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Regio- and Stereoselective Cross-Coupling Reaction of Optically Active Allylsilanes: Stereocontrol of Palladium-Mediated SE' Reactions

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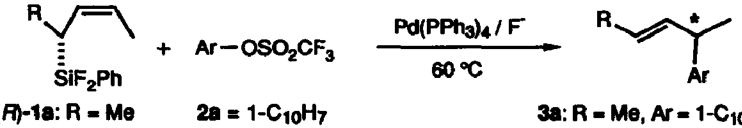
Abstract: Optically active allylsilanes undergo the γ-regioselective cross-coupling reactions with aryl triflates in the presence of a palladium catalyst and a fluoride salt; the absolute configuration and % ee of the coupled products could be controlled by the choice of the fluoride salt and the polarity of the solvent.

Although transition metal catalyzed, asymmetric allylic substitution with nucleophiles is a potentially versatile method for preparing a wide range of optically active compounds, low enantio- and regioselectivity in this process often severely limits the synthetic utility.[1] We have reported previously that the cross-coupling reaction of allyltrifluorosilanes with organic halides or triflates promoted by a palladium catalyst and a fluoride salt takes place exclusively at the γ-carbon of allyltrifluorosilanes, giving a coupled-product in regiochemically pure form.[2] This finding has prompted us to investigate the possibility of stereoselective cross-coupling reaction of optically active allylsilanes[3] with electrophiles as a route to the selective synthesis of optically active allyl compounds. We report herein that the stereochemistry of the cross-coupling reaction of optically active (allyl)(difluoro)(phenyl)silanes (1) with aryl triflates (2) is decisively influenced by the coordinating ability of solvent and the nature of a fluoride salt, and under suitable conditions provides accsess to cross-coupled products in a highly stereoselective manner.



(*R*)-**1a**: R = Me
(*R*)-**1b**: R = Et

2a = 1-$C_{10}H_7$
2b = 2-$C_{10}H_7$

3a: R = Me, Ar = 1-$C_{10}H_7$
3b: R = Me, Ar = 2-$C_{10}H_7$
3c: R = Et, Ar = 1-$C_{10}H_7$
3d: R = Et, Ar = 2-$C_{10}H_7$

To evaluate the effect of solvent polarity and fluoride salt on the stereochemistry of the cross-coupling reaction, optically active allylsilanes **1** were allowed to react with **2** in the presence of $Pd(PPh_3)_4$ at 60 °C (**Table 1**). The reaction of (*R*)-(*Z*)-4-(difluoro)(phenyl)silyl-2-pentene ((*R*)-**1a**) (65% ee) with 2-naphthyl triflate (**2b**), promoted by $Pd(PPh_3)_4$ (5.0 mol %) and $(Et_2N)_3S^+Me_3SiF_2^-$ (TASF)[4] (4.0 eq) as a fluoride ion source, smoothly proceeded in tetrahydrofuran (THF) to give a 4.4 : 1 mixture of (*S*)-(*E*)-4-(2-naphthyl)-2-pentene ((*S*)-(*E*)-**3b**) (41% ee) and (*R*)-(*Z*)-4-(2-naphthyl)-2-pentene ((*R*)-(*Z*)-**3b**) (58% ee) (entry 1). The magnitude of the enantiomeric excess and the *E*/*Z* ratio of the coupled products increased dramatically when the reaction was carried out in *N*,*N*-dimethylformamide (DMF). Thus, (*R*)-**1a** (67% ee) reacted with **2b** in DMF under the same conditions with 99% of stereoselectivity to give (*S*)-(*E*)-**3b** (66% ee) (entry 2).[5] A similar solvent dependence was also observed in the reactions of (*R*)-(*Z*)-4-(difluoro)(phenyl)silyl-2-hexene ((*R*)-**1b**) (69% ee) with **2a** or **2b**, affording (*S*)-(*E*)-**3c** or (*S*)-(*E*)-**3d** with high stereoselectivity especially in DMF (entries 4-7).

To our surprise, the absolute configuration of the coupled products was reversed when metal fluorides such as CsF or KF were employed in place of TASF in THF. Thus, the reaction of (*R*)-**1b** (69% ee) with **2b** conducted in THF using CsF afforded (*R*)-(*E*)-**3d** (51% ee) (entry 8). Also (*R*)-(*E*)-**3d** (10% ee) was isolated from the reaction of the same substrates using KF in THF (entry 10).[6] However, in DMF which can effectively solvate metal cation, the stereochemistry of the cross-coupling reaction was the same as that observed using TASF in this solvent. The reaction of (*R*)-**1b** (69% ee) with **2b** using CsF in DMF resulted in the selective formation of (*S*)-(*E*)-**3d** (62% ee) (entry 9). Upon addition of 18-crown-6 to CsF in THF, (*S*)-(*E*)-**3d** (13% ee) also predominated (entry 11). These observations suggest that metal coordination plays an important role in determining the absolute configuration of the product in THF.

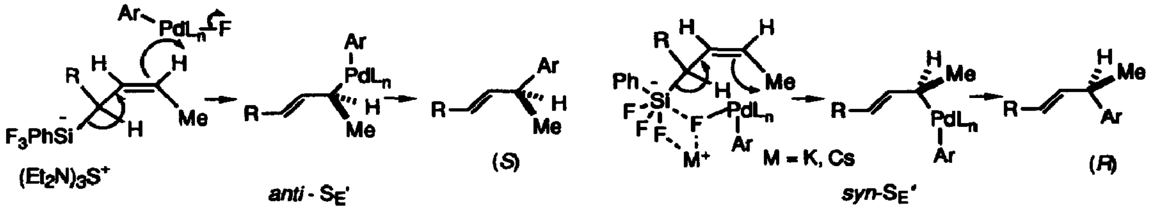
Table 1. Cross-coupling Rections of Optically Active Allyl(difluoro)phenylsilanes with Aryl Triflates Promoted by $Pd(PPh_3)_4$ and F^-

entry	allylsilane (% ee)	ArOTf[a]	F^-	solvent	product (% ee, confign)	% stereoselectivity[b]	% yield (*E*/*Z*)
1^{q}	**1a** (65)^{q}	**2b**^{q}	TASF^{q}	THF^{q}	(*E*)-**3b** (41,*S*)^{q}	63^{q}	64 (4.4)^{q}
					(*Z*)-**3b** (58,*R*)	89	
2	**1a** (67)	**2b**	TASF	DMF	(*E*)-**3b** (66,*S*)	99	70 (8.6)
3	**1a** (67)	**2a**	TASF	DMF	(*E*)-**3a** (59,*S*)	88	39 (3.1)
4	**1b** (69)	**2b**	TASF	THF	(*E*)-**3d** (53,*S*)	77	50 (9.3)
5	**1b** (69)	**2b**	TASF	DMF	(*E*)-**3d** (63,*S*)	91	64 (24)
6	**1b** (69)	**2a**	TASF	THF	(*E*)-**3c** (40,*S*)	58	68 (4.5)
7	**1b** (69)	**2a**	TASF	DMF	(*E*)-**3c** (67,*S*)	97	55 (4.3)
8	**1b** (69)	**2b**	CsF	THF	(*E*)-**3d** (51,*R*)	74	50 (42)
9	**1b** (69)	**2b**	CsF	DMF	(*E*)-**3d** (62,*S*)	90	50 (15)
10	**1b** (69)	**2b**	KF	THF	(*E*)-**3d** (10,*R*)	14	50 (100/0)
11	**1b** (69)	**2b**	CsF /18-crown-6	THF	(*E*)-**3d** (13,*S*)	19	38 (16)

[a] OTf = OSO_2CF_3 [b] % ee of **3** / % ee of **1**

The palladium catalyzed cross-coupling reaction of (allyl)(difluoro)(phenyl)silanes with aryl triflates is assumed to involve the electrophilic substitution (S_E' reaction) of an allylsilicate[7] by an arylpalladium complex and the reductive elimination of the resulting (η^1-allyl)(aryl)palladium complex (**Scheme 1**).[8] Since the reductive elimination of a diorganopalladium complex proceeds with retention of the configuration of the alkyl ligand,[9] the observed stereochemistry should reflect that of the S_E' reaction of the allylsilicate with the arylpalladium complex. To explain the above observations, we propose two plausible transition state models for this process as illustrated in Scheme 1.[10] In reactions conducted in THF using TASF, the arylpalladium complex attacks the double bond of the allylsilicate with *anti* selectivity with respect to the silyl leaving group, giving (*S*)-(*E*)-3. In contrast, in the presence of CsF or KF in THF, metal coordination to the fluoride ion might form a silicon-fluorine-metal bridge[10] and favors a cyclic transition state, wherein the electrophilic attack of the arylpalladium complex on the double bond of the allylsilicate takes place with *syn* selectivity so as to yield (*R*)-(*E*)-3. The presence of a crown ether in the THF/CsF system or the use of DMF may well cleave this bridge by coordination to the alkali metal, favoring *anti* attack of the arylpalladium complex to give (*S*)-(*E*)-3.

The stereochemistry of the S_E' reaction of allylsilanes has been of synthetic and mechanistic interest for a long time, and it is well-established that, in the absence of other constraints, the reaction takes place with *anti* selectivity.[11] In contrast, S_E' reactions with *syn* selectivity were exceptionally observed for highly biased, hindered allylsilanes such as 2-(trimethylsilyl)bicyclo[3,2,0]-3-hepten-7-one,[12] trans-3,6-bis(trimethylsilyl)-1-cyclohexene,[13] and 1-fluoro(dimethyl)silyl-1-trimethylsilyl-2-alkenes,[14] wherein stereochemistry of the electrophilic attack was determined by steric reasons. Present work, however, demonstrates that the *syn* selectivity can be realized for the S_E' reaction of unbiased, strain-free allylsilanes such as **1** when electrophilic attack is controlled by coordination between the silicon and the electrophile, mediated by fluoride ion and alkali metal.



Scheme 1

In conclusion, our results clearly show that the stereochemistry of the S_E' reaction of allylfluorosilanes can be controlled by choice of solvent and fluoride salt. The present reaction is particularly important as a method for accomplishing the stereoselective coupling of an allylic unit in a manner that allows the selective synthesis of both enantiomers from a common precursor.

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3. The optically active, allyl(difluoro)phenylsilanes used in this work were conveniently prepared by the asymmetric hydrosilylation of 1,3-dienes with PhF_2SiH in the presence of $PdCl_2$[(*R*)-(*S*)-PPFA], Hatanaka, Y.; Yamashita, F.; Goda, K.; Hiyama, T. to be published.
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5. The following procedure is representative (**Table 1**, entry 2): To a DMF solution of **2b** (66 mg, 0.24 mmol) and $Pd(PPh_3)_4$ (12 mg, 0.010 mmol, 4.3 mol%) were added (*R*)-**1a** (42 mg, 0.20 mmol, 67% ee) and then a DMF solution of TASF (0.97 M, 0.82 mL, 0.80 mmol). The resulting mixture was heated at 60

°C for 30 h under an argon atmosphere. Concentration and purification by column chromatography on silica gel impregnated with silver nitrate using hexane/ethyl acetate (8:1) gave (*E*)-**3b** (27 mg, 70%) and (*Z*)-**3b** (3 mg, 8%). To determine the absolute configuration and the % ee, (*E*)-**3b** was converted to methyl 2-(2-naphthyl)propanoate by oxidative cleavage of the C=C bond with $KMnO_4$/$NaIO_4$, followed by esterification with diazomethane. The % ee of the final product was estimated by HPLC analysis using a chiral column (Daicel CHIRALCEL AD, hexane). The absolute configuration was determined according to the literature: Menicagli, R.; Piccolo, O.; Lardicci, L.; Wis, M. L. *Tetrahedron* **1979**, *35*, 1301. (*S*)-(*E*)-**3b** : $[a]^{20}_{D}$ +18.46° (*c* 1.33, $CHCl_3$), 66% ee; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40 (d, *J* = 7.0 Hz, 3H), 1.70 (dt, *J* = 6.4, 1.4 Hz, 3H), 3.85 (m, 1H), 5.51 (dqd *J* = 15.3, 6.4, 1.2 Hz, 1H), 5.69 (ddq, *J* = 15.3, 6.6, 1.4 Hz, 1H), 7.35 (dd, *J* = 8.4, 1.7 Hz, 3H), 7.40 (td, *J* = 7.0, 1.5 Hz, 1H), 7.44 (td, *J* = 7.0, 1.5 Hz, 1H), 7.62 (s, 1H), 7.75-7.82 (m, 3H); IR (neat) 3048, 2960, 1375, 959, 813, 740 cm^{-1}. Anal. Calcd for $C_{15}H_{16}$: C, 91.78; H, 8.22. Found: C, 91.56; H, 8.28.

6. To examine the possibility of racemization of **1b** under the reaction conditions, a blank experiment was carried out. The solution of **1b**, KF, and $Pd(PPh_3)_4$ in THF was heated at 60 °C for 36 h; however, no loss of the optical purity of **1b** was observed, demonstrating that the low % ee of the product is due to the low stereoselectivity of the cross-coupling reaction.
7. The active species of this reaction is considered to be an anionic pentacoordinate species (allyl)(trifluoro)(phenyl)silicate.[2b] The transmetalation (S_E' reaction) of the silicate with the arylpalladium complex gives a (η^1-allyl)(aryl)palladium complex.
8. It is still controversial whether the intermediate in the palladium catalyzed cross-coupling reaction of allylic substrates is a η^1-allylpalldium or a η^3-allylpalladium complex. However, the high regiospecificity observed here can rule out the participation of η^3-allylpalladium intermediate, which should react with nucleophiles at both allylic termini, leading to loss of regiochemistry. For discussion on this subject, see: (a) Valle, L. D.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem.* **1990**, *55*, 3019, and references therein. (b) Shiba, K.; Kurosawa, H.; Kakiuchi, K.; Ikeda, I. *The 39 th Symposium on Organometallic Chemistry, Japan (Tokyo) Abstract*, A208, p. 160 (1992).
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