Chirality Transfer via the Palladium-Catalyzed Cross-Coupling Reaction of Optically Active 2-Cyclohexenylsilane: Stereochemical and Mechanistic Aspects

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Summary: Palladium-catalyzed cross-coupling reaction of optically active (2-cyclohexenyl)difluorophenylsilane with 4-iodoacetophenone in the presence of tetrabutylammonium fluoride furnishes the corresponding cross-coupled product with retention of the stereochemistry, whereas the reaction with the corresponding triflate using cesium fluoride affords the product with inversion. Regiochemistry of the cross-coupling reaction is studied with 4-d-labeled silane.

Introduction

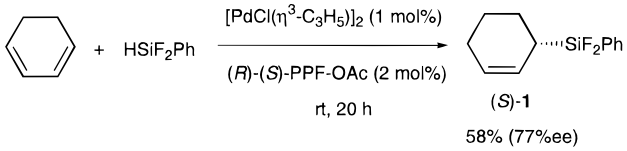
In view of straightforward and efficient carbon−carbon bond-forming reactions, transition metal catalyzed cross-coupling reactions of organometallic reagents with a wide variety of organic electrophiles have grown to be the method of choice.[1] In particular, organosilicon reagents have attracted much attention very recently and been applied to various types of carbon−carbon bond-forming reactions.[2] The stereochemistry of the silicon-based cross-coupling reaction has been a recent concern. For example, the cross-coupling reaction of an optically active allylic silane with an organic electrophile gives the corresponding optically active allylic coupled product through chirality transfer from a carbon−silicon bond to a carbon−carbon bond. The optically active silane reagent is available by asymmetric hydrosilylation of cyclic 1,3-dienes using a palladium catalyst and a chiral phosphine ligand (Scheme 1).[3] Thus, we focused onto the transformations of the chiral cyclic silane to the optically active carbogenic framework through the carbon−carbon bond formation. We herewith describe the chirality transfer of the palladium-catalyzed cross-coupling reaction of optically active (2-cyclohexenyl)silane with aryl halide. In addition, the reactions using the deuterated cyclohexenylsilane allowed us to clarify the reaction pathway.

Results and Discussion

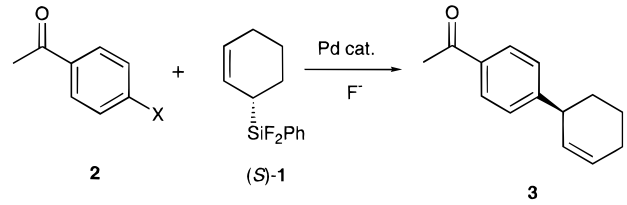
The cross-coupling reaction of an optically active allylic silane *(S)*-(2-cyclohexenyl)difluorophenylsilane {*(S)*-**1**, 64% ee} with 4-iodoacetophenone **(2a)** was carried out with a catalytic amount of $Pd(PPh_3)_4$ in the presence of tetrabutylammonium fluoride ((TBA)F) in THF at 90 °C for 3 h to yield the corresponding product **(3)** in 84% yield whose stereochemistry was found to be *(S)* with 52% ee (Scheme 2). Thus, the reaction proceeded with retention of the configuration (81% chirality transfer). The stereochemical outcome was found to considerably depend on the kind of the leaving group in **2**, fluoride reagent, and catalyst. Palladium catalysts with a variety of phosphine ligands were examined to result in giving relatively high degree of chirality transfer (67−84%) when iodide was used as a leaving group **(2a)**. When bromide **2b** was used as the halide species, on the other hand, the degree of chirality transfer decreased to ca. 30%. However, the bidentate ligand dppb was found to give the corresponding product with retention of the configuration, the degree of chirality transfer being as high as with iodide **2a**. In addition, triflate **2c** also gave the same product with considerably scrambled stereochemistry, but the reaction using dppb recovered the stereospecificity to 64% chirality transfer. Noteworthy is the effect of the fluoride ion species to result in the stereochemical outcome of the product **(3)** to be inversion when the reaction was performed using triflate **2c** with CsF. In contrast, the reactions of iodide **2a** using CsF and KF afforded **3** with retention with slightly lower degrees of chirality transfer (34−63%).[4] Results are summarized in Table 1.

Electrophilic substitution reactions of allylic metals occur, in general, in an S_E2 or S_E2' manner.[5] In addition, the substitution may result in *syn* or *anti* stereochemistry with respect to the original silicon

Scheme 1



Scheme 2



2a: X = I, **2b**: X = Br, **2c**: X = OTf

[⊗] Abstract published in *Advance ACS Abstracts,* December 1, 1996.

(1) Reviews on cross-coupling reactions of several metals: Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. Posner, G. H. *Org. React.* **1975**, *22*, 253.

(2) Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845. Hiyama, T.; Hatanaka, Y. *Pure Appl. Chem.* **1994**, *66*, 1471.

(3) (a) Ohmura, H.; Matsuhashi, H.; Tanaka, M.; Kuroboshi, M.; Hiyama, T. *J. Organomet. Chem.* **1995**, *499*, 167. See also: (b) Hayashi, T.; Kabeta, K.; Yamamoto, T.; Tamao, K.; Kumada, M. *Tetrahedron Lett.* **1983**, *24*, 5661. (c) Kitayama, K.; Tsuji, H.; Uozumi, Y.; Hayashi, T. *Tetrahedron Lett.* **1996**, *37*, 4169.

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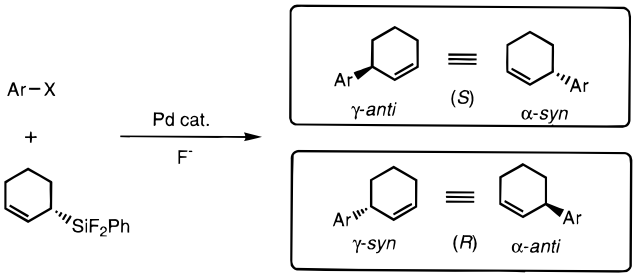
Table 1. Chirality Transfer via the Palladium-Catalyzed Cross-Coupling Reaction of 2 with *(S)*-1[a]

X	catalyst (mol %)−additive (mol %)	fluoride	time (h)	yield (%)	% ee (confign)	chirality transfer (%)
I	$Pd(PPh_3)_4$ (5)	(TBA)F	3	84	52 *(S)*	81
	$Pd(OAc)_2$ (5)−dppe[b] (5)		6	14	43 *(S)*	67
	$Pd(OAc)_2$ (5)−dppb[c] (5)		6	24	51 *(S)*	80
	$Pd(OAc)_2$ (5)−dppf[d] (5)		38	*e*		
	$[PdCl(\eta^3\text{-}C_3H_5)_2]_2$ (2.5)−PPh_3 (10)		3	89	52 *(S)*	81
	$[PdCl(\eta^3\text{-}C_3H_5)_2]_2$ (2.4)−dppe (5)		9	50	46 *(S)*	72
	$[PdCl(\eta^3\text{-}C_3H_5)_2]_2$ (2.5)−dppb (5)		3	53	54 *(S)*	84
	$Pd_2(dba)_3{\cdot}CHCl_3$ (2.5)−dbbp (5)		3	39	53 *(S)*	83
Br	$[PdCl(\eta^3\text{-}C_3H_5)_2]_2$ (2.5)−PPh_3 (10)		3	97	28 *(S)*	44
	$[PdCl(\eta^3\text{-}C_3H_5)_2]_2$ (2.5)−dppb (5)		6	61	45 *(S)*	70
OTf	$[PdCl(\eta^3\text{-}C_3H_5)_2]_2$ (2.5)−PPh_3 (10)		3	69	15 *(S)*	23
	$[PdCl(\eta^3\text{-}C_3H_5)_2]_2$ (2.5)−dppb (5)		6	55	41 *(S)*	64
I	$Pd(PPh_3)_4$ (5)	KF	93	7	40 *(S)*)	63
		CsF	108	39	22 *(S)*	34
OTf	$Pd(PPh_3)_4$ (5)	CsF	21	32[f]	4 *(R)*	6
			21	14[f,g]	23 *(R)*	36
			21	17[h]	24 *(R)*	38

[a] Unless noted, the reactions were carried out using (*S*)-**1** (2.0 mol) and fluoride (2.0 mol) at 90 °C in THF. [b] 1,2-Bis(diphenylphosphino)ethane. [c] 1,4-Bis(diphenylphosphino)butane. [d] 1,1′-Bis(diphenylphosphino)ferrocene. [e] 4-Acetylbiphenyl was obtained in 23% yield.[f] 4-Acetylbiphenyl was also obtained in 30% yield along with **3**. [g] Toluene was used as solvent. [h] Dichloromethane was used as solvent.

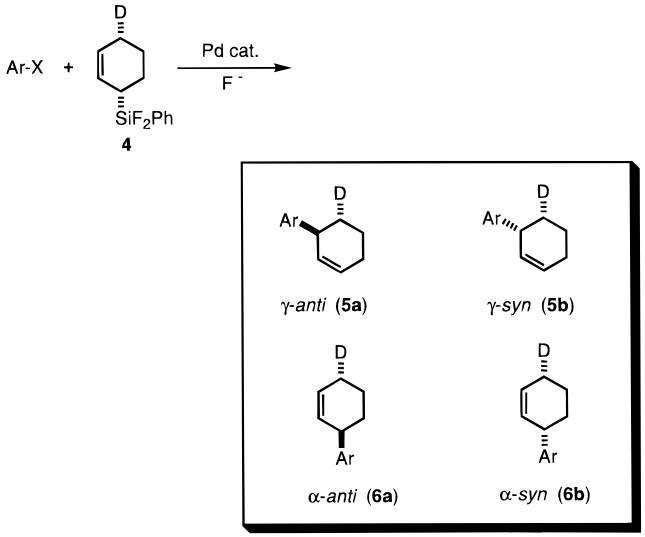
Scheme 3



functional group. Thus, four reaction pathways are possible: α-*syn*, α-*anti*, γ-*syn*, or γ-*anti* as summarized in Scheme 3. However, in the reaction of **1**, the reaction through an α-*syn* or a γ-*anti* pathway gives the identical product, whose stereochemical outcome is apparently retention of configuration. On the other hand, the reaction through α-*anti* or γ-*syn* results in inversion. Therefore, it is impossible to discriminate the reaction pathway of the cross-coupling reaction on the basis of the stereochemical results of the product **(3)**.

The regio- and stereochemistry of the palladium-catalyzed allylic cross-coupling reaction was clarified using deuterated allylic silane **4**.[6] As illustrated in Scheme 4, the γ-*anti* product **(5a)** and α-*syn* product **(6b)** are not identical, and thus structural assay of the product will allow us to assign the reaction course. Similarly, γ-*syn* and α-*anti* leads to discriminative

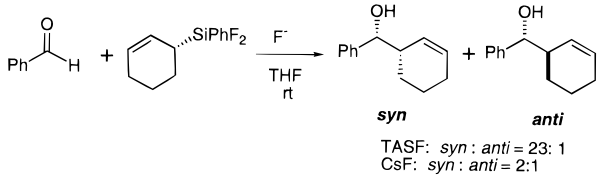
Scheme 4



products **6a** and **5b**, respectively. In fact, the reaction of **4** with **2a** using (TBA)F proceeded smoothly as was the case of optically active **1**. The ^1H NMR spectrum of the product showed two protons at the allylic position (around 2 ppm) and three protons at higher frequency region, suggesting that the deuterium atom was located at the β-position of the aryl substituent.

Thus the C−C bond formation has apparently occurred at the γ-position.[7] In addition, the ^{13}C NMR spectrum represents a triplet signal at 31.9 ppm (J = 39.4 Hz) due to the coupling with deuterium atom, also supporting the structure of the γ-coupled product. Taking into consideration these spectroscopic observations as well as the stereochemical outcome (retention of the configuration) in the coupling reaction all together, we can conclude that the reaction occurs at γ-*anti*. By contrast, the coupling products produced in the reaction of **2c** using CsF afforded complex ^1H NMR spectrum indicating the cross-coupling reaction occurred through several reaction pathways. Indeed, under these conditions, inversion of stereochemistry with moderate degree of chirality transfer was observed (vide supra).

(4) The stereochemical dependence on fluoride reagent was again observed in the reaction of **1** with aldehyde. The reaction of *(S)*-**1** with benzaldehyde in the presence of (TAS)F afforded the corresponding product with high degrees of chirality transfer (>95%) as well as high diastereoselectivity. However, the use of CsF as the activator considerably decreased the stereoselectivity. Hirabayashi, K.; Matsuhashi, H.; Mori, A.; Hiyama, T. Unpublished results.



See also: Kira, M.; Hino, T.; Sakurai, H. *Tetrahedron Lett.* **1989**, *30*, 1099. Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620.

(5) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

(6) The authors are grateful to Dr. K. Kitayam for fruitful suggestions. See also ref 3c.

(7) The $^1H-^1H$ COSY spectrum exhibits strong correlation between protons at C(3) and C(4) suggesting that both protons are axial.

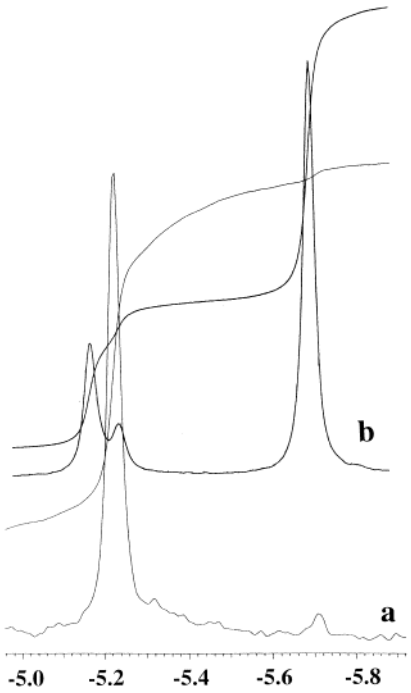


Figure 1. ^{2}H NMR spectrum of the product in the reaction of (a) **4** and **2a** in the presence of (TBA)F and (b) **4** and **2c** in the presence of CsF.

The ^{13}C NMR spectrum of the products indicated three triplet signals at 31.9, 31.8, and 24.5 ppm. The signal at 31.9 ppm should be attributed to **5a** as discussed above. The signal at 31.8 ppm might be characterized as the *γ-syn* product **5b**, and the one at 24.5 ppm, as the α-coupled product. At this stage, it is hard to determine α-*syn*, α-*anti*, or a mixture of these. The measurements of ^{2}H NMR enabled us to carry out quantitative analyses. Figure 1a shows the ^{2}H NMR spectrum of the product obtained by the reaction of **4** with **2a** using (TBA)F. The signal at −5.23 ppm suggests that the reaction has occurred at *γ-anti* position almost exclusively. This is consistent with the result of the chirality transfer using *(S)*-**1**. Figure 1b represents the spectrum of the product obtained by the reaction of **2c** using CsF and indicates that the products derived from *γ-anti*, *γ-syn*, and α-(*syn* and *anti*) coupling give signals at −5.16, −5.23, and −5.71 ppm, respectively, in a ratio of 3:1:8. Since the stereochemical outcome with *(S)*-**1** was inversion, the major pathway of the reaction should be α-*anti*.[8] It is noteworthy that the coupling position and the stereochemical course depend on the kind of the fluoride reagent. Although the enantiochemical diversity in the cross-coupling of acyclic chiral allylic silanes was observed depending on the kind of the fluoride reagent,[9] the stereochemical outcome was due to the facial selectivity at *γ*-position only. In addition, although the regiochemical control of the cross-coupling reactions in acyclic silane was realized by using phosphine ligands with various bite angles,[10] such effect was not observed in the present cyclic case. Therefore, the pathway of the cross-coupling reaction of cyclic and acyclic silanes is rather diverse.

Conclusion

Palladium-catalyzed cross-coupling reaction of an optically active allylic silane **1** with aryl halide or triflate **(2a−c)** in the presence of fluoride ion proceeded in the stereospecific manner. The reaction using (TBA)F afforded the corresponding product with retention of configuration, whereas the reaction using CsF gave the inversion product. Experiments using 4-*d*-labeled allylic silane **4** revealed that the retention reaction with (TBA)F could be attributed to the *γ-anti* pathway, and the inversion with CsF, to α-*anti* substitution. Regio- and stereochemistry in the cross-coupling of cyclic allylic silanes exhibited specific behavior compared with those of acyclic silanes.

Experimental Section

General Methods. ^{1}H NMR spectra were measured in $CDCl_3$, unless specified, with tetramethylsilane as an internal standard (0 ppm). ^{13}C NMR spectra were measured in $CDCl_3$ which also was an internal standard (77 ppm). ^{19}F NMR spectra were measured in $CDCl_3$ using $CFCl_3$ as an internal standard (0 ppm). ^{2}H NMR spectra were measured on a Varian Unity 500 spectrometer in $CHCl_3$ solution on unlocked mode, where $CDCl_3$ was an internal standard (0 ppm). Silica gel column chromatography was performed using Merck Kieselgel 60 (230−400 mesh). All the reactions were carried out under an argon atmosphere. Diethyl ether, THF, and benzene were distilled from sodium/benzophenone prior to use. Dichloromethane and toluene were distilled from CaH_2 and stored over MS-4A sieves under an argon atmosphere. Bidentate phosphine ligands dppe, dppb, and dppf were purchased from Kanto Chemical Inc. and used after recrystallization from an appropriate solvent. Optically active (2-cyclohexenyl)difluorophenylsilane **(1)** was prepared by asymmetric hydrosilylation as previously described.[3a] Other chemicals were purchased and used as such.

General Procedure for the Synthesis of 3-(4-Acetylphenyl)cyclohexene (3). To a solution of a palladium catalyst (0.010 mmol) and 4-iodoacetophenone (**2a**, 0.20 mmol) in a solvent (1 mL) placed in a sealed screw-capped glass tube were added sequentially (2-cyclohexenyl)difluorophenylsilane {*(S)*-**1** (64% ee, 0.40 mmol)} and (TBA)F (1 M THF solution, 0.60 mL, 0.60 mmol) at room temperature. The mixture was stirred for 10 min at room temperature and then heated at 90 °C. The reaction was monitored by TLC (hexane−EtOAc = 10:1) and allowed to continue until all of **2a** was consumed. The reaction mixture was passed through a short silica gel column (hexane−EtOAc = 10:1) to remove the Pd catalyst and salts. The product was further purified by flash column chromatography on a silica gel (hexane−EtOAc = 10:1) to provide **3** as a colorless oil. The absolute configuration of **3** was deduced from the result of HPLC analysis, with t_R = 28.9 min for the *(R)*-isomer and 32.2 min for the *(S)*-isomer (Daicel OD-H, hexane), as well as of optical rotation, with $[\alpha]^{29}_D$ − 92.3° (*c* 0.62, benzene).[11] ^{1}H NMR (200 MHz): δ 1.46−1.83 (m, 4H), 2.10 (m, 2H), 2.58 (s, 3H), 3.46 (m, 2H), 5.69 (m, 1H), 5.94 (m, 1H), 7.31 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.5 Hz,

(8) We also examined the cross-coupling reaction of **4** with the triflate **2c** using (TBA)F. The system corresponds to complete scrambling of stereochemistry when chiral **1** is used. Indeed we obtained the corresponding product in a ratio of *γ-anti*:*γ-syn*:α (*syn* and *anti*) = 3:2:1 on the basis of the ^{2}H NMR spectrum analysis. Thus, scrambling of the stereochemistry is ascribed to the low facial selectivity at *γ*-position.

(9) Hatanaka, Y.; Goda, K.-i.; Hiyama, T. *Tetrahedron Lett.* **1994**, *35*, 1279. See also: Hatanaka, Y.; Ebina, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 7075.

(10) Hatanaka, Y.; Goda, K.-i.; Hiyama, T. *Tetrahedron Lett.* **1994**, *35*, 6511.

(11) The absolute configuration of **3** was deduced from results on $[\alpha]_D$ value {lit. $[\alpha]^{29}_D$ = −159.6° (*c* 0.53, benzene) for the *(S)*-isomer} and HPLC data (Daicel OD-H, hexane; t_R = 9.12 min (minor enantiomer) and 11.35 min (major enantiomer) for 58% ee of the *(S)*-isomer) of the optically active (3-cyclohexenyl)benzene. Cf.: Consiglio, G.; Piccolo, O.; Roncetti, L.; Morandini, F. *Tetrahedron* **1986**, *42*, 2043.

2H). ^{13}C NMR (50.3 MHz): δ 20.10, 24.89, 26.50, 41.83, 127.89, 128.46, 129.03, 129.07, 135.19, 152.36, 197.78. IR (neat): 3021, 2930, 2859, 1684, 1605, 1358, 1267, 1127, 957, 830 cm^{-1}. Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.75; H, 7.97.

(*cis*-2-Cyclohexenyl-4-*d*)difluorophenylsilane (4) was synthesized by following the procedure of Hayashi with slight modification.[6] ^{1}H NMR (200 MHz): δ 1.46−2.19 (m, 6H), 5.66−5.87 (m, 2H), 7.35−7.73 (m, 5H). ^{19}F NMR (188 MHz): δ −145.51 (d, J = 20.3 Hz), −146.69 (d, J = 23.7 Hz).

3-(4-Acetylphenyl)cyclohexene-4-*d* (5a). The cross-coupling reaction of **4** with **2a** or **2c** was carried out in a similar manner as described in the reaction of **1**. ^{1}H NMR (200 MHz): δ 1.45−1.75 (m, 3H), 2.04−2.16 (m, 2H), 2.58 (s, 3H), 3.44−3.49 (m, 1H), 5.65−5.73 (m, 1H), 5.89−5.98 (m, 1H), 7.30 (d, J = 8.3 Hz, 2H), 7.89 (d, J = 8.3 Hz, 2H). ^{13}C NMR (50.3 MHz): δ 20.09, 24.86, 26.50, 31.90 (t, J = 20.0 Hz), 41.74, 127.89, 128.46, 129.03, 129.07, 135.20, 152.36, 197.63. ^{2}H NMR (76.75 MHz): δ −5.24 (s). MS [m/z (rel intensity)]: 201 (M^+, 88), 186 (100), 158 (70), 129 (85). HRMS: Calcd for $C_{14}H_{15}DO$, m/z 201.1263; found, m/z 201.1241.

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Supporting Information Available: ^{1}H, ^{13}C, ^{2}H, and ^{1}H−^{1}H COSY NMR spectra for the reactions of **4** with **2a**−**c** using (TBA)F and CsF (9 pages). Ordering information is given on any current masthead page.

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