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Direct Use of Allylic Alcohols for Platinum-Catalyzed Monoallylation of Amines

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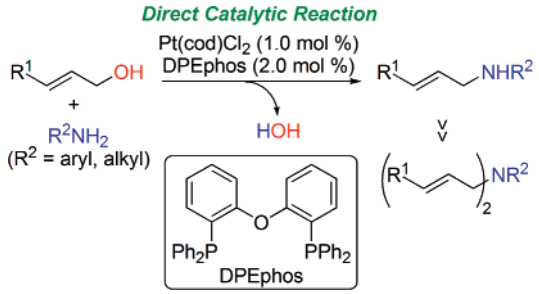
ABSTRACT



A new direct catalytic amination of allylic alcohols promoted by the combination of platinum and a large bite-angle ligand DPEphos was developed in which the allylic alcohol was effectively converted to a π-allylplatinum intermediate without the use of an activating reagent. The use of the DPEphos ligand was essential for obtaining high catalyst activity and high monoallylation selectivity of primary amines, allowing the formation of a variety of monoallylation products in good to excellent yield.

Allylamines are ubiquitous in various biologically active compounds and are highly useful substrates for many types of reactions,[1] such as asymmetric isomerization[2] and ring-closing metathesis.[3] For the synthesis of allylamines, a transition metal-catalyzed substitution reaction of activated allylic alcohol derivatives with nitrogen nucleophiles is one of the most powerful and reliable methods.[4] The reaction proceeds through π-allylmetal intermediates, generated by the oxidative addition of allylic substrates to a low-valence metal center, and following nucleophilic addition gives allylamines as a consequence of new C−N bond formation with high regio-, stereo-, and enantioselectivities. Since the pioneering work of π-allylpalladium chemistry by Tsuji and Trost,[4] various efficient catalyst systems have been developed and applied to the syntheses of natural and unnatural compounds.[1c] In terms of atom-economy[5] and environmental concerns, however, these catalyses still have much room for improvement. They usually require *preactivation of the parent allylic alcohol* to the corresponding allylic halides, carboxylates, carbonates, phosphates, and related compounds (Scheme 1, **1** → **2** → **4**). The activated substrates **2** cause the formation of more than stoichiometric amounts of unwanted salt waste both in the preactivation and amination steps. Thus, the development of *a direct catalytic substitution*

(1) For reviews, see: (a) Cheikh, R. B.; Chaabouni, R.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* **1983**, 685. (b) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689. (c) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(2) For reviews, see: (a) Akutagawa, S.; Tani, K. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000. (b) Noyori, R. In *Asymmetric Catalysis in Organic Synthesis*; Wiley-VCH: New York, 1994; Chapter 3, p 95.

(3) For reviews, see: (a) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vols 1−3. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlar, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490.

(4) For reviews, see: (a) Tsuji, J. *Transition Metal Reagents and Catalysis*; Wiley-VCH: Weinheim, Germany, 2000. (b) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000.

(5) Trost, B. M. *Science* **1991**, *254*, 1471.

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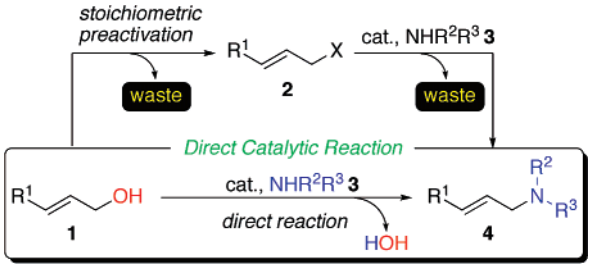
Scheme 1

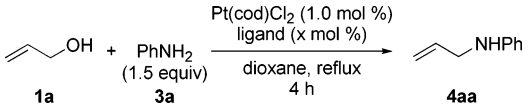


of allylic alcohols with amines, which produces the desired allylamines together with water as the sole coproduct, is highly desired (**1** → **4**).[6]

Due to the poor leaving ability of the hydroxyl group, the precedented direct aminations of allylic alcohols require stoichiometric or catalytic amounts of an activator, such as PPh_3-DEAD,[7] As_2O_3,[8] B_2O_3,[9] BF_3•Et_2O,[10] BEt_3,[11] BPh_3,[12,13] $SnCl_2$,[13] Ti(O-*i*-Pr)$_4$,[14] and CO_2,[15] including an efficient enantioselective variant.[16] Recently, palladium- and gold-catalyzed direct aminations of allylic alcohols without the use of an activator were developed by the research groups of Ozawa and Yoshifuji,[17] Ikariya,[18] Shinokubo and Oshima,[19] Le Floch,[20] and Liu,[21] realizing a highly atom economical synthetic process for allylamines.[22] The substrate generality of those reactions is, however, still limited. In particular, the reaction with primary alkylamines resulted only in the formation of the diallylation product[18,19] because of the higher nucleophilicity of the monoallylation product compared to that of the substrate. Herein, we report a direct conversion of allylic alcohols to allylamines catalyzed by 1 mol % of Pt-DPEphos complex with broad substrate generality. The use of the large bite-angle ligand DPEphos is essential for obtaining high catalyst activity. Moreover, a sterically congested active site created by the large bite-angle ligand led to the selective monoallylation of primary alkylamines.

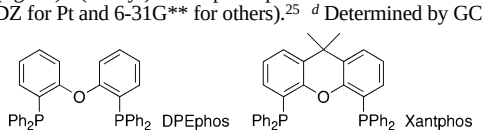
A rate-determining step of the above-mentioned Pd-catalyzed substitution reactions of allylic alcohol is the activation of the hydroxyl group to form a π-allyl complex. Based on the fact that the Pt−O bond is stronger than the Pd−O bond,[23] we anticipated that the platinum complex would be a good candidate for a direct amination catalyst for allylic alcohols. Thus, using Pt(cod)Cl_2 as a metal source, we first examined various phosphine ligands in the reaction of allyl alcohol (**1a**) and aniline (**2a**). No reaction proceeded in the absence of a phosphine ligand (Table 1, entry 1) and the use of monodentate ligands gave unsatisfactory results (entries 2−4), in contrast to the reports that Pd-monophosphine ligand complexes showed good catalyst activity.[18,19] Commonly used diphosphine ligands such as DPPE, DPPP, DPPF, and BINAP also led to low yields (entries 5−10).

Table 1. Ligand Effects on Pt-Catalyzed Direct Amination of Allyl Alcohol (**1a**)[a]



entry	ligand (x)	bite-angle (deg)[b]	yield (%)[d]
1	–		0
2	PPh_3 (4.0)		11
3	$P(OPh)_3$ (4.0)		7
4	P(2-furyl)$_3$ (4.0)		36
5	DPPE (2.0)	85	0
6	$(C_6F_5)_2PCH_2CH_2P(C_6H_5)_2$ (2.0)		1
7	DPPP (2.0)	90	0
8	$Ph_2P(CH_2)_5PPh_2$ (2.0)		9
9	DPPF (2.0)	90	29
10	BINAP (2.0)	93	4
11	DPEphos (2.0)	104 (106)[c]	91
12	Xantphos (2.0)	108 (108)[c]	86

[a] 1.0 mmol scale, dioxane (0.5 mL). [b] Bite-angle of Pd complex.[24] [c] Bite-angle of (ligand)Pt(π-allyl)Cl complex optimized with the B3LYP function (LANL2DZ for Pt and 6-31G** for others).[25] [d] Determined by GC analysis.



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(11) (a) Kimura, M.; Tomizawa, T.; Horino, Y.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **2000**, *41*, 3627. (b) Kimura, M.; Horino, Y.; Mukai, R.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10401. (c) Kimura, M.; Futamata, M.; Shibata, K.; Tamaru, Y. *Chem. Commun.* **2003**, 234.
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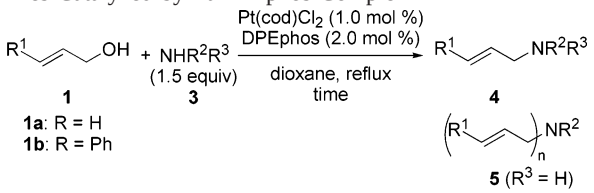
(16) Yamashita, Y.; Gopalarathnam, A.; Hartwig, J. F. *J. Am. Chem. Soc.* ASAP.
(17) (a) Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. *J. Am. Chem. Soc.* **2002**, *124*, 10968. (b) Ozawa, F.; Ishiyama, T.; Yamamoto, S.; Kawagishi, S.; Murakami, H.; Yoshifuji, M. *Organometallics* **2004**, *23*, 1698.
(18) Kayaki, Y.; Koda, T.; Ikariya, T. *J. Org. Chem.* **2004**, *69*, 2595.
(19) Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 4085.
(20) (a) Piechaczyk, O.; Doux, M.; Ricard, L.; Le Floch, P. *Organometallics* **2005**, *24*, 124. (b) Piechaczyk, O.; Thoumazet, C.; Jean, Y.; Le Floch, P. *J. Am. Chem. Soc.* **2006**, *128*, 14306. (c) Mora, G.; Deschamps, B.; van Zutphen, S.; Le, Goff, X. F.; Ricard, L.; Le Floch, P. *Organometallics* **2007**, *26*, 1846.
(21) Guo, S.; Song, F.; Liu, Y. *Synlett* **2007**, 964.
(22) Very recently, efficient bismuth-catalyzed direct substitution of allylic alcohols with sulfonamides, carbamates, and carboxamides via carbenium intermediate was reported, see: Qin, H.; Yamagiwa, N.; Matsunaga, S.; Masakatsu, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 409.
(23) Pedley, J. B.; Marshall, E. M. *J. Phys. Chem. Ref. Data* **1983**, *12*, 967.

The use of the large bite-angle ligands[24,25] DPEphos and Xantphos, however, dramatically improved catalyst activity of this reaction to afford the desired product **3aa** in 91% yield (entry 11) and 86% yield (entry 12), respectively. It was reported that the nucleophilic attack on the π-allylpalladium complexes with larger P−Pd−P bite-angles was faster than that with smaller bite-angles.[26] The results shown in Table 1 indicated that large bite-angle ligands are also quite effective for platinum-catalyzed direct conversion of allylic alcohol to the π-allylplatinum complex. To the best of our knowledge, this is the first example of a platinum catalyzed direct amination of allylic alcohols without the use of activators.[14d,27]

We next examined the effects of a platinum source together with palladium and nickel complexes using DPEphos as a ligand.[25] Although other Pt^{II} complexes such as $Pt(cod)(OTf)_2$ gave only moderate yield (up to 64%), the Pt^0 complex $Pt(PPh_3)_4$ showed comparable reactivity (89%). The combination of palladium with DPEphos gave only a low yield (up to 11%) and nickel complexes did not promote the reaction at all. Thus, in the presence of 1 mol % of $Pt(cod)Cl_2$ and 2 mol % of DPEphos, substrate generality was investigated. All reactions were performed in 4 mmol scale and the isolated yields of the products are summarized in Table 2. The reaction of various aniline derivatives with electron-donating (entries 2−4) and electron-withdrawing (entry 5) substituents proceeded smoothly to afford the corresponding monoallylation product **4aa**−**ae** in good yield along with a small amount of the corresponding diallylation product **5aa**−**ae** (**4**:**5** = >10:1). When ortho-substituted aniline derivatives were used as a substrate, the formation of diallylation products **5** was effectively prevented and monoallylation products **4** were obtained as the sole detectable products in good yield (entries 6 and 7). Secondary amine **3h** was also applicable to the present catalysis (entry 8). The reaction of *trans*-cinnamyl alcohol (**1b**) with aniline derivatives resulted in comparable yield and selectivity (entries 9−11), in which the corresponding *trans*-cinnamyl amine compounds were obtained predominantly and neither *cis*-cinnamyl amine compounds nor regioisomers were detected.

We then examined the use of alkylamines as nucleophiles. In the precedented direct aminations of allylic alcohols without the use of an activator, only monoallylation of the secondary alkylamines and diallylation of primary alkylamines were reported, and *monoallylation of the primary alkylamine has not yet been achieved.*[6,17−21] In view of the usefulness of the monoallylation products,[1] we first focused on the monoallylation of primary alkylamines. When benzylamine (**3i**) was used, the reaction proceeded smoothly, and all of substrate **1b** was consumed in 18 h, affording monoallylation product **4bi** in 59% yield and diallylation product **5bi** in 20% yield (Table 3, entry 1). This moderate

Table 2. Direct Amination of Allylic Alcohol with Aromatic Amines Catalyzed by Pt-DPEphos Complex[a]



entry	1	3		time (h)	yield of **4** (%)[b]	yield of **5** (%)[b]
1	**1a**	H_2N–	**3a**	6	86	6
2	**1a**	H_2N–Me	**3b**	6	89	5
3	**1a**	H_2N– (Me, Me)	**3c**	6	86	6
4	**1a**	H_2N–OMe	**3d**	6	82	8
5	**1a**	H_2N–CF_3	**3e**	8	79	6
6	**1a**	H_2N– (Me)	**3f**	6	86	nd[c]
7	**1a**	H_2N– (Cl)	**3g**	6	88	nd[c]
8	**1a**	MeHN–	**3h**	18	80	–
9	**1b**	**3a**		18	79	7
10	**1b**	**3f**		18	92	1
11	**1b**	**3h**		18	82	–

[a] 4.0 mmol scale, dioxane (2.0 mL for **1a** and 0.8 mL for **1b**). [b] Isolated yield. [c] Not detected in the reaction mixture.

selectivity, caused by the strong nucleophilicity of the alkylamine, was improved by increasing the amine amount from 1.5 to 3.0 equiv, and the desired product **4bi** was obtained in 79% yield (entry 2). Under these reaction conditions, monoallylation of 1-naphthylamine (**3j**) and *n*-hexylamine (**3k**) proceeded in the same efficiency to afford **4bj** and **4bk**, respectively, in 78% yield (entries 3 and 4). The use of sterically more congested amines **3l** improved the selectivity of the monoallylation with better yield of the desired products **4bl** (entry 5, 86%). Moreover, in the case of cyclohexylamine (**3m**), 1-phenethylamine (**3n**), and 1-adamantylamine (**3o**), even less amine (1.5 equiv) realized sufficient selectivity to produce the desired monoallylation products in up to 90% yield (entries 6−8). Furthermore, direct amination with secondary alkylamines proceeded quite efficiently to afford the desired products **4bp**−**br** in excellent yields (entries 9−11, up to 96% yield).

Catalytic direct amination of allylic alcohols **1** provides efficient access to various allylamines **4**. Having established this new process, the utility was demonstrated by one-step synthesis of the antifungal drug naftifine (**4bs**).[28] In the presence of 1 mol % of the catalyst, the substitution reaction of **1b** with 1 equiv of *N*-methyl-1-naphthylamine (**3s**) was

(24) Due to the lack of information about bite angles of platinum complexes, those of palladium complexes are shown in Table 1.

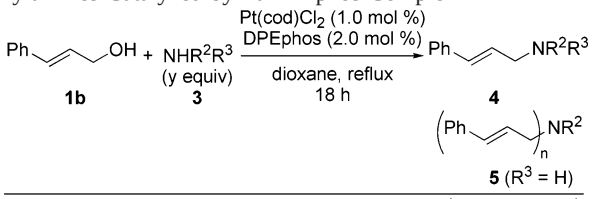
(25) See the Supporting Information for details.

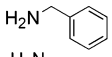
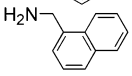
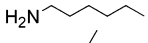
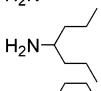
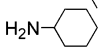
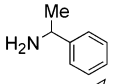
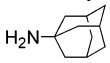
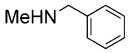
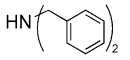
(26) Johns, A. M.; Utsunomiya, M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 1828.

(27) Pt-catalyzed direct amination of allylic alcohols with ammonia to provide a mixture of mono-, di-, and triallylation products was reported, see: Ishimura, Y.; Nagato, N. *Jpn. Kokai Tokkyo Koho* JP 63002958, 1988.

(28) Petranyi, G.; Ryder, N. S.; Stütz, A. *Science* **1984**, *224*, 1239.

Table 3. Direct Amination of Allylic Alcohol with Alkylamines Catalyzed by Pt-DPEphos Complex[a]

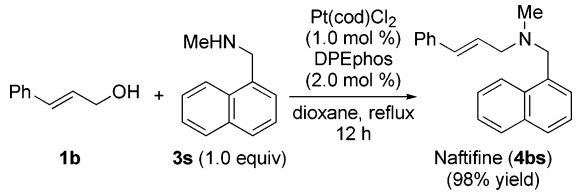


entry	3 (y)		yield of 4 (%)[b]	yield of 5 (%)[b]
1		**3i** (1.5)	59	20
2		**3i** (3.0)	79	10
3		**3j** (3.0)	78	9
4		**3k** (3.0)	78	10
5		**3l** (3.0)	86	6
6		**3m** (1.5)	82	9
7		**3n** (1.5)	86	7
8		**3o** (1.5)	90	3
9		**3p** (1.5)	89	–
10		**3q** (1.5)	96	–
11		**3r** (1.5)	94	–

[a] 4.0 mmol scale, dioxane (0.8 mL). [b] Isolated yield.

completed in 12 h, and ^{1}H NMR analysis of the crude mixture revealed the formation of almost pure naftifine (**4bs**) where water was the sole coproduct (Scheme 2). Purification

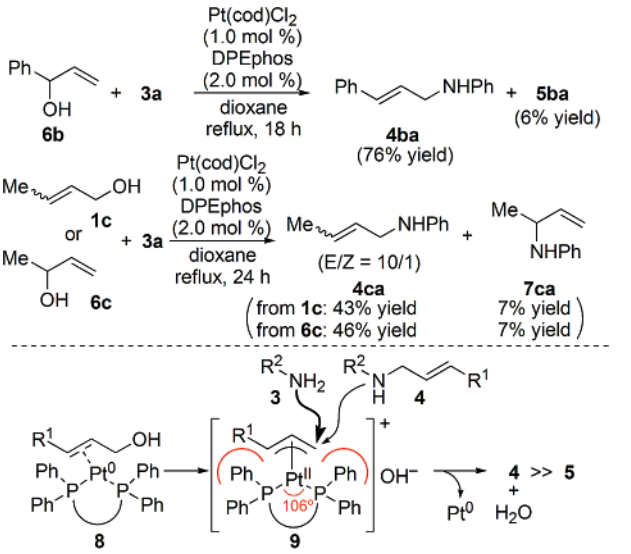
Scheme 2



by simple silica gel column chromatography gave **4bs** in 98% yield. Alternatively, treatment of the crude mixture with 1 M HCl in EtOH and recrystallization from EtOH/Et_2O provided pure naftifine hydrochloride (**4bs**·HCl) in 83% yield without chromatographic purification.

To gain insight into the mechanism of this platinum catalysis, we performed the following reactions. Direct amination of internal allylic alcohol 1-phenyl-2-propen-1-ol (**6b**) exclusively provided terminal allylamine **4ba**, which is the same product obtained by using terminal allylic alcohol **1b** (Table 2, entry 9). Moreover, reactions of both a terminal

Scheme 3



allylic alcohol **1c** and an internal allylic alcohol **6c** gave a mixture of products in almost the same distribution. These results strongly suggest that the platinum-catalyzed direct amination proceeds through a π-allylplatinum intermediate **9** and selective attack of the amine to the less hindered allyl carbon. Sterically congested electrophile **9** created by the large bite-angle ligand allows a selective reaction with substrate **3** in preference to monoallylation compound **4**.

In conclusion, we developed a new direct catalytic amination of allylic alcohols promoted by the combination of platinum and the large bite-angle ligand DPEphos without the use of an activating reagent. The DPEphos ligand was essential for obtaining high catalyst activity and high monoallylation selectivity of primary amines, allowing the formation of a variety of monoallylation products in good to excellent yield. Moreover, we demonstrated the synthetic utility of this catalysis by the one-step synthesis of the antifungal drug naftifine. Further mechanistic studies and application to enantioselective variants are ongoing in our group.

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Supporting Information Available: Experimental procedures, characterization of the products, and other detailed results. This material is available free of charge via the Internet at http://pubs.acs.org.

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