Platinum-Catalyzed Direct Amination of Allylic Alcohols

Takashi Ohshima[1] and Kazushi Mashima[2]

[1]*Graduate School of Pharmaceutical Sciences, Kyushu University*
Maidashi Higashi-ku, Fukuoka 812-8582, Japan

[2]*Department of Chemistry, Graduate School of Engineering Science, Osaka University*
Toyonaka, Osaka 560-8531, Japan

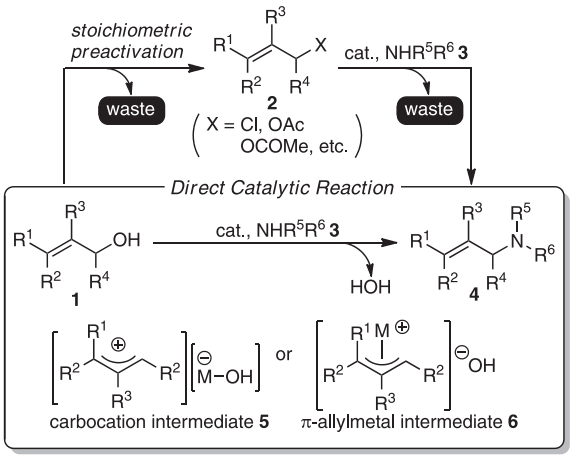
(Received July 18, 2012; E-mail: ohshima@phar.kyushu-u.ac.jp; mashima@chem.es.osaka-u.ac.jp)

Abstract: Transition metal-catalyzed amination of allylic compounds via a π-allylmetal intermediate is a powerful and useful method for synthesizing allylamines. Direct catalytic substitution of allylic alcohols with amines, which forms water as the sole coproduct, has recently attracted attention in terms of its environmental and economical advantages. Here, we describe the development of a direct catalytic amination of both aryl- and alkyl-substituted allylic alcohols with various amines including the smallest nitrogen nucleophile ammonia using Pt-Xantphos and Pt-DPEphos catalyst systems, which allow the selective synthesis of various monoallylamines including the biologically active compounds naftifine and flunarizine, in good to high yield without requiring any activator.

1. Introduction

Allylamines are ubiquitous components of biologically active compounds,[1] such as the antifungal drug naftifine[2a,b] and the calcium channel blocker flunarizine,[2c,d] and are versatile substrates used for different types of reactions, including asymmetric isomerization[3] and ring-closing metathesis.[4] Thus, as a reliable synthetic methodology to obtain a wide variety of allylamines and their derivatives, nucleophilic substitution reactions of allylic substrates with amines have been widely utilized.[5] These standard synthetic protocols usually require activated allylic compounds **2**, such as allylic halides, carboxylates, carbonates, and phosphates, which are usually derived from the corresponding allylic alcohol **1**, prior to metal catalyzed transformation; however, the use of the activated substrates **2** lead to the formation of more than stoichiometric amounts of unwanted salt waste both in the preactivation and amination steps (Scheme 1, **1**→**2**→**4**). Thus, direct catalytic amination of *underivatized* allylic alcohols **1**, which forms water as the sole coproduct, is highly desirable (**1**→**4**).[6] Such direct reactions, however, are rarely explored because of the poor leaving ability of the hydroxyl group. Nonetheless, for activating the hydroxyl group, two powerful and reliable methods are subjected; (1) Lewis or Brønsted acid-catalyzed direct amination via a *carbocation intermediate* (**1**→**5**→**4**) and (2) transition metal-catalyzed direct amination via a *π-allylmetal intermediate* (**1**→**6**→**4**). These two methods are complementary approaches to compensate weak point of each method. In general, the former method is efficient for electron-deficient nitrogen nucleophiles such as sulfonylamides, carbamates, simple amides, and anilines with electron-withdrawing groups (electron-rich nitrogen nucleophiles are not good substrates because they deactivate acid catalysts). In association with the former method, various Lewis and Brønsted acid catalyses have been developed.[7] We also successfully developed Au(III) salt-catalyzed direct aminations of allylic and benzylic alcohols with highly functionalized amine nucleophiles[8a] and $Al(OTf)_3$-catalyzed direct amination of allylic alcohols, benzylic alcohols, and benzhydrols bearing an electron-withdrawing F, Br, I, NO_2, or CN substituent.[8b] The latter method is available for electron-rich amines such as alkylamines and anilines with electron-donating groups (electron-deficient nitrogen nucleophiles are not good substrates because of their low nucleophilicity). We recently succeeded in the development of direct catalytic amination of both aryl- and alkyl-substituted allylic alcohols with various amines including ammonia using Pt-Xantphos and Pt-DPEphos catalyst systems, which allow for the selective synthesis of various *monoallylamines*.[9] In this account, we thus review the transition metal-catalyzed direct amination of allylic alcohols.

Scheme 1. Preparation of allylamine **4** from allylic alcohol **1**.



2. Transition Metal-Catalyzed Direct Amination of Allylic Alcohols (Background)

Since the pioneering work of π-allylpalladium chemistry by Tsuji and Trost, various efficient catalyst systems have been developed and are widely applied to the syntheses of natural and unnatural compounds.[5] A mechanism of transition metal-catalyzed substitution reaction of activated allylic alcohol

derivatives **2** with nitrogen nucleophiles **3** is well established to proceed through, the first oxidative addition of allylic substrates to a low-valence metal center, forming π-allylmetal intermediates **6**, followed by nucleophilic addition of amines gives allylamines due to the new carbon-nitrogen bond formation with high regio-, stereo-, and enantioselectivity.[5] In terms of atom-economy[10] and environmental impact, the development of a *direct* catalytic substitution of *underivatized* allylic alcohols **1** with amines **3**, which produces the desired allylamines **4** together with water as the sole coproduct (**1**→**6**→**4**), is more straightforward and desirable.[6] However, for overcoming the poor leaving ability of the hydroxyl group, the previously reported catalytic direct aminations require rather severe reaction conditions and/or the addition of considerable amounts of an activator such as As_2O_3,[11] B_2O_3,[12] $SnCl_2$,[13] PPh_3-DEAD,[14] Ti(O-*i*-Pr)$_4$,[15] BPh_3,[16] BF_3•Et_2O,[17] CO_2,[18] BEt_3,[19] and 1-AdCO_2H,[20] including an efficient enantioselective variant.[21] In 2002, Ozawa and Yoshifuji reported that several palladium complexes supported by sp^2-hybridized phosphorus ligands catalyzed direct aminations of allylic alcohols **1** without the use of an activator.[22] This pioneering work led to the development of a highly atom economical synthetic process for allylamines by several research groups of Ikariya,[23] Shinokubo and Oshima,[24] le Floch,[25] and Breit,[26] although the substrate generality of those reactions remained limited: in particular, the reaction with aliphatic primary amines resulted only in the formation of diallylation products,[23,24] consistent with the higher nucleophilicity of the monoallylation product compared to that of the starting substrate.

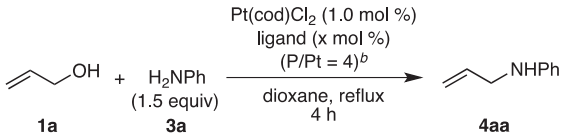
3. Platinum-Catalyzed Direct Amination of Allylic Alcohols

3.1 Development and Optimization of Platinum Catalysis

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. Because the Pt-O bond is stronger than the Pd-O bond,[27] we anticipated that the platinum complex would be a good candidate for a direct amination catalyst for allylic alcohols. We first examined various phosphine ligands in the reaction of allyl alcohol (**1a**) and aniline (**3a**) using Pt(cod)Cl_2 as a metal source.[9a] The reaction did not proceed in the absence of a phosphine ligand (Table 1, entry 1) and the use of monodentate ligands gave unsatisfactory results (entries 2-4), in sharp contrast to the reports that Pd-monophosphine ligand complexes have good catalyst activity.[23,24] Commonly used diphosphine ligands, such as DPPE, DPPP, DPPF, and BINAP also produced low yields (entries 5-10). In contrast, the use of the large bite-angle ligands,[28] such as DPEphos[29] and Xantphos[30] dramatically improved the catalyst activity for this reaction, giving rise to the desired product **4aa** in 91% yield (entry 11) and 86% yield (entry 12), respectively. To the best of our knowledge, this is the first example of a platinum-catalyzed direct amination of allylic alcohols without the use of any activators.[15d,31]

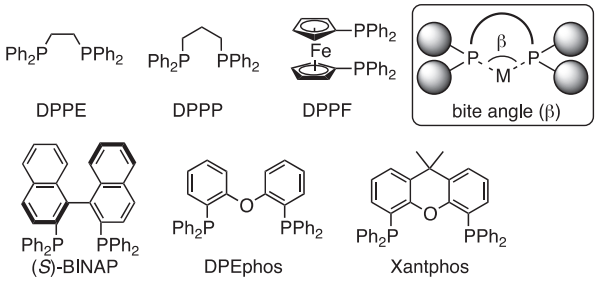
Table 1 shows that the bite-angle of the chelating ligands bound to the palladium atom is a good indicator for the platinum-catalyzed direct amination activity, in accordance with the reported tendency toward faster nucleophilic attack on π-allylpalladium complexes with larger P-Pd-P bite-angles than with smaller bite-angles.[28] Thus, we examined the ligand effects in more detail under the optimized conditions in DMF (*vide infra*).[9b] We tested various large bite-angle diphosphine

Table 1. Ligand effects on Pt-catalyzed direct amination of allyl alcohol (**1a**).[a]



entry	ligand (x)	bite-angle (β)[b]	yield (%)[c]
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°	91
12	Xantphos (2.0)	108°	86

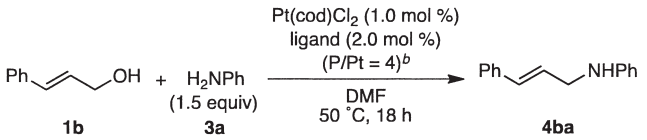
[a] 1.0 mmol scale, dioxane (0.5 mL). [b] Bite-angle of Pd complex.
[c] Determined by GC analysis.



ligands, and results are shown in Table 2. Because of the lack of information about the bite-angles of Pt(η^3-allyl)(diphosphine) complexes, the bite-angles (β) shown in Table 2 were obtained by geometry optimization using the B3LYP[32] hybrid density functional theory (LANL2DZ for Pt and 6-31G(d,p) for others). Although 1,2-bis(diphenylphosphino)benzene (β=87°), DPPP (β=96°), BINAP (β=97°), and SEGPHOS (β=98°) ligands, whose bite angles are smaller than 100°, did not promote the reaction (entries 1-4), larger bite-angle ligands such as 6-DPPon,[26] which *in situ* dimerizes in aprotic solvent through hydrogen bonding and acts as a bidentate ligand (β=104°),[33] and Trost ligand (β=107°),[34] had moderate reactivity to afford allylamine **4ba** in 40% (entry 5) and 19% (entry 6) yields, respectively. The use of DPEphos (β=107°)[29] and Xantphos (β=108°)[30] obviously improved catalyst activity with the best performance of Xantphos (entry 8, 80% yield). On the other hand, the use of the structurally related POP ligand (β=108°)[35] and *t*-Bu-Xantphos (β=112°)[36] afforded no product (entries 9 and 11) despite their large bite-angle. These findings clearly indicated that, in addition to a large bite-angle, an efficient chelating ligand should be composed of fully aryl- or alkenyl[37]-substituted phosphines. Moreover, the very low reactivity when using the Floriani ligand (β=111°)[38] (entry 10), which is a methylene-linked variant of DPEphos, strongly suggests the importance of the linker oxygen in DPEphos and Xantphos.

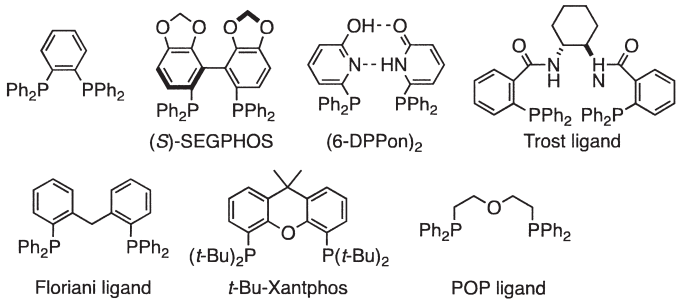
We next screened for the best platinum source together

Table 2. Effects of diphosphine ligands on Pt-catalyzed direct amination.[a]



entry	ligand	bite angle (β)[c]	yield of **4ba**[d]
1	C_6H_4-1,2-$(PPh_2)_2$	87°	nd[e]
2	DPPP	96°	nd[e]
3	BINAP	97°	nd[e]
4	SEGPHOS	98°	nd[e]
5[f]	6-DPPon	104°	40%
6	Trost ligand	107°	19%
7	DPEphos	107°	71%
8	Xantphos	108°	80%
9	POP ligand	108°	nd[e]
10	Floriani ligand	111°	8%
11	*t*-Bu-Xantphos	112°	nd[e]

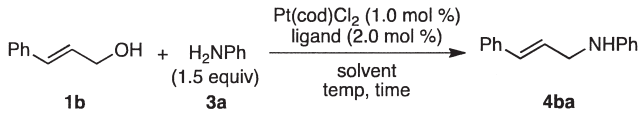
[a] 2.0 mmol scale, 0.4 mL of DMF was used. [b] Phosphine to platinum ratio (P/Pt). [c] Bite-angle of $[Pt(\eta^3\text{-allyl})(\text{diphosphine})]^+$ optimized with B3LYP function. [d] Determined by GC analysis. [e] Not detected in the reaction mixture. [f] 4 mol % of ligand was used to keep P/Pt to 4.



with the potential use of palladium and nickel complexes using DPEphos as a ligand. Under dioxane reflux conditions, Pt(II) complex $Pt(cod)Cl_2$ and Pt(0) complex $Pt(PPh_3)_4$ gave the product in high yield, though other Pt(II) complexes such as $Pt(cod)(OTf)_2$ gave low to moderate yield.[9a] On the other hand, under the optimized conditions in DMF as shown in Table 2, Pt(0) complex had only moderate catalytic activity.[9b] In addition, as part of our program studying the use of metal clusters as cooperative catalysts, we were interested in the use of tetraplatinum complex $Pt_4(\mu\text{-}OCOCH_3)_8$[39] and its derivatives[40,41] as the catalyst for direct amination. These phosphine-free tetraplatinum complexes also promoted the reaction; however, those catalytic activities were much lower than that of Pt-DPEphos complex.[42] The combination of palladium with DPEphos gave only a low yield[43] and nickel complexes did not promote the reaction at all.

Under the initial optimized conditions in dioxane as shown in Table 1, the platinum catalysis proceeded with high monoallylation selectivity of both aromatic (up to >88:1) and aliphatic (up to 30:1) primary amines.[9a] To further improve catalyst activity, we examined solvent effects at 110 ℃ or the solvent reflux temperature (Table 3, entries 1–7).[9b] To clarify the solvent effects, reactions were stopped after 3 h and the yield of allylamine **4ba** was determined by gas chromatographic analysis. Among the solvents examined, dioxane (entry 3, 72%), which was the initial best solvent,[9a] and DMF (entry 5, 79%) gave good results, in sharp contrast to the unsatisfactory result obtained with the closely related solvent DMA (entry 4, 22%). Interestingly, a marked difference between dioxane (entry 8, <1%) and DMF (entry 9, 89%) was observed at a lower temperature (50 ℃) with a prolonged reaction time (23 h). Using DMF as the solvent, the direct amination of **1b** proceeded even at room temperature, although the yield was moderate even after 78 h (entry 10, 52%). Further, platinum catalysis proceeded under solvent-free conditions with reasonably good reactivity (entry 7, 57%), providing great possibility for the development of a more efficient and environmentally friendly catalytic synthetic process of allylamines.

Table 3. Effects of solvents and reaction temperature on Pt-catalyzed direct amination with arylamine **3a**.[a]



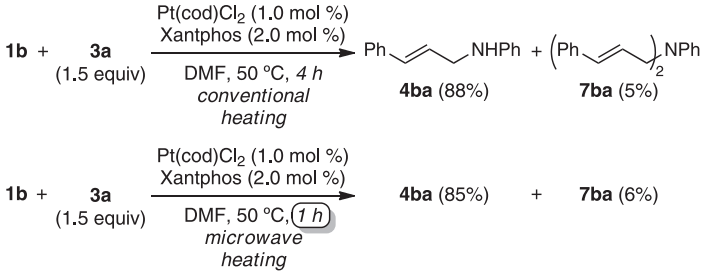
entry	solvent	temp	time (h)	yield of **4ba**[b]
1	toluene	110 °C	3	63%
2	1,2-dimethoxyethane	reflux (82 °C)[c]	3	38%
3	dioxane	reflux (101 °C)[c]	3	72%
4	DMA	110 °C	3	22%
5	DMF	110 °C	3	79%
6	DMSO	110 °C	3	63%
7	–[d]	110 °C	3	57%
8	dioxane	50 °C	23	<1%
9	DMF	50 °C	23	89%
10	DMF	rt	78	52%

[a] 2.0 mmol scale, 0.4 mL of solvent was used. [b] Determined by GC analysis. [c] Boiling point of pure solvent. [d] Solvent-free conditions.

Organic synthesis assisted by microwave heating has grown rapidly since the pioneering work of Gedye in 1986.[44] In many organic transformations, microwave heating dramatically decreases the reaction times and increases the product yields in comparison with conventional heating methods. Accordingly, we examined our Pt-catalyst reaction under microwave irradiation conditions (Scheme 2).[9b] To our surprise, upon using a CEM Discover single-mode microwave reactor, the reaction at 50 ℃ for 1 h was sufficient for full conversion compared with the 4 h conventional heating for completion.[45]

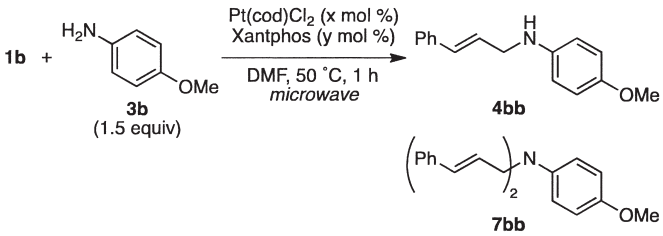
Finally, optimization of the best ratio between the chelating ligand, Xantphos, and platinum was performed using *para*-methoxyaniline (**3b**) under microwave irradiation condi-

Scheme 2. Effects of microwave irradiation on Pt-catalyzed direct amination.



tions, and results are shown in Table 4.[9b] The presence of the extra ligand stopped the reaction (entry 1), and optimal results were obtained with Xantphos to platinum ratio of 1:1 (entry 4), indicating that the active catalyst species would be a coordinately unsaturated Pt–xantphos 1:1 complex. Under the optimal reaction conditions, the use of only 0.5 mol % of the catalyst completed the reaction within 1 h to give the best yield of **4bb** (entry 5), and a turnover number of 570 was achieved upon reducing the catalyst loading to 0.1 mol % (entry 6).

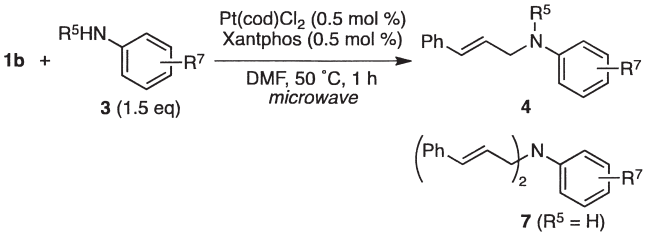
Table 4. Effects of ligand to platinum ratio on Pt–catalyzed direct amination with arylamine **3b**.[a]

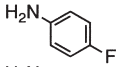
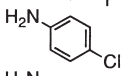
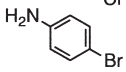
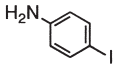
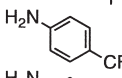
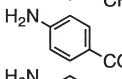
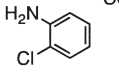
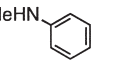


entry	$Pt(cod)Cl_2$ (x mol %)	Xantphos (y mol %)	yield of **4bb**[b]	yield of **7bb**[b]	TON[c]
1	1.0	3.0	nd[d]	nd[d]	–
2	1.0	2.0	76%	5%	86
3	1.0	1.5	80%	8%	96
4	1.0	1.0	84%	8%	100
5	0.5	0.5	85%	7.5%	200
6[e]	0.1	0.1	57%	<1%	570

[a] 2.0 mmol scale, 0.4 mL of DMF was used. [b] Isolated yield. [c] Turnover number of the platinum catalyst. [d] Not detected in the reaction mixture. [e] 4.0 mmol scale, 0.8 mL of DMF was used.

Table 5. Pt–catalyzed direct amination with various arylamines **3**.[a]



entry	arylamine **3**		yield of **4**[b]	yield of **7**[b]
1		**3a**	**4ba** (88%)	**7ba** (6%)
2		**3c**	**4bc** (85%)	**7bc** (5%)
3		**3d**	**4bd** (88%)	**7bd** (6%)
4		**3e**	**4be** (86%)	**7be** (5%)
5		**3f**	**4bf** (3%)	**7bf** (nd[c])
6[d]		**3g**	**4bg** (86%)	**7bg** (5%)
7		**3h**	**4bh** (87%)	**7bh** (4%)
8		**3i**	**4bi** (96%)	**7bi** (nd[c])
9[d]		**3j**	**4bj** (96%)	–

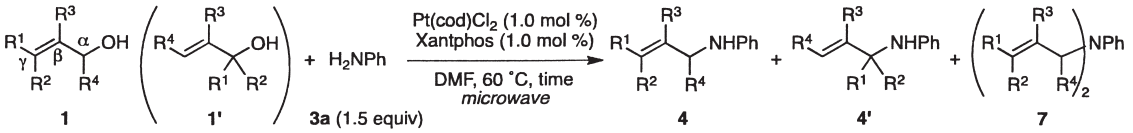
[a] 2.0 mmol scale, 0.4 mL of DMF was used. [b] Isolated yield. [c] Not detected in the reaction mixture. [d] Reaction time was 2 h.

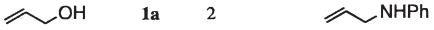
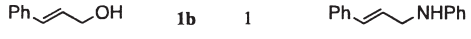
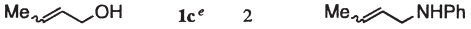
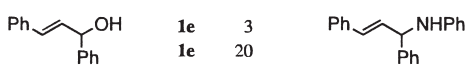
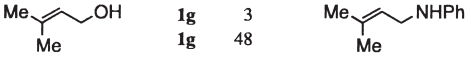
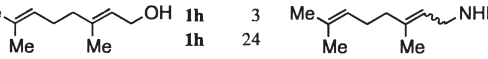
3.2 Direct Amination with Arylamines

With the optimized conditions (0.5 mol % of $Pt(cod)Cl_2$, 0.5 mol % of Xantphos, microwave irradiation, DMF, 50 ℃, 1 h) in hand, the scope and limitations of different arylamines **3** were next investigated (Table 5).[9b] The reactions of aniline (**3a**) and various *para*–substituted anilines **3c–h** with electron–withdrawing groups were efficiently promoted to provide the desired monoallylation product **4** in high yield and high monoallylation selectivity (entries 1–7). The reaction of *para*–iodoaniline (**3f**) was the only ineffective case with 3% of the product **4bf** and recovery of the unreacted **3f**, probably due to the oxidative addition of **3f** onto the *in situ* generated Pt(0) complex (entry 5). The sterically more congested *ortho*–chloroaniline (**3i**) completely prevented the undesired diallylation reaction and predominantly afforded the monoallylation product **4bi** (entry 8, 96%). Secondary amine **3j** was also a good substrate for this transformation (entry 9, 96%).

Direct amination of alkyl–substituted allylic alcohols remained an unsolved target. Because our catalytic system using microwave irradiation in DMF greatly improved the catalyst activity and lowered the reaction temperature to 50 ℃, we performed direct amination of ally alcohol (**1a**) and various aryl– and alkyl–substituted allylic alcohols **1b–h** with aniline (**3a**) (Table 6).[9b] The reaction of **1a** (entry 1) proceeded smoothly in a manner similar to γ–phenyl–substituted allylic alcohol **1b** (entry 2). Despite the moderate yield of γ–methyl–substituted **1c** under the previous reaction conditions (43% yield, dioxane, reflux, 18 h), the optimized conditions in DMF allowed for the full conversion of **1c** to the allylated products **4ca** (77%), **4ca'** (10%), and **7ca** (6%) without any undesired β–H elimination (entry 4). When α–substituted allylic alcohols **1b'** (entry 3) and **1c'** (entry 5) were used, the obtained regio–, stereo–, and monoallylation selectivities were almost the same as those using γ–substituted allylic alcohols **1b** (entry 2) and **1c** (entry 4), respectively, strongly suggesting that the reaction proceeds via π–allylplatinum intermediates. β–Methyl–substituted allylic alcohol **1d** (entry 6), cyclic allylic alcohol **1f** (entry 9), and α,α–disubstituted allylic alcohol **1g'** (entry 12) were also good substrates for the direct catalytic amination reaction to give the desired products in high yield. On the other hand, the reactions of α,γ–disubstituted allylic alcohol **1e** (entry 7) and γ,γ–disubstituted allylic alcohols **1g** (entry 10) and **1h** (entry 13) resulted in low to moderate yield with partial decomposition of the platinum species. Fortunately, conventional heating instead of microwave irradiation greatly improved the yield of **4ea** (entry 8, 91%), **4ga** (entry 11, 85%), and **4ha** (entry 14, 70%), though these reactions required a longer reaction time (20–48 h). Based on the fact that α,α–disubstituted allylic alcohol **1g'** reacts much faster than γ,γ–disubstituted allylic alcohol **1g**, the reactivity of the platinum catalysis is more strongly affected by steric congestion around the C=C double bond in allylic alcohol than that around the hydroxyl group, demonstrating the importance of the first η^2–coordination of the C=C double bond of allylic alcohols to the platinum atom prior to the generation of the π–allyl intermediates. Notably, all reactions of various allylic alcohols proceeded with quite high monoallylation selectivity. To the best

Table 6. Pt-catalyzed direct amination of various allylic alcohols **1**.[a]



entry	allylic alcohol **1**		time (h)	yield of **4**[b]		yield of **7**[b]
1[c]		**1a**	2	**4aa** (85%)		**7aa** (6%)
2[c,d]		**1b**	1	**4ba** (88%)		**7ba** (6%)
3		**1b'**	3	**4ba** (83%)		**7ba** (4%)
4		**1c**[e]	2	**4ca** (77%)[f]	**4ca'** (10%)	**7ca** (6%)
5		**1c'**	2	**4ca** (80%)[f]	**4ca'** (11%)	**7ca** (3%)
6[g]		**1d**	4	**4da** (82%)		**7da** (3%)
7		**1e**	3	**4ea** (18%)		
8[h]		**1e**	20	**4ea** (91%)		
9		**1f**	3	**4fa** (92%)		
10		**1g**	3	**4ga** (58%)	**4ga'** (1%)	**7ga** (1%)
11[h]		**1g**	48	**4ga** (85%)	**4ga'** (2%)	**7ga** (3%)
12		**1g'**	1	**4ga** (86%)	**4ga'** (1%)	**7ga** (5%)
13[g]		**1h**	3	**4ha** (28%)[i]		**7ha** (nd[j])
14[g,h]		**1h**	24	**4ha** (70%)[i]		**7ha** (nd[j])

[a]2.0 mmol scale, 0.4 mL of DMF was used. [b]Isolated yield. [c]Reaction temperature was 50 ℃. [d]0.5 mol % of $Pt(cod)Cl_2$ and 0.5 mol % of Xantphos were used. [e]*E*/*Z* mixture of **1c** (*E*/*Z*=97/3) was used. [f]**4ca** was obtained as an *E*/*Z* mixture (10/1). [g]Reaction temperature was 80 ℃. [h]Conventional heating conditions. [i]**4ha** was obtained as an *E*/*Z* mixture (5.8/1). [j]Not detected in the reaction mixture.

of our knowledge, this is the first time that such broad substrate generality (both aryl- and alkyl-substituted allylic alcohols and both arylamines and alkylamines) and high monoallylation selectivity were achieved in this type of direct reaction.

3.3 Direct Amination with Alkylamines

The direct substitution of allylic alcohol with alkylamines is more challenging because of its strong tendency towards overreaction.[9b] When benzylamine (**8a**) was used as a nucleophile, the conditions optimized for arylamines resulted in an unsatisfactory low yield of **9ba** (34%) and **10ba** (16%) along with unexpected byproduct **11**, which is an allylation product of dimethylamine (Scheme 3). In the reaction of arylamines, the byproduct **11** was not detected at all, suggesting that dimethylamine would not be generated by simple thermal decomposition of DMF, but was derived by platinum-catalyzed transamidation of DMF in the presence of highly nucleophilic benzylamine (**8a**). In fact, we confirmed that transamidation of DMF with benzylamine (**8a**) generated dimethylamine under this reaction condition. Later, this discovery led to the development of ammonium salt-accelerated transamidation, which enable deacylation of unactivated amides to amines under mild conditions.[46]

To avoid such an undesirable side reaction caused by DMF, we re-examined several polar and non-polar solvents other than DMF using benzylamine (**8a**) as the nucleophile.[9b] Among the tested solvents (toluene, 1,2-dichloroethane, chloroform, DMSO, and acetonitrile), 1,2-dicloroethane was best; however, the HCl salt of **8a** was formed, indicating that the chlorinated solvents decomposed the nascent Pt(0) species. Finally, we decided to use toluene as the solvent to further investigate of the reaction with alkylamines (Table 7). Even after 3 h microwave irradiation in toluene, direct amination of **1b** with **8a** resulted in only a moderate yield of **9ba** (58% yield) accompanied by the formation of black precipitates due to partial decomposition of the Pt(0) species. To stabilize the Pt(0) species in the reaction mixture, we performed the reaction with an extra amount of the ligand (2.0 equiv. to platinum), although we were concerned that it would generate a less active coordinately saturated Pt(0) complex $Pt(diphosphine)_2$ (Table 7). Surprisingly, despite the structural similarities of Xantphos and DPEphos, each ligand gave completely different

Scheme 3. Pt-catalyzed direct amination with alkylamine **8a** in DMF.

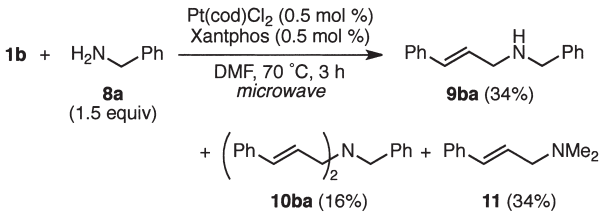
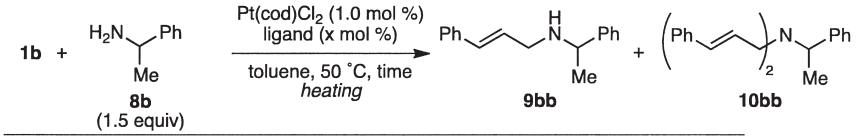


Table 7. Effects of ligand to platinum ratio on Pt–catalyzed direct amination with alkylamine **8b**.[a]



entry	ligand	x (mol %)	heating	time (h)	yield of **9bb**[b]	yield of **10bb**[b]
1	Xantphos	1.0	microwave	4	81%	4%
2	Xantphos	2.0	microwave	4	13%	nd[c]
3	DPEphos	1.0	microwave	3	32%	nd[c]
4	DPEphos	2.0	microwave	3	85%	3%
5	Xantphos	1.0	conventional	24	10%	nd[c]
6	Xantphos	2.0	conventional	24	nd[c]	nd[c]
7	DPEphos	1.0	conventional	24	trace	nd[c]
8	DPEphos	2.0	conventional	24	16	nd[c]

[a] 2.0 mmol scale, 0.4 mL of toluene was used. [b] Isolated yield. [c] Not detected in the reaction mixture.

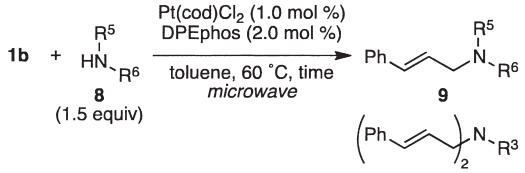
results (entries 1–4). In the case of Xantphos, the use of 2.0 equiv. of ligand to platinum substantially prevented the amination reaction (entry 2, 13%) with the formation of a yellow precipitate, which was the $Pt(xantphos)_2$ complex. The reason for the low reactivity was attributed to the insolubility of this complex in toluene. Moreover, the isolated 18–electron Pt(0) complex did not promote the reaction of **1b** with **8b** at all. On the other hand, 2.0 equiv. of DPEphos to platinum greatly improved the yield from 32% (entry 3) to 85% (entry 4) without decomposition of the platinum complex. These results clearly indicated that the *in situ* generated $Pt(dpephos)_2$ complex was highly soluble in toluene and easily released one DPEphos ligand to open the coordinately unsaturated active Pt(0) species. The same tendencies as shown in entries 1–4 were observed in the conventional heating reactions (entries 5–8), but the obtained yields of product **9bb** were much lower even after 24 h.

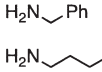
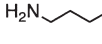
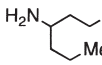
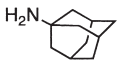
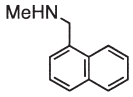
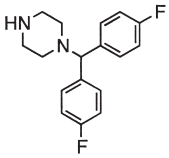
Under the efficient reaction conditions found for alkylamines (Table 7, entry 4), we performed the reaction with various primary and secondary alkylamines (Table 8).[9b] Although 3.0 equiv. of amine was used when sterically less congested primary alkylamines were employed (entries 1–5), monoallylation products **9** were obtained in high yield along with the formation of only small amounts of diallylation products **10** (entries 1–8). To our knowledge, such high monoallylation selectivity is only achieved by platinum catalysts bearing large bite–angle diphosphine ligands.[9a,37] The reactions also proceeded under solvent–free conditions (entries 3 and 5), resulting in high volumetric productivity and low waste generation. Moreover, direct amination with secondary alkylamines **8h–k** proceeded quite efficiently to afford the desired products **9bh–bk**, including the antifungal drug naftifine (**9bj**)[2a,b] and the calcium channel blocker flunarizine (**9bk**),[2c,d] in excellent yields (entries 9–12).

3.4 Direct Amination with Ammonia

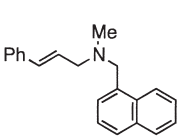
Ammonia is one of the most important chemical feedstocks for the chemical industry since the discovery of the Harber–Bosch process.[47] Direct synthesis of nitrogen–containing compounds from ammonia is the most desirable and economical synthetic route, and recent achievements regarding the direct use of ammonia have been remarkable.[48] Our interest has thus focused on the direct catalytic substitution of allylic

Table 8. Pt–catalyzed direct amination with various alkylamines **8**.[a]

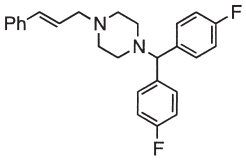


entry	alkylamine **8**		time (h)	yield of **9**[b]	yield of **10**[b]
1[c]		**8a**	4	**9ba** (80%)	**10ba** (10%)
2[c]		**8c**	4	**9bc** (60%)	**10bc** (17%)
3[c,d]		**8c**	7	**9bc** (65%)	**10bc** (6%)
4[c]		**8d**	6	**9bd** (74%)	**10bd** (5%)
5[c,d]		**8d**	5	**9bd** (86%)	**10bd** (5%)
6		**8e**	2	**9be** (85%)	**10be** (7%)
7		**8f**	6	**9bf** (77%)	**10bf** (10%)
8		**8g**	6	**9bg** (86%)	**10bg** (3%)
9		**8h**	3	**9bh** (96%)	–
10		**8i**	3	**9bi** (98%)	–
11		**8j**	5	**9bj** (95%)	–
12		**8k**	4	**9bk** (94%)	–

[a] 2.0 mmol scale, 0.4 mL of toluene was used. [b] Isolated yield. [c] 3.0 equiv. of alkylamine **8** was used. [d] Solvent-free conditions.



naftifine (**9bj**)

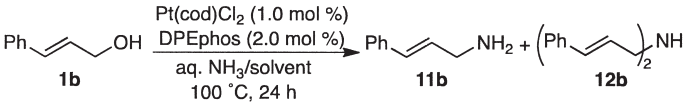


flunarizine (**9bk**)

alcohols with ammonia (Scheme 1, **1**→**4**, R^5=R^6=H) as the most rational synthetic protocol for *primary allylamines* in terms of the environmental and economic benefit.[6] The direct use of ammonia as a nucleophile has already been applied for the amination of allylic esters and carbonates (**2**→**4**) using a Pd-catalyst by Kobayashi *et al.*[49] and the enantioselective amination of allylic carbonates using a chiral Ir-catalyst by Hartwig *et al.*[50] Recently, Carreira *et al.* reported that optically active allylamines were prepared by the Ir-catalyzed stereospecific substitution reaction of optically active branched allylic alcohols with sulfamic acid as an ammonia equivalent.[51] In contrast, ammonia has never been used for the direct transformation of allylic alcohols into the corresponding primary allylamines, because the nucleophilicity of ammonia is much lower than that of alkylamines.

Our search was conducted for the allylic amination reaction of **1b** with degassed aq. ammonia as a test reaction using $PtCl_2$(cod)/DPEphos system, and the results are summarized in Table 9.[9c] When the reaction using 28% aq. ammonia (30 equiv., 1:5 [v/v] mixture of aq. ammonia and 1,4-dioxane) was conducted at 100 ℃ for 24 h, the corresponding linear monoallylated amine **11b** was obtained in 60% yield along with diallylated amine **12b** (**11b**:**12b**=82:18) with water as the sole co-product (entry 1). Branched allylamines was not detected in the ^{1}H NMR spectrum of the crude products. Because product **11b** has much higher nucleophilicity than ammonia and thus over-reaction of **11b** with **1b** to **12b** proceeds more readily, the monoallylation selectivity was lower than that when alkylamine was used as the nucleophile.[9a] This moderate monoallylation selectivity was improved to 90:10 by increasing the amount of ammonia (90 equiv.) to afford the desired product **11b** in 74% yield (entry 3). Unexpectedly, the reaction with excess amounts of ammonia resulted in a lower yield due to partial deactivation of the Pt catalyst at a higher concentration of ammonia (entry 4). At a lower reaction temperature (80 ℃), no reaction proceeded (entry 5). Under the same reaction conditions as for entry 3, Pt-Xantphos catalyst systems (P/Pt=4 and 2) were less efficient and **11b** was obtained in poor yield (34% and 29%, respectively; entries 6 and 7). Solvent effects were surveyed using a 1:1 [v/v] ratio of aq. ammonia and solvents. In THF and DME, **11b** was obtained in moderate yields, 52% and 59%, respectively (entries 8 and 9), whereas, in toluene, no reaction proceeded because of the biphasic reaction mixture (entry 10). Coordinative solvents such as acetonitrile and DMSO afforded the products in lower yields (entries 11 and 12). In DMF medium, *N*,*N*-dimethyl-3-phenylprop-2-en-1-amine was formed as the major product and a trace amount of the desired primary allylamine was detected in the crude reaction mixture (entry 13).[9b] In protic methanol media, the results were similar (entry 14) to those obtained in 1,4-dioxane. Other alcohols were less effective than MeOH in terms of the yield of **11b**. Furthermore, the reaction in aq. ammonia without organic solvent resulted in a very low yield of **11b** along with the recovered starting material (92%; entry 15). Finally, it is intriguing that the Pt-DPEphos in the mixed solvent system of aq. ammonia, 1,4-dioxane, and MeOH in a 3:2:1 [v/v/] proportion provided the best yield (79%) with high monoallylation selectivity (**11b**:**12b**=91:9; entry 16) as the best conditions. The reaction using only 0.5 mol % of catalyst also proceeded smoothly, although the yield of **11b** was slightly lower (entry 17).

Table 9. Optimization of the reaction conditions for direct amination of ammonia.[a]

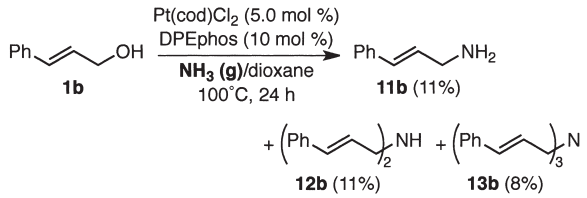


entry	solvent	aq. NH_3:solvent (equiv. of NH_3)	yield of **11b**[b]	selectivity of **11b**:**12b**[b]
1	dioxane	1:5 (20)	60	82:18
2	dioxane	1:2 (40)	71	89:11
3	dioxane	1:1 (60)	74	90:10
4	dioxane	2:1 (80)	51	94:6
5[c]	dioxane	1:1 (60)	nd[d]	–
6[e]	dioxane	1:1 (60)	34	94:6
7[e]	dioxane	1:1 (60)	29	97:3
8	THF	1:1 (60)	52	91:9
9	DME	1:1 (60)	59	92:8
10	toluene	1:1 (60)	nd[d]	–
11	CH_3CN	1:1 (60)	27	96:4
12	DMSO	1:1 (60)	30	94:6
13	DMF	1:1 (60)	4	80:20
14	MeOH	1:1 (60)	71	93:7
15	–	– (120)	7[f]	93:7
16	dioxane /MeOH	3:2:1 (60)	79 (72)[g]	91:9
17[h]	dioxane /MeOH	3:2:1 (60)	69	92:8

[a] 0.5 mmol scale, 28% aq. NH_3 and solvent (total volume 6.0 mL) was used in sealed tube. [b] Determined by ^{1}H NMR analysis. [c] Reaction temp. was 80 °C. [d] Not detected in the reaction mixture. [e] Xantphos was used instead of DPEphos. P/Pt = 4 (entry 6) and 2 (entry 7). [f] **1b** was recovered

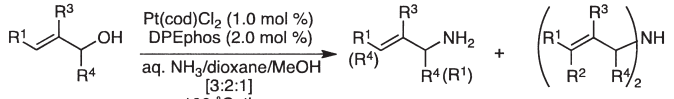
The use of aq. ammonia is essential for achieving the high yield of **11b** and high monoallylation selectivity. In fact, the reaction of **1b** with gaseous ammonia dissolved in 1,4-dioxane afforded **11b** in poor yield (11%) with contamination of a diallylated amine **12b** (11%) and a tertiary amine **13b** (8%) (Scheme 4).

Scheme 4. Pt-catalyzed direct amination with gaseous ammonia.



Because the reaction conditions were optimized for amination by aqueous ammonia, the scope of allylic alcohols **1** was assayed and the results are summarized in Table 10.[9c] Direct amination of a series of cinnamyl alcohol derivatives **1i**–**m** with aq. ammonia afforded the corresponding primary monoallylamines **11i**–**m** with high yield and high selectivity (entries 1–5). Branched allylic alcohols were efficiently converted to primary allylamines with a similar distribution of **11**/**12** (entries 7–9). Sterically congested 1,3-disubstituted allylic alcohols were good substrates for the present catalysis,

Table 10. Pt-catalyzed direct amination of various allylic alcohols with aqueous ammonia.[a]



entry	allylic alcohol **1**		monoallylated amine **11**		time (h)	yield (%) of **11**[b]	selectivity of **11**:**12**[b]
1	4-MeC_6H_4	**1i**	4-MeC_6H_4	**11i**	24	76 (68)	93:7
2	4-$MeOC_6H_4$	**1j**	4-$MeOC_6H_4$	**11j**	48	78 (70)	91:9
3	2-$MeOC_6H_4$	**1k**	2-$MeOC_6H_4$	**11k**	48	73 (68)	91:9
4	1-naphtyl	**1*l***	1-naphtyl	**11*l***	48	77 (70)	94:6
5	2-naphtyl	**1m**	2-naphtyl	**11m**	48	75 (69)	91:9
6	Ph	**1b'**	Ph	**11b**	24	77 (66)	91:9
7	3-FC_6H_4	**1n'**	3-FC_6H_4	**11n**	24	77 (66)	93:7
8	4-FC_6H_4	**1o'**	4-FC_6H_4	**11o**	24	81 (71)	91:9
9	4-$CF_3C_6H_4$	**1p'**	4-$CF_3C_6H_4$	**11p**	24	71 (69)	91:9
10	Ph, Ph	**1e**	Ph, Ph	**11e**	48	88 (78)	>99:1[c]
11[d]	4-$MeOC_6H_4$, Ph	**1q**	Ar, Ar'	**11q**[e]	65	84 (72)	>99:1[c]
12[d]	Ph, 4-$MeOC_6H_4$	**1q'**		**11q**[e]	65	84	>99:1[c]
13	Ph, Me	**1r**	Ph, Me	**11r**	48	80 (65)	>99:1[c]
14	Me, Ph	**1r'**		**11r**	48	71 (61)	>99:1[c]
15	4-$MeOC_6H_4$, Me	**1s**	4-$MeOC_6H_4$, Me	**11s**	48	70 (62)	>99:1[c]
16[f]		**1f**		**11f**	64	78 (66)	>99:1[c]
17[f]	Ph, Me	**1t**	Ph, Me	**11t**[g]	48	76 (70)	>99:1[c]
18[f]	S	**1u**	S	**11u**	48	72 (67)	92:8
19	O	**1v'**	O	**11v**[h]	13	(64)	94:6

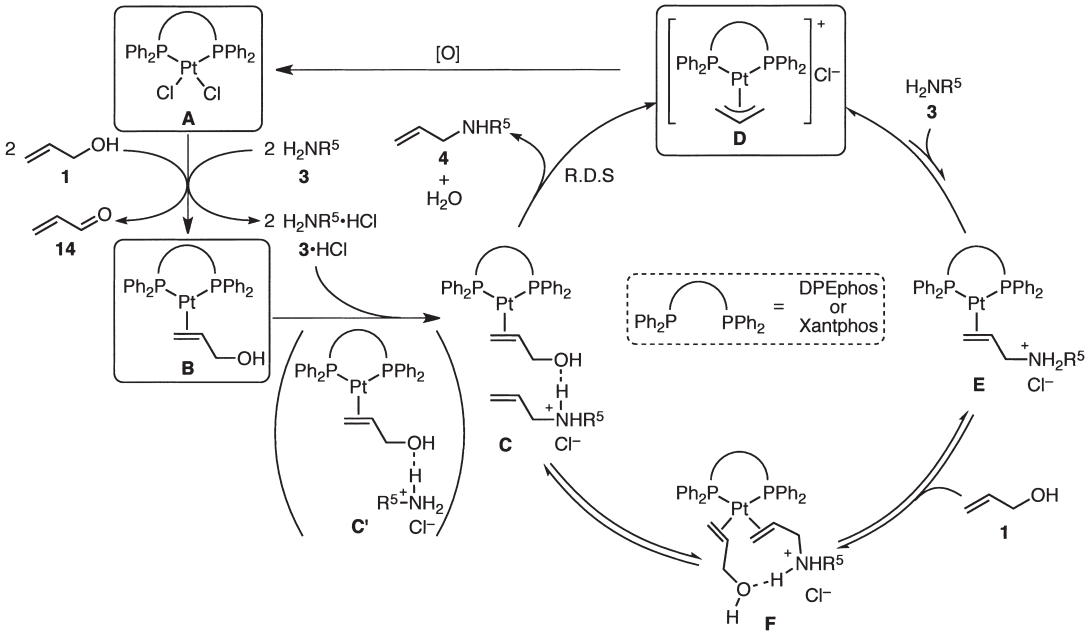
[a] 0.5 mmol scale, 28% aq. NH_3, dioxane and MeOH (3:2:1, total volume 6.0 mL) was used in a sealed tube. Starting material **1** was consumed except entries 5 and 17. [b] Determined by ^{1}H NMR analysis. The number in parentheses is the yield of the isolated product after Boc protection. [c] **12** was not detected by either ^{1}H NMR or CI-MS analysis of the crude reaction mixture. [d] 2.5 mol% of catalyst was used. [e] A mixture of regioisomers (53:47) was obtained. [f] 3.0 mol% of catalyst was used. [g] *E*/*Z* mixture (88:12) was obtained. [h] *E*/*Z* mixture (95:5) was obtained.

and, notably, the corresponding diallyl products were not detected by ^{1}H NMR or CI-MS analysis of the crude reaction mixture (entries 10–12). The reactions of alkyl-substituted allylic alcohol also resulted in the good conversion of allylic alcohols to the corresponding monoallylated amines with quite high **11**/**12** selectivity (>99:1; entries 13–15). Since both cyclic and β-substituted allylic alcohols **1f** (entry 16) and **1t** (entry 17) were less reactive substrates, their reactions required the use of 3.0 mol % of catalyst loading. Additionally, highly unstable γ-thiophene and furan substituted allylic alcohols **1u** (entry 18) and **1v** (entry 19) were also successfully converted to the corresponding primary amines without any decomposition.

4. Mechanistic Studies

We revealed a plausible catalytic cycle of the platinum-catalyzed direct amination of allylic alcohol to be as depicted in Scheme 5 based on our intensive experiments including ^{1}H and ^{31}P{^{1}H} NMR analysis, isolation of several catalytic intermediates, confirmation of the structure of [Pt(η^3-allyl)(xantphos)]OTf (**D**$_{OTf}$) by X-ray crystallographic analysis, and crossover experiments.[9b] Since we described above that Pt(0) species were less effective catalyst precursors and Pt(cod)Cl_2 was found to be the best precursor,[9a,b] we first investigated the compound that reduced Pt(II) to Pt(0). Candidate reagents are phosphine ligand, amine, or allylic alcohol. Among them, we confirmed that the Pt(II) species was reduced to the Pt(0) species by allylic alcohol **1** through β-H elimination of alkoxy-Pt(II) species to give a Pt(0) complex, Pt(η^2-C_3H_5OH)(diphosphine) (**B**), which was alternatively prepared and isolated by reduction of Pt(xantphos)Cl_2 (**A**) with $NaBH_4$ in the presence of allyl alcohol (**1a**) in 94% yield, along with α,β-unsaturated

Scheme 5. Proposed catalytic cycle of the platinum–catalyzed direct amination of allylic alcohol.[a,b]



[a]Substituents of allylic alcohol 1 are omitted for clarity. [b]Structurally characterized complexes are boxed.

aldehyde **14**. In the catalytic cycle, the following species is a π–allyl complex: we synthesized and isolated $\mathbf{D_{OTf}}$ in 84% yield by the reaction of Pt(xantphos)Cl_2 (**A**), allyltributylstannane (1.0 equiv.), and AgOTf (1.0 equiv.). The structure of $\mathbf{D_{OTf}}$ confirmed by X–ray crystallographic analysis is shown in Figure 1. The bite–angle of the crystal (107°) is almost the same as that obtained by density functional theory calculations (Table 2, 108°), and there is no direct interaction between the Pt atom and the oxygen atom of the ligand.

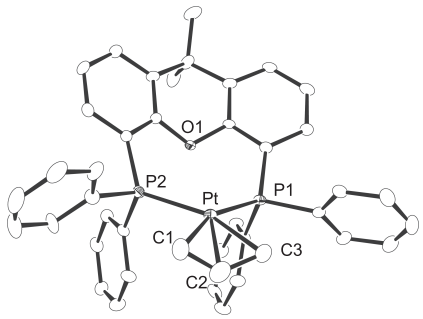
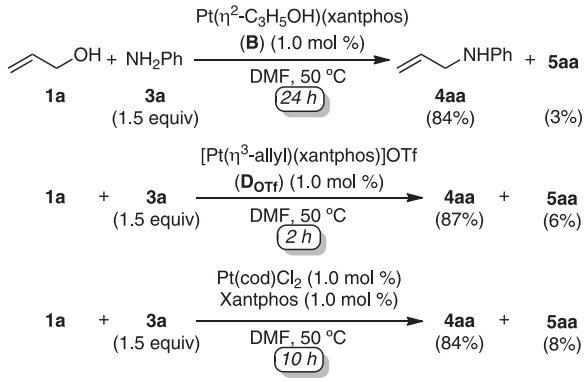


Figure 1. ORTEP drawing of [Pt(η^3–allyl)(xantphos)]OTf ($\mathbf{D_{OTf}}$) with thermal ellipsoids at the 50% probability level. The hydrogen atoms, counter anions, and solvent are omitted for clarity.

The catalyst activities of **B** and $\mathbf{D_{OTf}}$ were checked by the reaction of **1a** and **3a**. Since both complexes promoted the reaction to give the product (Scheme 6), these complexes are proved to be involved in the catalytic cycle. Notable point is that the reactivity of these complexes differed from that of the Pt(cod)Cl_2–Xantphos system. Under conventional heating conditions at 50 ℃, complex **B** required 24 h for full conversion, while the reactions using Pt(cod)Cl_2–Xantphos and $\mathbf{D_{OTf}}$ completed in 10 h and 2 h, respectively. The higher catalyst activities of Pt(cod)Cl_2–Xantphos and $\mathbf{D_{OTf}}$ than **B** might be due to the ammonium salts HNR^5R^6•HCl and $H_2NR^5R^6$•HOTf, which could potentially act as more efficient activators of the hydroxyl group to accelerate the elimination of hydroxide through hydrogen bonding of ammonium salts with a hydroxyl group of allylic alcohol (**C**→**D**). In contrast, the addition of NH_4Cl (2.0 equiv. to substrate) to the direct amination with ammonia under aqueous conditions did not significantly improve the catalytic activity.[9c] Thus, it is likely that the aqueous condition contributed to the hydrogen bonding effects of water to activate the hydroxyl group of allylic alcohols.[24]

Scheme 6. Catalytic activities of Pt(η^2–C_3H_5OH)(xantphos) (**B**) and [Pt(η^3–allyl)(xantphos)]OTf ($\mathbf{D_{OTf}}$).



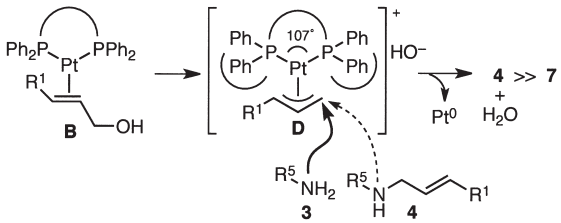
The addition of 2.0 equiv. **4aa**•HCl salt to the Pt(0) complex **B** at room temperature led to the exclusive formation of [Pt(η^3–allyl)(xantphos)]Cl (**D**) within 5 min; however, only free allyl alcohol (**1a**) was detected, and not free *N*–allylaniline (**4aa**) or water, strongly suggesting that π–allylplatinum complex **D** was not generated through the elimination of water from the allyl alcohol (**1a**) coordinated to the Pt(0) atom (**C**→**D**, clockwise direction), but rationally through the elimination of aniline (**3a**) from *N*–allylaniline (**4aa**) (**C**→**F**→**E**→**D**, counterclockwise direction). The existence of this rapid retro reaction was further supported by crossover experiments.[9b]

^{1}H and ^{31}P{^{1}H} NMR spectroscopic monitoring of a mix-

ture of $\mathbf{D}_{\mathrm{OTf}}$ and 12.0 equiv. of **3a** in DMF-d_7 indicated that almost no reaction occurred even after 6 h of heating at 50 ℃. In contrast, when allyl alcohol (**1a**) was added to this mixture with **3a**, clear conversion of **1a** to the allylated products **4aa** (62%) and **5aa** (38%) was detected by ^{1}H NMR, though only the starting $\mathbf{D}_{\mathrm{OTf}}$ was detected on ^{31}P{^{1}H} NMR spectroscopy. Recently, le Floch and co-authors reported that, in the case of [Pt(η^3-allyl)(dpp-xantphos)]PF_6, the addition of benzylamine (**8a**) led to the formation of a new complex, tentatively assigned as Pt(η^2-H_2C=$CHCH_2NH_2Bn^+PF_6^-$)(dpp-xantphos) **E**.[37] In sharp contrast to their results, our results suggested that (1) complexes **D**, **E**, **F**, and **C** were in rapid equilibrium, even at room temperature; (2) among them, **D** was the most stable species even in the presence of excess amounts of nucleophile **3**; and (3) the formation of **D** from **C** through the elimination of water (**C**→**D**) was the rate-determining step of this catalytic cycle and required a reaction temperature of 50 ℃.

The excellent high monoallylation selectivity in the present Pt catalysis likely originates from the selective attack of the smaller amine nucleophile **3** on the π-allylplatinum intermediate, where the large bite-angled diphosphine ligand DPEphos or Xantphos produced a congested environment around the Pt center, compared with the corresponding monoallylated amine **4** (Scheme 7).

Scheme 7. Plausible mechanism for high monoallylation selectivity.



5. Conclusions

Here we introduced the development of a Pt-catalyzed direct amination of allylic alcohols with amine including the smallest nitrogen nucleophile ammonia without prior activation of the allylic alcohol.[9] Overall, this Pt-catalytic system provides a new protocol for the direct amination of allylic alcohols with a wide substrate scope, offering an efficient direct access to a variety of primary, secondary, and tertiary monoallylamines in an atom-economical and environmentally benign manner. Further investigation of the application to the use of other types of nucleophile, and of the scope of the syntheses of highly functionalized bioactive natural and unnatural compounds, along with the studies on enantioselective variants, one-pot sequential reaction, and flow systems are ongoing in our group.

Acknowledgements

We deeply acknowledge our coworkers, Dr. Masaru Utsunomiya, Yoshiki Miyamoto, Junji Ipposhi, Dr. Kalpataru Das, Yasuhito Nakahara, Ryozo Shibuya, and Nicolas Germain, for their extensive contributions to this work. This work was supported by Encouragement of Young Scientists (A) from Japan Society for the Promotion of Science, a Grant-in-Aid for Science Research in a Priority Area (No. 20037040, "Chemistry of Concerto Catalysis") and Grant-in-Aid for Scientific Research (B) (21390003) from the Ministry of Education, Culture, Sports, Science and Technology, Japan, The Core Research for Evolutional Science and Technology (CREST) program of the Japan Science and Technology Agency (JST), The Grand-in-Aid for Scientific Research on Innovative Area "Reaction Integration" (No. 2105), the Uehara Memorial Foundation, and Mitsubishi Chemical Corporation Foundation.

References and Notes

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) (a) Petranyi, G.; Ryder, N. S.; Stütz, A. *Science* **1984**, *224*, 1239. (b) Kanno, H.; Taylor, R. J. K. *Tetrahedron Lett*. **2002**, *43*, 7337. (c) Olesen, J. J. *Neurol* **1991**, *238*, S23. (d) Marín, M. T.; Margarit, M. V.; Salcedo, G. E. *Il Farmaco* **2002**, *57*, 723.
3) 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.
4) For reviews, see: (a) *Handbook of Metathesis*, Vols 1-3, Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003. (b) Nicolaou, K. C.; Bulger, P. G., Sarlar, D. *Angew. Chem. Int. Ed*. **2005**, *44*, 4490.
5) For reviews, see: (a) Tsuji, J. *Transition Metal Reagents and Catalysis*; Wiley-VCH: Weinheim, **2000**. (b) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000. (c) Trost, B. M.; Crawley, M. L. *Chem. Rev*. **2003**, *103*, 2921.
6) For review, see: (a) Muzart, J. *Tetrahedron* **2005**, *61*, 4179. (b) Tamaru, Y. *Eur. J. Org. Chem*. **2005**, 2647. (c) Muzart, J. *Eur. J. Org. Chem*. **2007**, 3077.
7) Lewis acid-catalyzed direct substitution of allylic, propargylic, and benzylic alcohols with electron-deficient nitrogen nucleophiles were reported. For representative examples, see: (a) Nishibayashi, Y.; Milton, M. D.; Inada, Y.; Yoshikawa, M.; Wakiji, I.; Hidai, M.; Uemura, S. *Chem. Eur. J*. **2005**, *11*, 1433. (b) Terrasson, V.; Marque, S.; Georgy, M.; Campagne, J.-M.; Prim, D. *Adv. Synth. Catal*. **2006**, *348*, 2063. (c) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem. Int. Ed*. **2007**, *46*, 409. (d) Guo, S.; Song, F.; Liu, Y. *Synlett* **2007**, 964. (e) Reddy, C. R.; Madhavi, P. P.; Reddy, A. S. *Tetrahedron Lett*. **2007**, *48*, 7169. (f) Sreedhar, B.; Reddy, P. S.; Reddy, M. A.; Neelima, B.; Arundhathi, R. *Tetrahedron Lett*. **2007**, *48*, 8174. (g) Jana, U.; Maiti, S.; Biswas, S. *Tetrahedron Lett*. **2008**, *49*, 858. (h) Wang, G.-W.; Shen, Y.-B.; Wu, X.-L. *Eur. J. Org. Chem*. **2008**, 4367. (i) Huang, W.; Shen, Q.-S.; Wang, J.-L.; Zhou, X.-G. *Chin. J. Chem*. **2008**, *26*, 729.
8) (a) Ohshima, T.; Nakahara, Y.; Ipposhi, J.; Miyamoto, Y.; Mashima, K. *Chem. Commun*. **2011**, *47*, 8322. (b) Ohshima T.; Ipposhi J.; Nakahara Y.; Shibuya R.; Mashima K. *Adv. Synth. Catal. accepted*.
9) (a) Utsunomiya, M.; Miyamoto, Y.; Ipposhi, J.; Ohshima, T.; Mashima, K. *Org. Lett*. **2007**, *9*, 3371. (b) Ohshima, T.; Miyamoto, Y.; Ipposhi, J.; Nakahara, Y.; Utsunomiya, M.; Mashima, K. *J. Am. Chem. Soc*. **2009**, *131*, 14317. (c) Das, K.; Shibuya, R.; Nakahara, Y.; Germain, N.; Ohshima, T.; Mashima, K. *Angew. Chem. Int. Ed*. **2012**, *51*, 150.
10) Trost, B. M. *Science* **1991**, *254*, 1471.
11) Lu, X.; Lu, L.; Sun, J. *J. Mol. Catal*. **1987**, *41*, 245.
12) Lu, X.; Jiang, X.; Tao, X. *J. Organomet. Chem*. **1988**, *344*, 109.
13) (a) Masuyama, Y.; Takahara, J. P.; Kurusu, Y. *J. Am. Chem. Soc*. **1988**, *110*, 4473. (b) Masuyama, Y.; Kagawa, M.; Kurusu, Y. *Chem. Lett*. **1995**, 1121.
14) Lumin, S.; Falck, J. R.; Capdevila, J.; Karara, A. *Tetrahedron Lett*. **1992**, *33*, 2091.
15) (a) Itoh, K.; Hamaguchi, N.; Miura, M.; Nomura, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2833. (b) Satoh, T.; Ikeda, M.; Miura, M.; Nomura, M. *J. Org. Chem*. **1997**, *62*, 4877. (c) Yang, S.-C.; Hung, C.-W. *J. Org. Chem*. **1999**, *64*, 5000. (d) Yang, S.-C.; Tsai, Y.-C.; Shue, Y.-J. *Organometallics* **2001**, *20*, 5326. (e) Shue, Y.-J.; Yang, S.-C.; Lai, H.-C. *Tetrahedron Lett*. **2003**, *44*, 1481.
16) Stary, I.; Stará, I. G.; Kocovsky, P. *Tetrahedron Lett*. **1993**, 34, 179.
17) Tsay, S.; Lin, L. C.; Furth, P. A.; Shum, C. C.; King, D. B.; Yu, S. F.; Chen, B.; Hwu, J. R. *Synthesis* **1993**, 329.
18) Sakamoto, M.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn*. **1996**, *69*, 1065.

19) (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.
20) Yang, S.-C.; Hsu, Y.-C.; Gan, K.-H. *Tetrahedron*, **2006**, *62*, 3949.
21) Yamashita, Y.; Gopalarathnam, A.; Hartwig, J. F. *J. Am. Chem. Soc*. **2007**, *129*, 7508.
22) (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.
23) Kayaki, Y.; Koda, T.; Ikariya, T. *J. Org. Chem*. **2004**, *69*, 2595.
24) Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett*. **2004**, *6*, 4085.
25) (a) Piechaczyk, O.; Doux, M.; Ricard, L.; Le Floch, P. *Organometallics* **2005**, *24*, 124. (b) Thoumazet, C.; Grützmacher, H.; Deschamps, B.; Ricard, L.; le Floch, P. *Eur. J. Inorg. Chem*. **2006**, 3911. (c) Piechaczyk, O.; Thoumazet, C.; Jean, Y.; Le Floch, P. *J. Am. Chem. Soc*. **2006**, *128*, 14306. (d) Mora, G.; Deschamps, B.; van Zutphen, S.; Le Goff, X. F.; Ricard, L.; Le Floch, P. *Organometallics* **2007**, *26*, 1846.
26) Usui, I.; Schmidt, S.; Keller, M.; Breit, B. *Org. Lett*. **2008**, *10*, 1207.
27) Pedley, J. B.; Marshall, E. M. *J. Phys. Chem. Ref. Data* **1983**, *12*, 967.
28) For reviews on the influence of the bite-angle of bidentate phosphane ligands, see: (a) van Haaren, R. J.; Oevering, H.; Coussens, B. B.; van Strijdonck, G. P. F.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Eur. J. Inorg. Chem*. **1999**, 1237. (b) Oestreich, M. *Eur. J. Org. Chem*. **2005**, 783. For a recent example, see: (c) Johns, A. M.; Utsunomiya, M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc*. **2006**, *128*, 1828.
29) (a) Dube, G.; Selent, D.; Taube, R. *Z. Chem*. **1985**, *25*, 154. (b) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3081.
30) For a review, see: (a) Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Acc. Chem. Res*. **2001**, *34*, 895. For initial studies, see: ref. 32b and (b) Hillebrand, S.; Bruckmann, J.; Krüger, C.; Haenel, M. W. *Tetrahedron Lett*. **1995**, *36*, 75.
31) Pt-catalyzed direct amination of allylic alcohols with ammonia to provide a mixture of mono-, di-, and triallylation products were reported, see: Ishimura, Y.; Nagato, N. *Jpn. Kokai Tokkyo Koho JP* 63002958, 1988.
32) (a) Becke, A. D. *J. Chem. Phys*. **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
33) For a review of self-assembling ligand, see: (a) Breit, B. *Angew. Chem. Int. Ed*. **2005**, *44*, 6816. For catalyses using 6-DPPon, see: (b) Breit, B.; Seiche, W. *J. Am. Chem. Soc*. **2003**, *125*, 6608. (c) Chevallier, F.; Breit, B. *Angew. Chem. Int. Ed*. **2006**, *45*, 1599. (d) Weis, M.; Waloch, C.; Seiche, W.; Breit, B. *Angew. Chem. Int. Ed*. **2007**, *46*, 3037. (e) Smejkal, T.; Breit, B. *Organometallics* **2007**, *26*, 2461.
34) For a review, see: (a) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res*. **2006**, *39*, 747. For an initial study, see: (b) Trost, B. M.; Van Vranken, D. L. *Angew. Chem*., *Int. Ed. Engl*. **1992**, *31*, 228.
35) (a) Sacconi, L.; Gelsomini, J. *Znorg. Chem*. **1968**, *7*, 291. (b) Greene, P. T.; Sacconi, L. *J. Chem. Soc. A* **1970**, 866. (c) Dapporto, P.; Sacconi, L. *J. Am. Chem. Soc*. **1970**, *92*, 4133. (d) Dapporto, P.; Sacconi, L. *J. Chem. Soc. A* **1971**, 1914. (e) Thewissen, D. H. M. W.; Timmer, K.; Noltes, J. G.; Marsman, J. W.; Laine, R. M. *Inorg. Chim. Acta* **1985**, *97*, 143.
36) Mispelaere-Canivet, C.; Spindler, J.-F.; Perrio, S.; Beslin, P. *Tetrahedron* **2005**, *61*, 5253.
37) Mora, G.; Piechaczyk, O.; Houdard, R.; Mézailles, N.; Le Goff, X.-F.; le Floch, P. *Chem. Eur. J*. **2008**, *14*, 10047.
38) Lesueur, W.; Solari, E.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Inorg. Chem*. **1997**, *36*, 3354.
39) (a) Stephenson, T. A.; Morehouse, S. M.; Powell, A. R.; Hefer, J. P.; Wilkinson, G. *J. Chem. Soc*., *Chem. Commun*. **1965**, 3632. (b) Carrondo, M. A. A. F. de C. T.; Skapski, A. C. *J. Chem. Soc*., *Chem. Commun*. **1976**, 410. (c) Carrondo, M. A. A. F. de C. T.; Skapski, A. C. *Acta Crystallogr*., *Sect. B*: *Struct. Crystallogr. Cryst. Chem*. **1978**, *B34*, 1857. (d) Carrondo, M. A. A. F. deC. T.; Skapski, A. C. *Acta Crystallogr*., *Sect. B*: *Struct. Crystallogr. Cryst. Chem*. **1978**, *B34*, 3576.
40) (a) Yamaguchi, T.; Sasaki, Y.; Nagasawa, A.; Ito, T.; Koga, N.; Morokuma, K. *Inorg. Chem*. **1989**, *28*, 4311. (b) Yamaguchi, T.; Sasaki, Y.; Ito, T. *J. Am. Chem. Soc*. **1990**, 112, 4038. (c) Yamaguchi, T.; Ueno, T.; Ito, T. *Inorg. Chem*. **1993**, *32*, 4996. (d) Yamaguchi, T.; Abe, K.; Ito, T. *Inorg. Chem*. **1994**, *33*, 2689. (e) Yamaguchi, T.; Shibata, A.; Ito, T. *J. Chem. Soc*., *Dalton Trans*. **1996**, 4031. (f) Shibata, A.; Yamaguchi, T.; Ito, T. *Inorg. Chim. Acta* **1997**, *256*, 179. (g) Yamaguchi, T.; Saito, H.; Maki, T.; Ito, T. *J. Am. Chem. Soc*. **1999**, *121*, 10738. (h) Yamaguchi, T.; Shibata, A.; Ito, T. *Chem.-Eur. J*. **2001**, *7*, 5409.
41) (a) Ohashi, M.; Yagyu, A.; Yamagata, T.; Mashima, K. *Chem. Commun*. **2007**, 3103. (b) Tanaka, S.; Yagyu, A.; Kikugawa, M.; Ohashi, M.; Yamagata, T.; Mashima, K. *Chem.-Eur. J*. **2011**, *17*, 3693. (c) Shinji, T.; Kazushi, M. *Inorg. Chem*. **2011**, *50*, 11384.
42) Unpublished results.
43) Recently, Pd-Xantphos/proline catalyzed α-allylation reaction of enolizable ketones and aldehydes with allylic alcohols was reported, see: Usui, I.; Schmidt, S.; Breit, B. *Org. Lett*. **2009**, *11*, 1453.
44) For recent reviews, see: (a) Kappe, C. O. *Angew. Chem. Int. Ed*. **2004**, *43*, 6250. (b) Hayes, B. L. *Aldrichim. Acta* **2004**, *37*, 66. (c) Roberts, B. A.; Strauss, C. R. *Acc. Chem. Res*. **2005**, *38*, 653. For a recent study on nonthermal microwave effects, see: Herrero, M. A.; Kremsner, J. M.; Kappe, C. O. *J. Org. Chem*. **2008**, *73*, 36.
45) Although the reaction temperature was monitored using a standard IR temperature monitoring system and controlled by microwave irradiation power (standard mode) with an airflow cooling system (20 psi), IR temperature sensors in microwave reactors are not highly reliable for monitoring the reaction temperature because they only record the outer surface temperature of the reaction vessel and not the internal reaction temperature. Thus, the reaction temperature was also checked with an alcohol thermometer immediately after turning off the irradiation, revealing that the error in the IR temperature monitoring system was within 5 ℃. Later, we confirmed this finding using fiber-optic temperature probes. These results indicate that microwave irradiation has beneficial effects despite the fact that a number of recent studies reported that nonthermal microwave effects in organic chemistry do not exist.[44]
46) Shimizu, Y.; Morimoto, H.; Zhang, M.; Ohshima, T. *Angew. Chem. Int. Ed*. **2012**, *51*, 8654.
47) (a) Appl, M. in *Ammonia*: *Principles and Industrial practice*, Wiley-VCH, Weinheim, **1999**. (b) Appl, M. in *Ammonia*: *Ullmann's Encyclopedia of Industrial Chemistry*, 7th Ed, Wiley-VCH, New York, **2010**.
48) For reviews, see: (a) Roundhill, D. M. *Chem. Rev*. **1992**, *92*, 1. (b) Lawrence, S. A. in *Amines*: *Synthesis Properties*, *and Application*, Cambridge University Press, Cambridge, **2004**. (c) Willis, M. C. *Angew. Chem. Int. Ed*. **2007**, *46*, 3402. (d) Vlugt, J. I. van der *Chem. Soc. Rev*. **2010**, *39*, 2302. (e) Klinkenberg, J.; Hartwig, J. F. *Angew. Chem. Int. Ed*. **2011**, *50*, 86.
49) Nagano, T.; Kobayashi. S. *J. Am. Chem. Soc*. **2009**, *131*, 4200.
50) (a) Pouy, M. J.; Leitner, A.; Weix, D. J.; Ueno, S.; Hartwig, J. F. *Org. Lett*. **2007**, *9*, 3949. (b) Pouy, M. J.; Stanley, L. M.; Hartwig, J. F. *J. Am. Chem. Soc*. **2009**, *131*, 11312.
51) (a) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem. Int. Ed*. **2007**, *46*, 3139. (b) Roggen, M.; Carreira, E. M. *J. Am. Chem. Soc*. **2010**, *132*, 11917.

PROFILE

Takashi Ohshima is a Professor of Kyushu University. He was born in 1968 in Ehime, Japan. He received his bachelor's degree from The University of Tokyo in 1991 under the direction of Professor Masaji Ohno and received his Ph.D. degree from The University of Tokyo in 1996 under the direction of Professor Masakatsu Shibasaki. On the following year, he joined Otsuka Pharmaceutical Co., Ltd. for one year. After two years as a postdoctoral fellow at The Scripps Research Institute with Professor K. C. Nicolaou (1997–1999), he returned to Japan and joined Professor Shibasaki's group in The University of Tokyo as an assistant professor. He was appointed as Associate Professor of Osaka University in 2005. In 2010, he was promoted a full professor of Kyushu University. His research interests include development of highly atom–economical and environmentally benign catalytic process for the synthesis of biologically active compounds.

Kazushi Mashima received his Doctor degree (1986) from Osaka University. He became an Assistant Professor at Institute for Molecular Science, Okazaki National Institutes in 1983. He moved to Faculty of Engineering, Kyoto University as an Assistant Professor in 1989, and then to Faculty of Science, Osaka University in 1991. He was promoted to an Associate Professor at Faculty (now Graduate School) of Engineering Science, Osaka University in 1994, and then to a full Professor at Graduate School of Engineering Science, Osaka University in 2003. He worked with Professor M. A. Bennett, Australian National University in 1992 and Professor W. A. Herrmann, Technisch Universität München in 1993. His current research interests lie in the area of organometallic and inorganic chemistry, emphasizing directions to asymmetric and polymerization catalysis as well as catalysis composed of polynuclear assembled metals.