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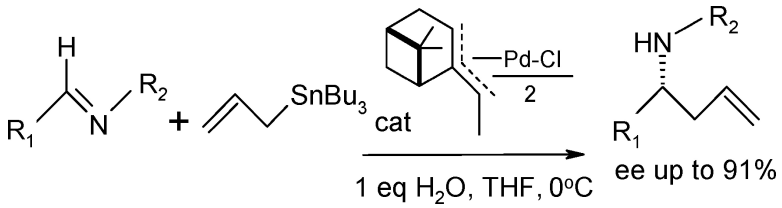

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Chiral Bis-π-allylpalladium Complex Catalyzed Asymmetric Allylation of Imines: Enhancement of the Enantioselectivity and Chemical Yield in the Presence of Water

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Abstract: The chiral π-allylpalladium complex **2a**, prepared from exoethylidenenorpinane **7**, catalyzed the allylation of diverse imines with allyltributylstannane in the presence of 1 equiv of water in good to high enantioselectivities. The catalyst prepared from a 1:1 mixture of (*E*)- and (*Z*)-**7** was found to be consisting of two stereoisomers **2a** and **2b** in 1.3:1 ratio. On separation, **2a** catalyzed the allylation of imines in much higher enantioselectivities than **2b**, giving the same major enantiomer and thereby justifying the need to separate **2a** free of **2b**. We have achieved the highest separation ratio of >400:1 for **2a**:**2b** by repeated recrystallizations. Isomerization of **2b** to **2a** during recovery of **2a** from the filtrates was observed as more of **2a** was recovered each time during recrystallization. Although dry THF was the best solvent, we tried various additives and found that addition of *one equivalent of water* gave the best results with respect to shorter reaction time, higher yields and enantioselectivities. Thus, we have developed a more general, reproducible, robust and a non-Lewis acid catalyzed procedure for catalytic asymmetric allylation of imines under essentially neutral conditions.

Introduction

The allylation of carbonyl compounds such as aldehydes, ketones, and their derivatives is one of the most important C−C bond forming reactions because of the versatility of homoallylic alcohols and amines as useful synthetic intermediates.[1] Although many methods have been developed, research in this field seeking new and more efficient methods are unabated. Among the various allylmetal reagents, allylstannanes and allylsilanes are very useful because of their modest reactivity, which in turn can be increased by catalyst activation and thus allow for application to catalytic enantioselective reactions. Imine activation methods using Lewis or Bronstead acids have also been developed.[1] However, these acids coordinate strongly with amine products, making the catalyst inactive. It is also reported that fluoride anions or alkoxides also activate the C−Si bond of allylsilanes by coordinating to the silicon atom.[2] Recently, chiral sulfoxides as neutral coordinate organocatalyst (NCOs) were used in the allylation of N-acylhydrazones.[3] Although the reactions with aldehydes have been well investigated,[4] very few reports have appeared on the asymmetric allylation of imines.[5] Our group[6] reported the first catalytic asymmetric allylation of imines in 1998 using allyltributylstannane in the presence of a chiral π-allylpalladium complex.

In contrast to the Lewis acid mediated allylations, known from previous studies that require at least a stoichiometric amount of promoter, these reactions were shown to occur readily in the presence of catalytic amounts of Pd (II) or Pt (II) complexes. Mechanistic studies of the Pd (II)-catalyzed reaction revealed that bis-π-allylpalladium complex (e.g., **3**) is a key intermediate[7] for the catalytic cycle and reacts with imines as a nucleophile, although the ordinary π-allylpalladium complexes such as π-allylPdX (X = OAc and halides, e.g., **1**) act as electrophiles[8] (Scheme 1). We have also shown that bis-π-allylpalladium complex has an amphiphilic character.[9] It was our earlier

(1) For recent reviews on allylmetal additions, see: (a) Puentes, C. O.; Kouznetsov, V. *J. Heterocycl. Chem.* **2002**, *39*, 595. (b) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VHC: Weinheim, 2000; Chapter 10. (c) Chemler, S. R.; Roush, R. W. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VHC: Weinheim, 2000; Chapter 11. (d) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (e) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (f) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. (f) Yamamoto, Y.; Asano, N. *Chem. Rev.* **1993**, *93*, 2207.

(2) For leading references on fluoride- or alkoxide-promoted allylation of imines with allylsilanes, see: (a) Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 6536. (b) Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 2614. (c) Wang, D.-K.; Zhou, Y.-G.; Tang, Y.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* **1999**, *64*, 4233. (d) Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1996**, *61*, 6901. (e) Sakurai, H. *Synlett* **1989**, 1.

(3) Kobayashi, S.; Ogawa, C.; Konishi, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 6610.

(4) (a) Oi, S.; Moro, M.; Fukuhara, H.; Kawanishi, T.; Inoue, Y. *Tetrahedron* **2003**, *59*, 4351. (b) Yanagisawa, A.; Kageyama, H.; Nakatsuka, Y.; Asakawa, K.; Matsumoto, Y.; Yamamoto, H. *Angew. Chem. Int. Ed.* **1999**, *38*, 3701 and references therein. Also see ref. (2a).

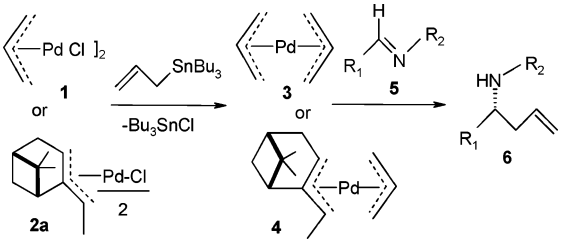
(5) For leading references on enantioselective allylation of imines, see: (a) Gastner, T.; Ishitani, H.; Akiyama, R.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2001**, *40*, 1896. (b) Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell, R. G.; Jorgensen, K. A. *J. Org. Chem.* **1999**, *64*, 4844. (c) Ferraris, D.; Dudding, T.; Young, B.; Drury, W. J., III.; Lectka, T. *J. Org. Chem.* **1999**, *64*, 2168.

(6) (a) Bao, M.; Nakamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 131. (b) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242. For use of allyltrimethylsilane instead of allyltributylstannane, see reference (2b).

(7) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641. (b) Nakamura, H.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 1273.

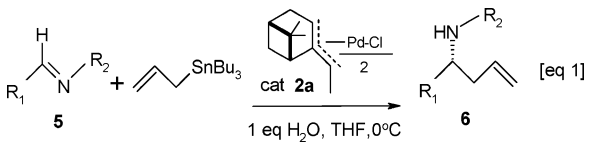
10.1021/ja037272x CCC: $25.00

Scheme 1. Concept of Chiral Allylation with Bis-π-Allylpalladium Complexes



investigation that, with the proper choice of the two allyl ligands of bis-π-allylpalladium complexes, catalytic asymmetric allylation was also possible. This is due to the fact that a sterically bulky π-allyl group acts as a nontransferable π-allyl ligand, whereas the other reacts with imines as a nucleophile in a chiral way.[6b] Among the various π-allylpalladium chloride complexes prepared from (1*R*)-(+)-camphor, (1*S*)-β-(−)-pinene, and (1*S*)-(+)-3-carene, the one based on (1*S*)-β-(−)-pinene gave around 50% enantiomeric excess, whereas the others were unsuccessful.[6b] The exomethylene of (1*S*)-β-(−)-pinene was converted to exoethylidene, and the corresponding π-allylpalladium chloride **2a** obtained was reacted with allyltributylstannane to give the bis-π-allylpalladium complex **4**, which transferred the allyl group to the imines **5** to furnish homoallylamines **6** in good enantioselectivities (up to 82% ee).[6b] Later, when we applied this catalytic asymmetric allylation to several imines under the conditions reported in the communication,[6b] nonreproducible results were obtained; often, lower enantioselectivities and chemical yields were obtained, and the reason for this fluctuation was unclear. This situation left sufficient room for improvement of the reaction rate, yield, and enantioselectivity.

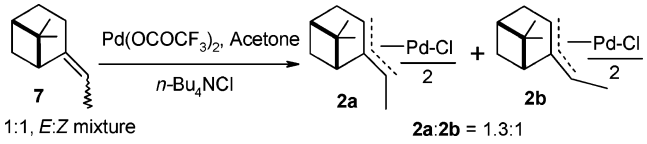
Now we wish to report in detail that the asymmetric allylation of imines with allyltributylstannane in the presence of a catalytic amount of chiral π-allylpalladium complex **2a** and *1 equiv of water* gives more general, reproducible, and robust results over a wide range of imines (eq 1).



Results and Discussion

Preparation of Catalyst. Trost et al.[10] reported that the π-allylpalladium complex obtained from **7** was a single complex and assigned the syn configuration (Scheme 2). They also stated that the stereochemistry of the olefin did not determine the stereochemistry of the product. However, on careful investigation using ^{1}H NMR, we found that the π-allylpalladium complex, obtained from a 1:1 mixture of (*E*)- and (*Z*)−**7**,[11] consisted of a 1.3:1 mixture of two stereoisomers **2a** and **2b** (Scheme 2). We first tried to separate **2a** and **2b** by column chromatography. However, although we could get a small amount of **2b** separated in pure form, **2a** always contained **2b**. We opted then for repeated recrystallization. On two recrystallizations in CH_2Cl_2/hexane, we got **2a**:**2b** = 12.3:1 (see the Supporting Information). Although these results could not be exactly reproduced, we later concluded through several trials that any material having ratio of **2a**:**2b** > 7 could best be upgraded by propionitrile recrystallization.[12] Thus, two successive propionitrile recrystallizations gave **2a**:**2b** = 100:1, having $[\alpha]^{22}_D = -19.4$ (c 0.4, $CHCl_3$). Further recrystallization in propionitrile gave the catalyst with **2a**:**2b** = >400:1,[13] having $[\alpha]^{22}_D = -19.9$ (c 0.4, $CHCl_3$)[14] which was almost constant on further recrystallization. The filtrates were combined to recover[15] the catalyst and more of **2a** was always obtained, indicating isomerization of **2b** to **2a** during recrystallization. Thus, with the upgraded catalyst in hand we next planned to examine the catalytic asymmetric allylation reaction.

Scheme 2. Catalyst Preparation for Asymmetric Allylation (for separation of **2a** and **2b** See Supporting Information).



Catalytic Asymmetric Allylation: Unprecedented Influence of Water. We first examined the allylation reaction of **8a** in the presence of **2a** (5 mol %) in THF solvent at 0 °C under anhydrous conditions (eq 2). Although we carried out the reaction several times under seemingly identical conditions, nonreproducible results and lower enantioselectivities were obtained. Also, under anhydrous conditions, catalyst decomposition was observed. Among many trials, the best results under the standard conditions using dry THF (dried over Na or $LiAlH_4$) are shown in entries 1 and 2 of Table 1. We did not understand why the data on ee and the chemical yield of eq 2 were fluctuating. However, addition of 1 equiv of water resulted in an improved yield and enantioselectivity (entry 3). More importantly, in the presence of water, the data on ee and

(8) (a) Tsuji, J. In *Palladium Reagents and Catalysis*; John Wiley and Son: 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) Collmann, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. In *Principles and Applications of Organotransition Metal Chemistry*; Mill Valley, 1987; p 417.

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

(10) (a) Trost, B. M.; Strege, P. E.; Weber, L.; Fullerton, T. J.; Dietsche, T. J. *J. Am. Chem. Soc.* **1978**, *100*, 3407. Other references for synthesis of chiral-π-allylpalladium complex complexes, see: (b) Rosset, J.-M.; Glenn, M. P.; Cotton, J. D.; Willis, A. C.; Kennard, C. H. L.; Byriel, K. A.; Riches, B. H.; Kitching, W. *Organometallics* **1998**, *17*, 1968. (c) Heck, R. F. In *Palladium Reagents in Organic Syntheses*; Academic Press: London, 1985; pp 1−18. (d) Trost, B. M.; Metzner, P. J. *J. Am. Chem. Soc.* **1980**, *102*, 3572.

(11) Olefin **7** (*E*:*Z* = 1:1) was prepared starting from (1*S*)-(−)-β-pinene available in Aldrich Chemical Co. in 97% ee. Though (1*R*)-(+)-nopinone (90% ee) is also available, we preferred to prepare it from (1*S*)-(−)-β-pinene by ozonolysis of exocyclic double bond. Further Wittig reaction with ethyltriphenylphosphonium bromide and ^{t}BuOK gave **7** (*E*:*Z* = 1:1) [see: Brown, H. C.; Weissman, S. A.; Perumal, P. T.; Dhokte, U. P. *J. Org. Chem.* **1990**, *55*, 1217].

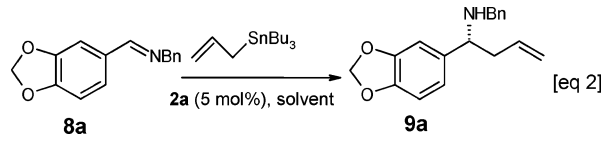
(12) The solvents tried were 2-butanone, propionitrile, 2-propanol, and diisopropyl ether. Among all, propionitrile gave best upgradation ratio of **2a**:**2b** and recovery of catalyst during recrystalization. Though the catalyst is not freely soluble in propionitrile, warming to 90 °C gave clear solution. Higher temperatures or boiling should be avoided to prevent catalyst decomposition.

(13) See the Supporting Information for ^{1}H NMR of **2a**:**2b** = 1.3:1, 100:1, and >400:1.

(14) There is no literature value of $[\alpha]_D$ of **2a** available. In our earlier communication (ref 6b), the catalyst used had $[\alpha]^{22}_D$ −13.3 (c 0.4, $CHCl_3$). From the ^{1}H NMR spectrum available the ratio of the catalyst **2a**:**2b** was 20:1. To the best of our knowledge, this is the first report of preparation of the catalyst **2a** and separated from its undesired stereoisomer with a ratio of **2a**:**2b** >400:1.

(15) For recovery of catalyst **2a**, the later filtrates (see the Supporting Information) were combined and concentrated to yellow powder. This was dissolved in propionitrile and crystallized out. The successive three recrystallizations gave **2a**:**2b** = 100:1, having $[\alpha]^{22}_D$ −17.2 (c 0.4, $CHCl_3$). This was further upgraded to **2a** (**2a**:**2b** >400:1), having $[\alpha]^{22}_D$ −19.8 (c 0.4, $CHCl_3$). See the Supporting Information for more details.

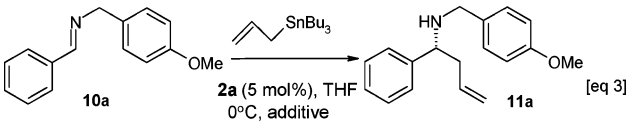
Table 1. Optimization of Reaction Conditions[a]



entry	equiv of allylSnBu$_3$	solvent	temp °C	time (h)	%yield of **9a**	%ee
1	1	dry THF[b]	0	120	51	84
2	1	dry THF[c]	0	120	64	82[d]
3	1	dry THF + 1 equiv H_2O	0	120	73	88
4	1.25	dry THF + 1 equiv H_2O	0	84	76	90
5	1.25	dry THF + 1 equiv H_2O	0	96	72	86[d]
6	1.25	dry THF + 5 equiv H_2O	0	135	64	86
7	1.25	dry THF + 0.5 equiv H_2O	0	96	68	83
8	1.25	dry THF + 1 equiv H_2O	−20	192	50	83
9	1.25	dry THF + 1 equiv H_2O	rt	120	70	63
10	1.25	dry THF + 1 equiv H_2O	0	168	42	17[e]

[a] Standard reaction conditions: To a solution of **8a** (0.5 mmol) in dry THF (1.25 mL, commercial dehydrated THF) was added allylSnBu$_3$ (0.5 mmol) and the mixture was cooled to 0 °C. Catalyst **2a** (5 mol %) was added and the reaction mixture stirred for specified time (GC−MS monitored). [b] Dried on Na. [c] Dried on $LiAlH_4$. [d] Stannane added last. [e] Using the catalyst **2b**.

Table 2. Effect of an Additive on the Reaction Time, Chemical Yield, and Enantioselectivity



additive	equiv	time (h)	%yield of **11a**	%ee
no additive		78	76	83
H_2O	1	73	89	90
TBAF	1	102	81	86
Na_2CO_3	2	171	51	57
KOAc	2	91	54	86
4 A° MS	100 mg/mmol	72	81	87
MeOH	1	89	76	87
i-PrOH	1	90	75	86
AcOH	1	147	71	87

chemical yield were not fluctuating, and a reproducible result was obtained. The use of 1.25 equiv of stannane shortened the reaction time and gave higher yield and enantioselectivity (entry 4). When the order of addition was changed, with catalyst addition first and then stannane (entries 2 and 5), it required a longer reaction time and gave slightly lower enantioselectivity. Excess of water (5 equiv, entry 6) or less than 1 equiv (0.5 equiv, entry 7) gave inferior results in comparison to entry 4. The reaction at −20 °C required longer reaction time for completion and resulted in poor yields (entry 8). Similarly poor results were obtained at room temperature (entry 9). When the catalyst **2b** was employed, the imine **8a** was not completely consumed even after 168 h and a poor yield and unsatisfactory enantioselectivity were obtained (entry 10). Although catalyst **2b** produces the same enantiomer, it is necessary to separate **2b** from **2a**.

Apart from water, we were interested in trying out other additives. The reaction of **10a** with allyltributylstannane in the presence of **2a** (5 mol %) and additives in dry THF at 0 °C gave **11a** (eq 3). It can be seen in Table 2, that addition of 1 equiv of water gave the best results concerning both chemical yield and ee. Comparable results were obtained with molecular sieves and MeOH. We do not understand at present the almost comparable behavior of molecular sieves with the results obtained with water though they are contradictory in activity. TBAF, *i*-PrOH, and KOAc gave slightly lower enantioselectivity, whereas the latter gave lower yield. Na_2CO_3 proved unsatisfactory. The reaction required longer time for completion and resulted in lower yield and enantioselectivity. AcOH gave comparable results with water, but required longer reaction time and gave lower yields. Thus, we found that addition of 1 equiv of water furnished the best results.

The general procedure is as follows: Imine (0.5 mmol) was taken in a Wheaton microreactor (5 mL capacity), and the reactor was kept under Ar atmosphere. Dry THF (1.25 mL), degassed water (9 μL, 0.5 mmol, 1 equiv) and allyltributylstannane (194 μL, 0.625 mmol, 1.25 equiv) were added sequentially. The mixture was cooled to 0 °C and the chiral palladium chloride complex **2a** (14.56 mg, 0.025 mmol, 5 mol %) was added under argon. The reaction mixture was flushed with argon and stirred at 0 °C for specified time. The reaction progress was monitored with GC−MS or TLC. After completion, the turbid reaction mixture was quenched with 1N HCl (2.5 mL). CH_3CN[16] (1 mL) was added and the reaction mixture was stirred at room temperature for 10 min. The two layered solution was extracted with hexane (2 × 3 mL). The hexane layer was discarded, the aqueous layer was basified with 10% NaOH aq (1.25 mL), and the resulting solution was stirred for 5 min. The solution was extracted with EtOAc (2 × 5 mL), dried (Na_2SO_4) and concentrated. Purification by silica gel column chromatography (hexane/EtOAc = 5:1) gave the corresponding homoallylamines. The enantiomeric excesses were determined by HPLC.[17]

Under the above procedure, most imines reacted in shorter time, with high yields and moderate to good enantioselectivities (Table 3, entries 1−5). *N*-Benzylidenebenzylamine **12a** reacted in 48 h to give **13a** in 85% ee. The imines **12b** and **12e** furnished **13b** and **13e** in 85% and 70% ee, respectively, though a longer reaction time was needed for completion. The imine **12c** with *para*-methyl group gave **13c** in high yield and 90% ee. We anticipated that an *ortho*-chelating group such as methoxy might help in rigidifying the transition state through chelation and higher ee would result. The *ortho*-methoxy substituted imine **12d** produced **13d** in very good enantioselectivity of 88%, but a marked contrast between **12d** and **12b** (*para*-methoxy substituted) was not observed.

N-Cyclohexylidenebenzylamine **14** furnished the homoallylamine **15** in 40% ee requiring 111 h for completion of reaction by our earlier procedure;[6b] however, it gave **15** in 50% ee and reacted in 74 h by our above new procedure (entry 6). Similarly, the imine **16** produced **17** in high yield and good enantioselectivity of 69% (entry 7). The heterocyclic imines **18a** and **18b** reacted well to give **19a** (67% ee) and **19b** (53% ee), respectively, in high yields and moderate ees (entries 8−9) without polymerization, which is sometimes noticed under Lewis acid-catalyzed conditions. Next, we examined the imines with chelating methoxy substituent either on the aryl group of aldehyde portion or on benzyl group on imine nitrogen. The imines **10a**−**10c** with *para*-methoxybenzyl group gave high yields of homoallylamines **11a**−**11c** with excellent enantio-

(16) CH_3CN was added for better solubilization of stannane byproducts.
(17) Details for each compound are giving in the Supporting Information.

Table 3. Catalytic Asymmetric Allylation of Imines with Allyltribuylstannane in the Presence of the Catalyst **2a**[a]

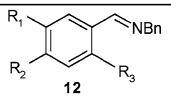
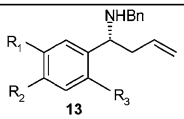
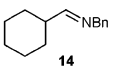
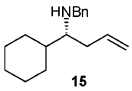
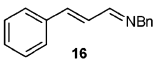
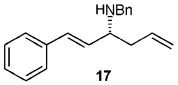
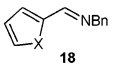
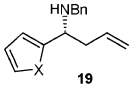
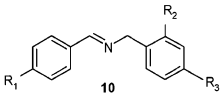
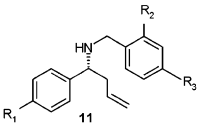
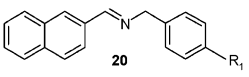
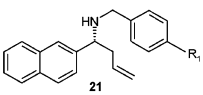
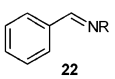
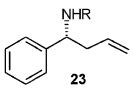
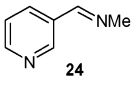
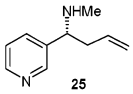
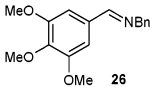
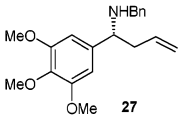
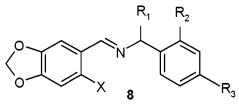
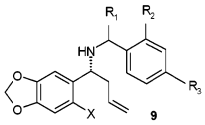
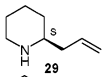
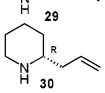
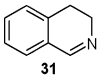
entry	substrate	product	time(h)	% yield	%ee
	 **12**	 **13**			
1	**12a** $R_1 = R_2 = R_3 = H$	**13a**	48	86	85
2	**12b** $R_1 = R_3 = H$, $R_2 = OMe$	**13b**	98	82	85
3	**12c** $R_1 = R_3 = H$, $R_2 = Me$	**13c**	67	92	90
4	**12d** $R_1 = R_2 = H$, $R_3 = OMe$	**13d**	73	78	88
5	**12e** $R_1 = R_2 = OMe$, $R_3 = H$	**13e**	116	76	70
6	 **14**	 **15**	74	84	50
7	 **16**	 **17**	72	84	69
	 **18**	 **19**			
8	**18a** X = O	**19a**	73	90	67
9	**18b** X = S	**19b**	90	90	53
	 **10**	 **11**			
10	**10a** $R_1 = R_2 = H$, $R_3 = OMe$	**11a**	73	89	90
11	**10b** $R_1 = R_3 = OMe$, $R_2 = H$	**11b**	88	78	85
12	**10c** $R_1 = Me$, $R_2 = H$, $R_3 = OMe$	**11c**	72	81	86
13	**10d** $R_1 = NO_2$, $R_2 = H$, $R_3 = OMe$	**11d**	70	94	42
14	**10e** $R_1 = R_3 = H$, $R_2 = OMe$	**11e**	78	82	89
	 **20**	 **21**			
15	**20a** $R_1 = H$	**21a**	96	70	91
16	**20b** $R_1 = OMe$	**21b**	74	81	82
	 **22**	 **23**			

Table 3. (Continued)

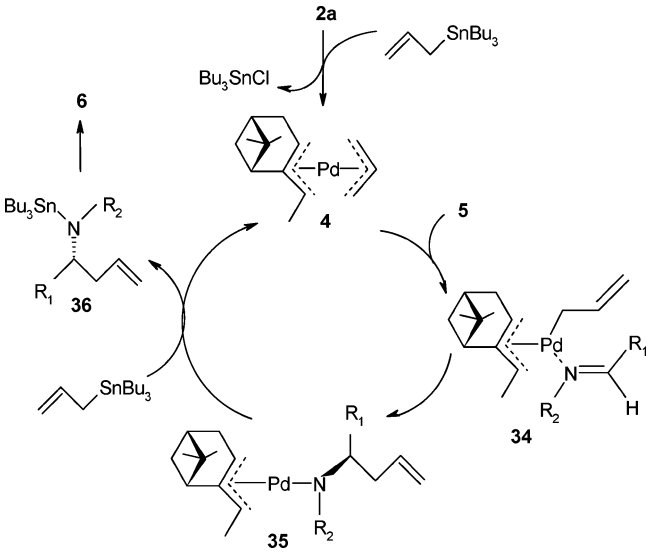
entry	substrate	product	time(h)	% yield	%ee
17	**22a** R = allyl	**23a**	78	82	78
18	**22b** R = SO_2Ph	**23b**	144	<10[b]	---
19	 **24**	 **25**	168	42	55
20	 **26**	 **27**	120	75	34
	 **8**	 **9**			
21	**8a** X = R_1 = R_2 = R_3 = H	**9a**	84	76	90
22	**8b** X = R_1 = R_2 = H, R_3 = OMe	**9b**	72	76	89
23	**8c** X = R_1 = R_3 = H, R_2 = OMe	**9c**	79	68	89
24	**8d** X = Cl, R_1 = R_2 = R_3 = H	**9d**	89	84	87
25	**8e** X = Br, R_1 = R_2 = R_3 = H	**9e**	99	87	88
26	**8f** X = R_2 = R_3 = H, R_1 = Ph	**9f**	126	30	83
27	 **28**	 **29**	20	38	02
		 **30**	20	63	18[c]
28	 **31**	 **32**	41	77	07[d]
		 **33**	43	73	19[c,d]

[a] All reactions were carried out with 1.25 equivalent of allyltributylstannane and one equivalent of water in the presence of 5 mol % of **2a** and at 0 °C for the specified time. In some cases additional 0.5 equivalent of allyltributylstannane was added if it was completely consumed and the reaction was not complete (checked by GC−MS); for determination of absolute configuration, see ref 6b. [b] Determined by ^{1}H NMR of the crude reaction mixture with CH_3NO_2 as internal standard. [c] Using catalyst **2b**. [d] ee based on known $[\alpha]_D$ values (see the Supporting Information)

selectivities of 90%, 85%, and 86%, respectively (entries 10−12). The imine **10d** with nitro group in *para*-position of the aldehyde portion gave **11d** in excellent yield, but an unsatisfactory enantioselectivity was obtained. The reason for this decrease of enantioselectivity is not clear at present. The imine **10e** with *ortho*-methoxybenzyl group gave **11e** with 89% ee (entry 14). *N*-2-Naphthylidenebenzylamine **20a** produced **21a** in excellent enantioselectivity (91% ee) under our new procedure (entry 15). However, **20b** having a *para*-methoxybenzyl group afforded **21b** with lower ee in comparison to **20a** (entry 16). We have also tried the reaction of imines bearing a group, other than benzyl, on the imine nitrogen. Thus, the N-allyl imine **22a** furnished the allylated homoallylamine **23a** in good yield and 78% ee (entry 17). The reaction of the imine **22b** was very sluggish to give the product **23b** in less than 10% yield even after 144 h, though the imine was completely consumed in the reaction. The probable reason for this sluggish reaction is explained in the mechanistic section. *N*-3-Pyridylidenemethylamine **24** required longer reaction time and gave **25** in moderate ee. The reaction of the bulky imine **26** with three methoxy groups was slow to furnish **27** in unsatisfactory 34% ee.

We were more interested in the amine **9a** obtained by allylation of the imine **8a**. Complete reduction of the double bond and removal of benzyl protection in **9a** would give (*R*)-α-propylpiperonylamine. This chiral butylamine is an important building block of human leukocyte elastase inhibitor L-694,458.

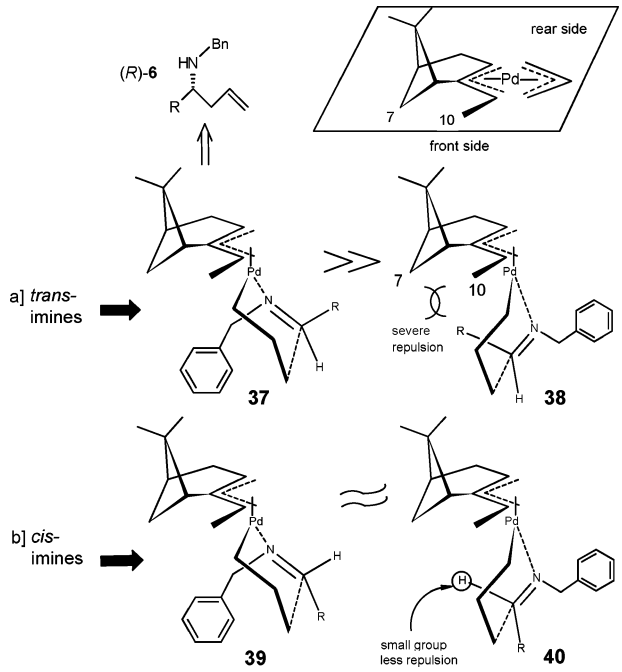
Scheme 3. Plausible Mechanism of Allylation



A few syntheses of this amine have been reported earlier.[18] Allylation of the imine **8a** gave **9a** in 76% yield with high enantioselectivity of 90% (entry 21). This could be easily converted into (*R*)-α-propylpiperonylamine by hydrogenation of the double bond and benzyl deprotection. We examined the allylation of the arylimines bearing other substituents on the aryl portion or having different substituents on the benzyl group with a hope to enhance the ee of the amine. Thus, **8b** with para-methoxybenzyl group and **8c** with ortho-methoxybenzyl group gave **9b** and **9c**, respectively, in comparable results with 89% ee (entries 22−23). Introduction of either Cl^- or Br^- substituent at the ortho-position of the aryl group could show no difference (entries 24−25). Introduction of a bulky group such as diphenylmethylene on the imine nitrogen could hardly show any improvement. Thus, the imine **8f** gave **9f** in low yield of 30% with 83% ee. Finally, we tried the allylation of the *cis*-cyclic imines **28** and **31** (entries 27−28). Interestingly, the *cis*-imines proved to be poorer substrates in the chiral allylation by this procedure. The reason for this dramatic difference between the *trans*- and *cis*-imines is discussed in the mechanistic section.

Mechanistic Explanations. A plausible mechanism for allylation is shown in Scheme 3. As shown earlier[7] the bis-π-allylpalladium complex **4** is the reactive intermediate, in which an allyl ligand acts as a transferable group and the other nontransferable allyl group determines the stereocontrol of allylation. Thus, the transmetalation between **2a** and allyltributylstannane would produce tributylstannyl chloride and the bis-π-allylpalladium complex **4**, which would react with the imine **5** to give the π-allylpalladium amide **35** via complex **34**. The key step for chiral induction could be the coordination stage of imine **5** to the bis-π-allylpalladium complex **4** to give **34** and the subsequent allylation would proceed in a six-membered chair like transition state to give **35**. The subsequent transmetalation of allyltributylstannane to palladium would produce the corresponding stannyl homoallylamide **36** and regenerate **4** to complete the catalytic cycle. Hydrolysis of **36** would give the product homoallylamine **6**. The role of water in this reaction

Scheme 4. Transition State Models



could be to form the pentacoordinate allylstannate, in which water coordinates to the tetravalent stannane, and thereby facilitates the C−Sn bond cleavage and enhances the transmetalation step in giving **4** and **36**. This contributes to a faster reaction rate and higher yields.[19] The sulfonyl imine **22b** (entry 18) failed to give the product amine in reasonable yield, though it was consumed in the reaction. This probably could be due to stabilization and decrease in nucleophilicity of nitrogen atom by the electron withdrawing tosyl group[20] in the intermediate corresponding to **35**. This intermediate could not undergo transmetalation with allyltributylstannane to give the product amine and reproduce **4**. Thus, the catalytic cycle must be blocked.

For the *trans*-imines, the probable transition state models are shown in Scheme 4a. 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 rear side. The nitrogen of imine coordinates to palladium atom and the C−C bond formation occurs through the six-membered cyclic chair like transition state. In the case of **38**, 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 **37** to give the (*R*)-homoallylamine predominantly. In the case of the *cis*-imines (Scheme 4b), there is not much repulsion between the H of the imine (model **40**) and the C-7 methylene group, H being a small atom. Hence, cyclic *cis*-imines without α-substituent to nitrogen should not undergo severe steric interactions with the allylic ligand within any of the proposed activated complexes. Thus, there is not much energy difference between the transition state models **39** and **40** resulting in poor enantioselectivity.

Conclusion

We have now improved our earlier allylation procedure and most *trans*-imines reacted in shorter time, with good to high

(18) (a) van der Sluis, M.; Dalmolen, J.; de Lange, B.; Kaptein, B.; Kellogg, R. M.; Broxterman, Q. B. *Org. Lett.* **2001**, *3*, 3943. (b) Cvetovich, R. J.; Chartrain, M.; Hartner, F. W., Jr.; Roberge, C.; Amato, J. S.; Grabowski, E. J. J. *J. Org. Chem.* **1996**, *61*, 6575.

(19) However, the enhancement of enantioselectivity by water is not clear. Formation of pentacoordinate Si is known, see reference (2), probably similar is the case with stannane.

(20) A similar explanation is given by Hou, see: ref (2c).

yields and moderate to high enantioselectivities. The catalyst prepared is refined and separated from the undesired stereoisomer by an easy recrystallization procedure. We have discovered that addition of 1 equiv of water shortens the reaction time, enhances the yields, and enantioselectivities. We are now in a position to synthesize diverse chiral homoallylamines from achiral imines in catalytic manner with a more general, reproducible, and robust procedure. The Pd-catalyzed asymmetric allylation proceeds under essentially neutral conditions in contrast to the Lewis acid catalyzed reaction, making it feasible to use the substrates with labile functional groups (even the halogens) and as well to apply the allylation to heterocyclic substrates which otherwise sometimes are prone to polymerization. Although at this stage we could not justify the exact role of water in the ee enhancement, further investigations are in progress.

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Supporting Information Available: Experimental details for catalyst preparation and separation and characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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