Catalytic Asymmetric Allylation of Imines via Chiral Bis-π-allylpalladium Complexes

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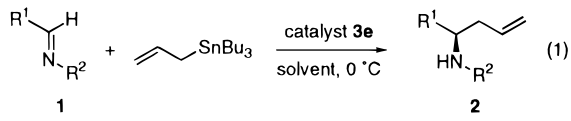
Enantioselective formation of carbon−carbon bonds between achiral substrates using catalytic amounts of chiral sources is a main goal in asymmetric synthesis. Recently, various Lewis acid catalysts have been synthesized and applied to asymmetric reactions of carbonyl compounds.[1] However, very few examples have been reported on catalytic asymmetric reactions of imines so far,[2] since the amines produced from the imines coordinate to Lewis acids strongly, making the catalysts inert. We recently found that imines underwent allylation reaction in the presence of palladium catalysts to afford the corresponding homoallylamines in high yields.[3] The mechanistic studies reveal that bis-π-allylpalladium complex is a reactive intermediate for this allylation[3b,4] and reacts with imines as a nucleophile, although ordinary π-allylpalladium complexes such as π-allylPdX (X = OAc and halides) act as an electrophile.[5] Furthermore, we have quite recently reported that bis-π-allylpalladium complex has an amphiphilic character.[6] It occurred to us that, by proper choice of the two allyl groups of bis-π-allylpalladium complexes, one of the allyl groups could react with imines as a nucleophile and the other could stay on the palladium atom. If a chiral π-allyl group is introduced as the nontransferable π-allyl ligand, the allylation may proceed enantioselectively with catalytic amounts of the chiral reagent. Herein, we report the first catalytic asymmetric allylation of imines **1** with allyltributylstannane in the presence of chiral π-allylpalladium complex **3e** (eq 1).

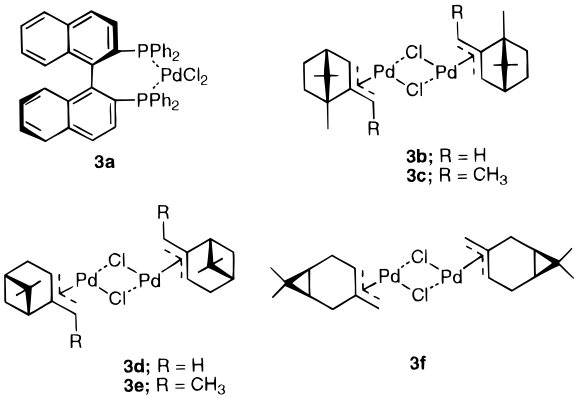
Chiral BINAP-palladium **3a** and π-allylpalladium catalysts **3b**−**f** were prepared according to the literature procedures.[7] The reaction of imine **1a** (1 equiv) with allyltributylstannane (1.2 equiv) in DMF was carried out in the presence of various palladium catalysts **3** (5 mol %) at 0 °C under Ar atmosphere.



1 **2**

a; R^1 = Ph, R^2 = Bn
b; R^1 = Ph, R^2 = p-$MeOC_6H_4CH_2$
c; R^1 = Ph, R^2 = Ph
d; R^1 = Ph, R^2 = Pr
e; R^1 = p-$MeOC_6H_4$, R^2 = Bn
f; R^1 = 2-naphtyl, R^2 = Bn
g; R^1 = PhCH=CH, R^2 = Bn
h; R^1 = *c*-Hex, R^2 = Bn

The use of chiral BINAP-palladium **3a** gave the corresponding homoallylamine **2a** in 39% yield and the enantiomeric excess of the product was 0%. Although the reactions using the chiral



π-allylpalladium chloride complexes (**3b,c**), which were prepared from (1*R*)-(+)-camphor, resulted in very low enantiomeric excess (ee), the use of the chiral catalyst **3d** which was derived from (1S)-β-(−)-pinene gave **2a** in 62% yield with the enantiomeric excess of 50%. The exomethylene of β-(−)-pinene was converted to exoethylidene, and the corresponding π-allylpalladium chloride **3e** was prepared.[7] The allylation of **1a** using this catalyst **3e** afforded **2a** in 62% yield with the enantiomeric excess of 81% (entry 1 in Table 1). The catalyst **3f**, which was prepared from (1*S*)-(+)-3-carene, was not effective for this asymmetric allylation. THF was also an effective solvent in this asymmetric allylation. The reaction of **1a** in THF proceeded smoothly in the presence of **3e**, giving **2a** in 72% yield with the same high level of ee (entry 1 vs 2).

We next examined the various imines using the complex **3e** as a catalyst. The imine **1b** underwent this allylation reaction with 80% ee in DMF (entry 3) and 82% ee in THF (entry 4). The allylation of imine **1c** derived from aniline resulted in ∼0% ee (entry 5). Perhaps, sterically bulky phenyl group would prevent efficient coordination of nitrogen atom of the imine to palladium atom, diminishing the influence of the chiral ligand on the asymmetric induction. The imine **1d** derived from benzaldehyde and propylamine gave **2d** in 70% ee (entry 6). These results suggest that a sterically less bulky group should be attached to the nitrogen atom in order to obtain high ee values. Not only the imines derived from benzaldehyde but also those from *p*-methoxybenzaldehyde and 2-naphthylaldehyde (**1e** and **1f**) underwent the allylation with enantiomeric excesses of 78% and

(1) Catalytic asymmetric allylation: (a) Costa, A. L.; Piazza, M. G.; Tagiavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc*. **1993**, *115*, 7001. (b) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc*. **1993**, *115*, 8467. (c) Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc*. **1996**, *118*, 4723. (d) Yu, C.-M.; Choi, H.-S.; Jung, W.-H.; Lee, S.-S. *Tetrahedron Lett*. **1996**, *37*, 7095. Catalytic asymmetric Aldol reaction: (e) Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem*. **1995**, *60*, 2648. (f) Evans, D.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc*. **1996**, *118*, 5814. (g) Evans, D.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **1997**, *119*, 7893.

(2) Asymmetric addition of organolithium reagents to imines in the presence of chiral ligands has been reported, although one equivalent amount (or more than 1 equiv in certain cases) of the ligands is needed in most cases. (a) Shindo, M.; Koga, K.; Tomioka, K. *J. Am. Chem. Soc*. **1992**, *114*, 8732. Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc*. **1997**, *119*, 2060 (two examples for catalytic use of the ligand are reported). (b) Demmark, S. E.; Nakajima, N.; Nicaise, O. J.-C. *J. Am. Chem. Soc*. **1994**, *116*, 8797. Demmark, S. E.; Nicaise, O. J.-C. *J. Chem. Soc., Chem. Commun*. **1996**, 999 (four examples of substrates are reported for catalytic asymmetric addition). More recently, catalytic asymmetric Mannich-type reactions using chiral zirconium catalyst has been reported: (c) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc*. **1997**, *119*, 7153.

(3) (a) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun*. **1996**, 1459. (b) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc*. **1996**, *118*, 6641.

(4) Nakamura, H.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun*. **1995**, 1273.

(5) (a) Tsuji, J. In *Palladium Reagents and Catalysts*; John Wiley and Sons: Chichester, 1995; p 61. (b) Codleski, S. A. In *Comprehensive Organic Synthesis*; Semmelhack, M. F., Ed.; Pergamon Press: Oxford, 1991; Vol. 4, p 585. (c) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. In *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; p 417.

(6) Nakamura, H.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc*. **1997**, *119*, 8113.

(7) For the synthesis of chiral π-allylapalladium complexes, see: (a) Heck, R. F. In *Palladium Reagents in Organic Syntheses*; Academic Press: London, 1985; pp 1−18. (b) Trost, B. M.; Strege, P. E.; Weber, L.; Fullerton, T. J.; Dietsche, T. J. *J. Am. Chem. Soc*. **1978**, *100*, 3407. For the reactions using chiral π-allylapalladium catalysts, see: (c) Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S.-I. *J. Am. Chem. Soc*. **1981**, *103*, 2318. Hosokawa, T.; Okuda, C.; Murahashi, S.-I. *J. Org. Chem.* **1985**, *50*, 1282.

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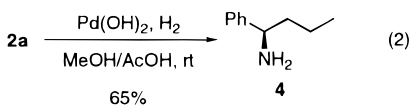
Table 1. Asymmetric Allylation of Imines **1** Catalyzed by Chiral π-allylpalladium Complex **3e**

entry	imine 1	solvent	reaction time (h)	yield of **2** (%)[a]	ee (%)[b]
1	**1a**	DMF	90	62	81
2	**1a**	THF	119	72	80[c]
3	**1b**	DMF	60	50 (62)	80
4	**1b**	THF	116	61 (66)	82
5	**1c**	DMF	20	74	~0
6	**1d**	DMF	156	30 (62)	70
7	**1e**	DMF	173	48 (63)	78
8	**1f**	DMF	62	69 (79)	79
9	**1f**	THF	124	83	71
10	**1g**	DMF	90	68	61
11	**1h**	DMF	111	44 (64)	40

[a] Isolated yields based on **1**. The yields determined by ^{1}H NMR using *p*-xylene as an internal standard were indicated in the parentheses. In general, the isolated yields were lower than the NMR yields. In certain cases, separation of Bu_3Sn residue was difficult (for example, entries 6 and 7), leading to decrease of the isolated yields. [b] Determined by HPLC analysis (see the Supporting Information). [c] During several experiments, **2a** was obtained with an ee of 78−80%.

79%, respectively (entries 7 and 8). The use of THF as a solvent gave **2f** in 83% yield with 71% ee (entry 9). The reaction of vinylic and aliphatic imines (**1g,h**) proceeded smoothly to afford the corresponding homoallylamines (**2g,h**) with allowable enantioselectivities (entries 10 and 11).

The absolute configuration of homoallylamine **2a** was determined by converting it to 1-phenylbutylamine **4** (eq 2). The hydrogenation of **2a** in the presence of $Pd(OH)_2$ catalyst gave **4** in 65% yield. The literature value of (*S*)-1-phenylbutylamine was



(2)

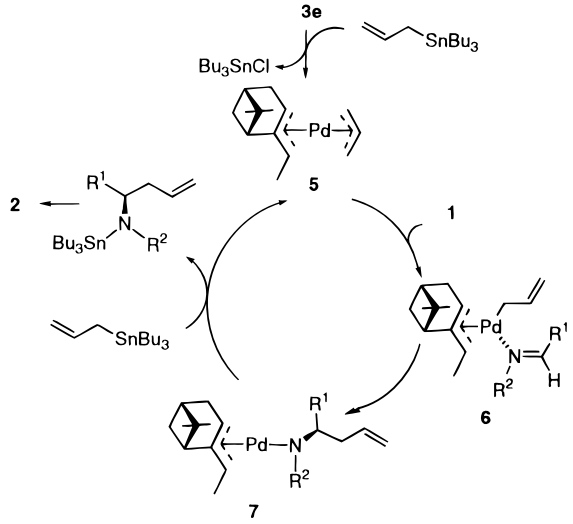
$[\alpha]_D$ −21.3 (*c* 1.3, $CHCl_3$),[8] and the optical rotation of **4** exhibited an opposite + value. Therefore, it was confirmed that the absolute configuration of **2a** is (*R*).

A representative procedure is as follows. To a solution of imine **1a** (0.4 mmol) and allyltributylstannane (0.4 mmol) in dry DMF (1 mL) at 0 °C was added the chiral palladium chloride catalyst **3e** (0.02 mmol). The mixture was stirred for 90 h at 0 °C. After the reaction was quenched with water, the mixture was extracted with ether and a saturated KF aqueous solution was added. The mixture was stirred for 3 h, and the aqueous layer was removed. The organic layer was washed with a saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and then concentrated. Purification by silica gel column chromatography (hexane/ethyl acetate = 10:1) gave **2a** in 62% yield. The optical purity was determined by HPLC analysis using a chiral column.[9]

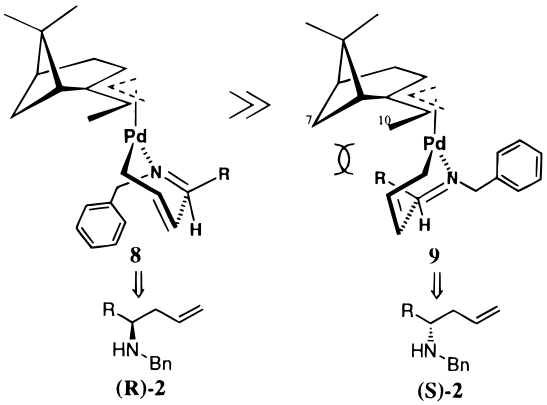
A plausible mechanism is shown in Scheme 1. The transmetalation of allyltributylstannane to palladium would produce bis-π-allylpalladium complex **5**, which would react with imine **1** to give the π-allylpalladium amide **7** via complex **6**. A key step for the chiral induction would be the coordination stage of imine **1** to bis-π-allylpalladium complex **5**. The transmetalation of allyltributylstannane to palladium would produce the corresponding stannyl homoallylamide and **5**.

The chiral catalyst **3e** exhibited higher ee than **3d**. To help clarify the mechanism of the catalytic allylation, we investigated the change of ee with the percent completion of the reaction of **1a**. The allylation was carried out in THF at 0 °C; the detailed results are shown in Figure 1 of the Supporting Information. Essentially the same level of ee (~80% ee) was obtained via **3e** with the progress of the reaction. However, the ee values via **3d** decreased with the progress of the reaction (reaction time, yield

Scheme 1



Scheme 2. Probable Transition-State Models



of **2a**, ee of **2a**): (10 h, 8%, 57%), (20 h, 20%, 55%), (125 h, 54%, 45%). It is most probable that, in the case of **3d**, the η^3-pinene chiral group of the π-allyl-π-pinenyl palladium intermediate is not a nontransferable ligand and achiral bis-π-allylpalladium complex intervenes with the progress of the reaction. On the other hand, η^3-10-methylpinene chiral group of **3e** is a nontransferable ligand and the catalytic cycle proceeds essentially as shown in Scheme 1.

Probable transition-state models are shown in Scheme 2. The front side of η^3-10-methylpinene group of the palladium catalyst is highly crowded by the methyl at C-10 position, and thus an imine is forced to approach from the less-hindered backside. The nitrogen of the imine coordinates to palladium atom and the C−C bond formation takes place through six-membered cyclic transition state. In the case of **9**, there is severe steric repulsion between R group of the imine and C-7 methylene group. Accordingly, the reaction proceeds through a transition state model **8** to give (*R*)-2 products predominantly.

We are now in a position to synthesize homoallylamines from imines in catalytic asymmetric manner. The Pd-catalyzed asymmetric allylation proceeds *under essentially neutral conditions in contrast to the reactions via Lewis acid catalysts*, making it possible to introduce labile functional groups in substrates. Further extension of the catalytic asymmetric allylation is now in progress.

Supporting Information Available: Spectral data for the compounds (**2a**−**h**) and the experimental results of the ee variation with the percent completion of the reaction of **1a** (13 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(8) Yamamoto, Y.; Shimota, H.; Oda, J.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3247.
(9) Details are shown in the Supporting Information.