

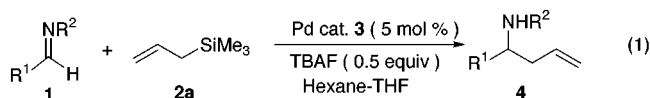
Chiral π -Allylpalladium-Catalyzed Asymmetric Allylation of Imines: Replacement of Allylstannanes by Allylsilanes

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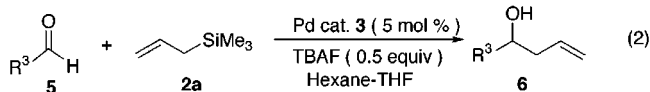
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The stereoselective addition of allylmetal reagents to aldehydes and imines is one of the most powerful and important reactions for carbon–carbon bond formation.¹ Among various allylmetal reagents, allylsilanes and allylstannanes are utilized very frequently in organic synthesis; the former reagents are in general more stable, less reactive, and less toxic, whereas the latter reagents are less stable, more reactive, and significantly toxic. We recently reported that imines undergo catalytic asymmetric allylation reaction with allyltributylstannanes in the presence of chiral π -allylpalladium catalysts.^{2,3} However, the use of allyltributylstannanes is not necessarily desirable from the point of *green chemistry*. The use of allylsilanes is more desirable, but in general the reaction of imines with allylsilanes is quite sluggish.⁴ We have solved this dilemma and herein report a novel allylation reaction of imines, as well as aldehydes, with allyltrimethylsilanes using a palladium–TBAF cocatalyst system⁵ (eqs 1 and 2) and its extension to asymmetric allylation of imines using a chiral π -allylpalladium catalyst (eq 1).



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| 1a ; R ¹ = Ph, R ² = Bn | 1e ; R ¹ = 4-MeOC ₆ H ₄ , R ² = Bn |
| 1b ; R ¹ = Ph, R ² = Ph | 1f ; R ¹ = (E)-PhCH=CH, R ² = Bn |
| 1c ; R ¹ = Ph, R ² = 4-MeOC ₆ H ₄ | 1g ; R ¹ = Ph, R ² = 4-MeOC ₆ H ₄ CH ₂ |
| 1d ; R ¹ = Ph, R ² = <i>n</i> -Pr | 1h ; R ¹ = 2-Naphthyl, R ² = Bn |



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|--|---|
| 5a ; R ³ = Ph | 5e ; R ³ = PhCH ₂ CH ₂ |
| 5b ; R ³ = 4-(NO ₂)C ₆ H ₄ | 5f ; R ³ = <i>n</i> -C ₅ H ₁₁ |
| 5c ; R ³ = 4-MeOC ₆ H ₄ | 5g ; cyclohexanone |
| 5d ; R ³ = (E)-PhCH=CH | |

First we examined the palladium-catalyzed allylation of imines **1** with allyltrimethylsilane **2a**. The results are

(1) For recent reviews of allylmetal additions, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Marshall, J. A. *CHEMTRACTS* **1992**, *5*, 75. (c) Roush, W. R. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, pp 1–53.

(2) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242.

(3) For the allylation of aldehydes and imines catalyzed by bis- π -allylpalladium complexes, see: Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641.

(4) Allylation and crotylation reaction of aldimines by allyltrifluorosilane with cesium fluoride: (a) Kira, M.; Hino, T.; Sakurai, H. *Chem. Lett.* **1991**, 277. Allylation reaction of aromatic *N*-galactosyl imines by allyltrimethylsilane in the presence of SnCl₄: (b) Laschat, S.; Kunz, H. *Synlett* **1990**, 51. (c) Laschat, S.; Kunz, H. *J. Org. Chem.* **1991**, *56*, 5883.

(5) For the palladium-catalyzed coupling reactions of organosilicon compounds, see: (a) Hatanaka, Y.; Goda, K.; Hiyama, T. *Tetrahedron Lett.* **1994**, *35*, 6511. See also: (b) Horn, K. A. *Chem. Rev.* **1995**, *95*, 1317.

summarized in Table 1. The reaction of **1a**, derived from benzaldehyde and benzylamine, with **2a** (2 equiv) proceeded very smoothly at room temperature in the presence of a catalytic amount of π -allylpalladium chloride dimer **3a** (5 mol %) and TBAF (0.5 equiv) in *n*-hexane–THF (4:1) cosolvent, giving the corresponding homoallylamine **4a** in 69% yield (entry 1).⁶ The use of THF as a solvent gave **4a** in lower yield (~30%). Other palladium catalysts such as PdCl₂(PPh₃)₂, PdCl₂(dppe), or PtCl₂(PPh₃)₂, other fluoride ion sources such as CsF, KF–crown ether, 3HF–NEt₃, TBAH₂F₃, or TBAHF₂,⁷ and other allylsilanes such as allyltriethoxysilane or allyltrichlorosilane were not effective. The imines **1b** and **1c** gave the corresponding homoallylamines **4b** and **4c**, respectively, in high yields (entries 2 and 3). The imine **1d** reacted slowly even in the presence of 3 equiv of **2a** to afford **4d** in 50% yield (entry 4). The allylation reaction of **1e** and **1f** resulted in modest yields (57% and 62%, respectively; entries 5 and 6). Needless to say, the allylation products were not obtained in the absence of palladium catalysts and/or TBAF. The use of palladium–TBAF cocatalyst is essential for obtaining good to high yields of the allylation products.

The reaction of imine **1a** with **2a** is representative. To a solution of **1a** (0.5 mmol) and **3a** (0.025 mmol) in *n*-hexane (2 mL) was added **2a** (1.0 mmol). The resulting mixture was stirred for about half an hour, and then TBAF (0.25 mmol, 1.0 M solution in THF) and THF (0.25 mL) were added. The reaction mixture became two phases: the upper phase was a homogeneous *n*-hexane–THF solution and the bottom phase contained a TBAF solution. The mixture was stirred for 31 h at room temperature. The reaction progress was monitored by TLC and ¹H NMR. After **1a** was consumed completely, the reaction was quenched with water. The reaction mixture was extracted with ether. The organic layer was washed with a saturated aqueous NaCl solution, dried over anhydrous MgSO₄, and then concentrated. Purification by silica gel column chromatography (*n*-hexane/ethyl acetate = 10:1) gave **4a** in 69% yield.

We next examined the allylation of various aldehydes using the palladium–TBAF cocatalyst system. The allylation reaction of aromatic and alkenyl aldehydes **5a–d** gave the corresponding homoallyl alcohols **6a–d** in modest to good yields (entries 7–10). However, the allylation reaction of aliphatic aldehydes **5e** and **5f** resulted in poor yields (entries 11 and 12). The cyclic ketone **5g** also underwent the allylation to give **6g** in 21% yield (entry 13). It is known that the allylation of aldehydes with **2a** proceeds in the presence of a catalytic amount of fluoride ions at higher temperatures (under reflux of THF).⁸ The present allylation proceeds at room temperature; obviously palladium catalysts facilitate the allylation.

Inspired by the above results, we applied the palladium–TBAF cocatalyst system to the asymmetric allylation of imines **1** using chiral π -allylpalladium catalyst **3b**² (5 mol %) at 0 °C. The results are summarized in Table 2. The allylation reaction of **1a** gave **4a** in 79% yield with an enantiomeric excess of 80% (entry 1).⁹ The reaction of **1g**

(6) The allylation reaction proceeded even in the presence of 0.1 equiv of TBAF in 70% yield. On the other hand, the use of 2.0 equiv of TBAF in *n*-hexane solvent was not effective; **4a** was obtained in 45% yield.

(7) TBAH₂F₃ = tetra *n*-butylammonium dihydrogen trifluoride, TBAHF₂ = tetra *n*-butylammonium hydrogen difluoride; Kuroboshi, M.; Hiyama, T. *Tetrahedron Lett.* **1991**, *32*, 1215.

(8) (a) Hosomi, A.; Shirahata, A.; Sakurai, H. *Tetrahedron Lett.* **1978**, 3043. For reviews, see: (b) Sakurai, H. *Pure Appl. Chem.* **1982**, *54*, 1. (c) Sakurai, H. *Pure Appl. Chem.* **1985**, *57*, 1759.

(9) The absolute configuration of the homoallylamine **4a** was determined to be *R* by converting it to 1-phenylbutylamine. Details are shown in ref 2.

Table 1. π -Allylpalladium–TBAF-Catalyzed Allylation of Imines and Aldehydes with Allyltrimethylsilane^a

entry	imine 1 or aldehyde 5	reactn time (h)	product	yield (%) ^b
1	1a	31	4a	69
2	1b	19	4b	96
3	1c	15	4c	89
4	1d	139	4d	50 ^c
5	1e	155	4e	57
6	1f	17	4f	62
7	5a	20	6a	84
8	5b	17	6b	82
9	5c	32	6c	67
10	5d	28	6d	75
11	5e	97	6e	28
12	5f	28	6f	36
13	5g	97	6g	21

^a Unless otherwise specified, the reaction was carried out using π -allylpalladium chloride dimer **3a** (5 mol %), allyltrimethylsilane **2a** (2 equiv), TBAF (0.5 equiv), and imines **1** or aldehydes **5** (1 equiv) in *n*-hexane–HF at room temperature for indicated times.

^b Isolated yield. ^c Three equivalents of **2a** were used.

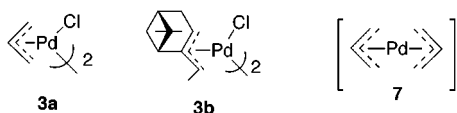
Table 2. Chiral π -Allylpalladium–TBAF-Catalyzed Asymmetric Allylation of Imines with Allyltrimethylsilane^a

entry	imine 1	reactn time (h)	product	yield (%) ^b	ee (%) ^c
1	1a	46	4a	79	80 ^d
2	1g	53	4g	79	79
3	1b	36	4b	95	3
4	1c	48	4c	96	5
5	1d	155	4d	34	76
6	1e	136	4e	60	84
7	1f	41	4f	77	64
8	1h	47	4h	88	68

^a The reaction was carried out using π -allylpalladium chloride dimer **3b** (5 mol %), allyltrimethylsilane **2a** (2 equiv), TBAF (0.5 equiv), and imines **1** (1 equiv) in *n*-hexane–THF at 0 °C for indicated times. ^b Isolated yield. ^c Determined by HPLC analysis (see ref 2). ^d The absolute configuration was determined to be *R* (see ref 2).

gave **4g** in 79% yield with 79% ee (entry 2). Although the allylation of **1b** and **1c** proceeded very smoothly, an almost racemic mixture of the products was obtained (entries 3 and 4). Perhaps the sterically bulky phenyl group prevented efficient coordination of the nitrogen atom of the imine to the palladium atom, diminishing the influence of the chiral ligand on the asymmetric induction. The reaction of **1d** was very sluggish as mentioned above and gave the corresponding homoallylamine **4d** in low yield, but with modest enantiomeric excess (76% ee; entry 5). The reaction of **1e** proceeded slowly to give **4e** in 60% yield with the highest enantiomeric excess among the imines examined (84% ee; entry 6). These results suggest that a sterically less bulky group attached to the nitrogen atom produces a higher ee than sterically bulky groups. The imines **1f** and **1h** underwent the asymmetric allylation to give **4f** and **4h** in good yields with modest enantiomeric excesses (64% ee and 68% ee, respectively; entries 7 and 8).

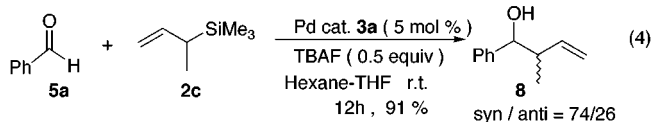
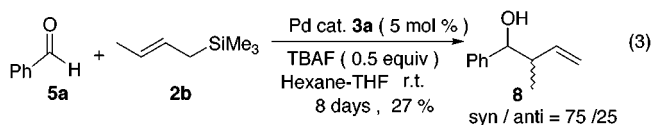
To clarify the mechanism of the allylation reaction catalyzed by the palladium–TBAF cocatalyst system, the structure of an intermediate produced from a stoichiometric reaction of **2a** and **3a** and TBAF in CDCl₃ was investigated.¹⁰ The ¹H NMR spectra of this mixture at 25 °C indicated clearly the formation of bis- π -allylpalladium complex **7**.¹⁰



(10) The experimental procedure similar to that described in ref 3 was used again.

The addition of benzaldehyde **5a** to the mixture caused the disappearance of the signals due to **7**, and new signals assigned to the corresponding homoallyl alcohol appeared. On the basis of these observations, it is clear that the allylation reaction would proceed via **7**. Perhaps fluoride ions would coordinate **2a** to produce the corresponding pentacoordinate allylsilicate, which would undergo quite easily transmetalation to Pd(II), giving the key intermediate **7**. As mentioned above, the allylation did not proceed in the absence of palladium catalysts. Therefore, the role of fluoride ions in the present allylation reaction is not to produce free allyl anions, which may react with aldehydes and imines.^{8,11} It is reported that certain pentacoordinate allylsilicates react with aldehydes¹² and imines^{4a} to give the corresponding allylated products, but we confirmed that [(allyl)SiMe₃F][–] formed in situ from **2a** and TBAF did not react with them under the reaction conditions.¹³

The allylation reaction with **2b** and **2c**¹⁴ was investigated (eqs 3 and 4). The reaction of benzaldehyde **5a** with **2b** (trans/cis = 87/13) was very sluggish at room temperature, and after 8 days only the γ -addition product **8**¹⁵ was obtained in 27% yield. Interestingly, the reaction of **2c** was



faster than that of **2b** and was completed in 12 h, giving only the α -addition product **8** in 91% yield. Furthermore, in both cases, the syn/anti diastereomer ratios of the products were almost same; 75/25 and 74/26 (see eqs 3 and 4).¹⁵ These results suggest that the rate-determining step of the allylation reaction is the transmetalation step; the transmetalation from **2b** is very slow whereas that from **2c** is faster, and the same bis- π -allylpalladium is produced from **2b** and **2c**.¹⁶

We have found that smooth allylation of imines and aldehydes with allylsilanes and catalytic asymmetric allylation of imines proceed in the presence of a palladium–TBAF cocatalyst system. We are now in a position to switch allylstannanes to nontoxic allyltrimethylsilane and approach green chemistry.

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(11) For proposed mechanisms, see: Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *Chem. Rev.* **1993**, *93*, 1371.

(12) (a) Hosomi, A.; Kohra, S.; Tominaga, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1517. (b) Kira, M.; Kobayashi, M.; Sakurai, H. *Tetrahedron Lett.* **1987**, *28*, 4081. (c) Cerveau, G.; Chuit, C.; Corriu, R. J. P.; Reye, C. *J. Organomet. Chem.* **1987**, *328*, C 17 (d) Kira, M.; Zhang, L. C.; Kabuto, C.; Sakurai, H. *Organometallics* **1996**, *15*, 5335.

(13) A referee pointed out that the fluoride anion is only present in a catalytic amount; therefore turnover would require breaking the notoriously stable silicon–fluoride bond. There are few examples for the reactions using a catalytic amount of fluoride ions: see ref 9a and Noyori, R.; Yokoyama, K.; Sakata, J.; Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1977**, *99*, 1265.

(14) For preparation of allylsilanes reagents **2b** and **2c**, see: (a) Slutsky, J.; Kwart, H. *J. Am. Chem. Soc.* **1973**, *95*, 8678. (b) Hosomi, A.; Iguchi, H.; Sakurai, H. *Chem. Lett.* **1982**, 223.

(15) The structure and the diastereomer ratios of the resulting homoallyl alcohols were determined by comparison with the reported data: Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1981**, *103*, 1969.

(16) Normally, in the allylation reactions of aldehydes and imines with allylmetal reagents, which would proceed via the six-membered cyclic transition state, the geometries of starting allylmetal reagents should have an effect on the corresponding products. For example, see refs 1 and 4a. See also: Yamamoto, Y.; Nishii, S.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Am. Chem. Soc.* **1986**, *108*, 7778.