5PdCl)_2$.

0022-3263/89/1954-0268$01.50/0

Table I. Pd-Catalyzed Coupling of Dimethylfluorosilanes with Organic Iodides

	silane	organic iodide	conditions[a] reaction time, h	product	% yield[b]
1			A 16		83
2			A 21		89
3			A 22		69
4			A 24		78
5			A 24		85
6			B 14		84
7			B 19		74
8			B 12		79
9			C 22		83
10			C 22		74
11			A 15		70
12			A 12		55
13			A 5.5		67
14			A 24		45
15			A 24		43

[a] Unless otherwise stated, the reaction was carried out by using alkenylsilane (0.20–0.25 mmol) and the iodide (0.20 mmol) under the following conditions. A: $(\eta^3\text{-}C_3H_5PdCl)_2$ (2.5 mol %) in THF, 1.5 molar equiv of TASF. B: $Pd(PPh_3)_4$ (5 mol %) in DMF, 1.5 molar equiv of TASF. C: $(\eta^3\text{-}C_3H_5PdCl)_2$ (2.5 mol %) in THF, 1.5 molar equiv of TBAF. [b] All the compounds gave satisfactory spectral data and GLC retention times as compared with authentic samples. [c] A 9:1 mixture of *E* and *Z* isomers was used. [d] Two molar equivalents of the iodoarene was employed. [e] A 9:1 mixture of *E* and *Z* isomers was obtained. [f] A 1:4 mixture of *E* and *Z* isomers was used. [g] A 1:4 mixture of *E* and *Z* isomers was obtained.

We can take advantage of the reactivity of the FMe_2Si group over the Me_3Si group. When (*E*)-1-(dimethylfluorosilyl)-2-(trimethylsilyl)ethene was allowed to react with (*E*)- or (*Z*)-1-iodooctene, (*E*,*E*)- or (*E*,*Z*)-1-(trimethylsilyl)-1,3-decadiene was obtained respectively (entries 11 and 12).[9] Similarly, the (*E*)-β-(trimethylsilyl)-styrene derivative is now readily accessible (entry 13). Using bis(dimethylfluorosilyl)ethene, we could achieve a double coupling reaction to form two C–C bonds in a single step (entries 14 and 15).

The following procedure (conditions A) is representative. To a THF (1.5 mL) solution of (*E*)-1-iodo-1-octene (48 mg, 0.20 mmol) and $(\eta^3\text{-}C_3H_5PdCl)_2$ (2.1 mg, 0.057 mmol, 2.8 mol %) were added (*E*)-1-(dimethylfluorosilyl)-1-octene (47 mg, 0.25 mmol) and then a THF solution of TASF (0.71 M, 0.36 mL, 0.25 mmol) under an argon atmosphere, and the mixture was heated at 60 °C for 16 h. Concentration under reduced pressure followed by purification by column chromatography (silica gel) with hexane as the eluent afforded (7*E*,9*E*)-7,9-hexadecadiene (37 mg, 83%).

The alkenylfluorosilanes used in this work can be conveniently prepared by the substitution reaction of the corresponding alkenylchlorosilanes with copper fluoride.[10] An alternative approach is the fluorinative protodesilylation reaction of 1-alkenyldimethylmethallylsilane with potassium hydrogen fluoride and trifluoroacetic acid, a modified procedure reported by Tamao and Ishida.[11] It is noteworthy that the methallyl group is selectively converted into F with the alkenyl–Si bond intact. Thus, the

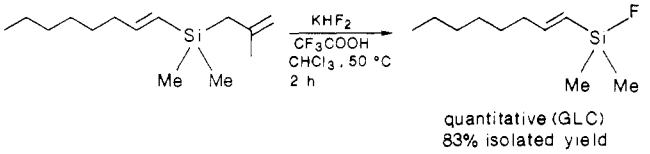
(8) In the presence of palladium catalyst, TASF delivers the methyl group to aryl halides. See: Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1988**, *29*, 97.

(9) For the synthesis of 1-silyl-1,3-butadiene using a palladium-catalyzed cross-coupling reaction, see: Fiandenes, V.; Machese, G.; Mascolo, G.; Naso, F.; Ronzini, L. *Tetrahedron Lett.* **1988**, *29*, 3705.

(10) Tamao, K.; Kakui, T.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshida, J.; Kumada, M. *Tetrahedron* **1983**, *39*, 983.

(11) Tamao, K.; Ishida, N. *Tetrahedron Lett.* **1984**, *25*, 4249.

methallyl-Si moiety is deemed to be a protected form of F-Si. An example follows.



quantitative (GLC)
83% isolated yield

In conclusion, the study reported herein has shown that fluorine substituent(s) on the silyl group of alkenylsilanes accelerate the F^--promoted cross-coupling reactions of alkenylsilanes with alkenyl iodide. By choosing the appropriate catalyst and solvent, we could perform a highly stereospecific, chemoselective synthesis of a conjugated polyene system free from any stereoisomers. Thus, the silicon-based cross-coupling reaction may find wide application in the field of total synthesis of natural products. Research in this area is in progress in our laboratories.

Yasuo Hatanaka, Tamejiro Hiyama*

Sagami Chemical Research Center
4-4-1 Nishiohnuma, Sagamihara
Kanagawa 229, Japan

Received November 10, 1988

Articles

Synthesis of (1*S*,2*R*)- and (1*S*,2*S*)-1-Amino[2-^{2}H]cyclopropane-1-carboxylic Acids: The Total ^{1}H NMR Assignment of *Cyclo*[ACC-α-methyl-Phe]

Pullachipatti K. Subramanian, Douglas M. Kalvin, Kondareddiar Ramalingam, and Ronald W. Woodard*

Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Michigan, Ann Arbor, Michigan 48109-1065

Received August 3, 1988

An asymmetric synthesis of stereospecifically monodeuteriated ACC's, (1*S*,2*R*)- and (1*S*,2*S*)-1-amino[2-^{2}H]-cyclopropane-1-carboxylic acids, is described. The reduction of methyl (*Z*)-2-acetamido-4-methoxybut-2-enoate with $^2H_2$ gas in the presence of the asymmetric reduction catalysts, (*R*,*R*)-dipamp and (*S*,*S*)-chiraphos, afforded, after acid hydrolysis, (2*S*,3*R*)-[2,3-$^2H_2$]- and (2*R*,3*S*)-[2,3-$^2H_2$]homoserine lactones, respectively. The chiral synthon bis(lactim ethers) were derived from the chiral auxiliary reagent (*R*)-(+)-2-methyl-3-phenylalanine by coupling with the above dideuteriated homoserine lactones by utilizing standard procedures. The cyclopropane ring systems are formed by treating each bis(lactim ethers) derivative with butyllithium. The stereochemistry of this intramolecular cyclization to form the cyclopropane ring is discussed. The desired cyclopropane derivatives are obtained by successive treatments with first 0.25 N HCl and then heating at reflux with 6 N HCl. The proton NMR assignment has been made for all four diastereotopic hydrogens of ACC when incorporated into the diketopiperazine ring [bis(lactim ethers) derivative] {*cyclo*[ACC-α-methyl-Phe]} as well as in the underivatized parent compound.

Introduction

The various enzymatic steps in the biosynthetic pathway in which *S*-adenosyl-L-methionine (SAM) is converted to ethylene, the plant-ripening hormone, have recently been the subject of investigation in a number of laboratories.[1a-p] Our laboratory has been involved in the investigation of the stereochemistry of the enzymatic reaction in which the PLP-dependent enzyme ACC synthase converts SAM into the immediate biosynthetic precursor of ethylene, 1-aminocyclopropane-1-carboxylic acid (ACC), in the rate-limiting step, the partial results of which have been recently reported by both our group[1m] and the Arigoni group.[1n]

In our approach to answer[2] the final question remaining concerning the stereochemical mechanism of ACC synthase, namely the enzymatic events at the α-amino acid center, it became necessary to determine the chemical shift values of (or differentiate between) all four of the hydrogen

(1) For examples, see the following: (a) Adams, D. O.; Yang, S. F. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 170-174. (b) Boller, T.; Herner, R. C.; Kende, H. *Planta* **1979**, *145*, 293-303. (c) Yu, Y.-B.; Adams, D. O.; Yang, S. F. *Arch. Biochem. Biophys.* **1979**, *198*, 280-286. (d) Adlington, R. M.; Aplin, R. T.; Baldwin, J. E.; Rawlings, B. J.; Osborne, D. *J. Chem. Soc., Chem. Commun.* **1982**, 1086-1087. (e) Hoffman, N. E.; Yang, S. F.; Ichihara, A.; Sakamura, S. *Plant. Physiol.* **1982**, *70*, 195-199. (f) Adlington, R. M.; Baldwin, J. E.; Rawlings, B. J. *J. Chem. Soc., Chem. Commun.* **1983**, 290-292. (g) Pirrung, M. C.; McGeehan, G. M. *J. Org. Chem.* **1983**, *48*, 5143-5144. (h) Pirrung, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 7207-7209. (i) Oskouee, S. K.-; Jones, J. P.; Woodard, R. W. *Biochem. Biophys. Res. Commun.* **1984**, *121*, 181-187. (j) Peiser, G. D.; Wang, N. E.; Hoffman, N. E.; Yang, S. F.; Liu, H. W.; Walsh, C. T. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 3059-3063. (k) Baldwin, J. E.; Adlington, R. M.; Lajore, G. A.; Rawlings, B. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1496-1498. (l) Pirrung, M. C.; McGeehan, G. M. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1044-1045. (m) Ramalingam, K.; Lee, K.-M.; Woodard, R. W.; Bleecker, A. B.; Kende, H. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7820-7824. (m) Wiesendanger, R.; Martinoni, B.; Boller, T.; Arigoni, D. *Experientia* **1986**, *42*, 207-209. (o) Pirrung, M. C. *Biochemistry* **1986**, *25*, 114-119. (p) Wiesendanger, R.; Martinoni, B.; Boller, T.; Arigoni, D. *J. Chem. Soc., Chem. Commun.* **1986**, 238-239.

(2) After completion of this synthesis, the Arigoni group published the results from a study involving one regiospecifically dideuteriated SAM analogue, which indicates that the stereochemical event(s) at the α-amino acid center of SAM involve inversion of configuration (or an odd number of inversions), see ref 1p. We have synthesized both [2*S*,3*R*,4*S*,*S*(*S*)]- and [2*S*,3*S*,4*R*,*S*(*S*)]-3,4-$^2H_2$]SAM, incubated with them individually with ACC synthase, measured the ^{1}H NMR of the resulting ACC's, and, based on the chemical shift values obtained from the present work and the information presented in ref 17, have determined the stereochemical outcome of the events at the α-center to involve an inversion of configuration, which is in agreement with their findings.

0022-3263/89/1954-0270$01.50/0