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Chemoselective Palladium-Catalyzed Reaction in Aqueous Media: Selectivity in the Reaction of Haloanilines with 1,1-Dimethylallyl Alcohol

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Dedicated to Professor Masakatsu Shibasaki on the occasion of his 60th birthday.

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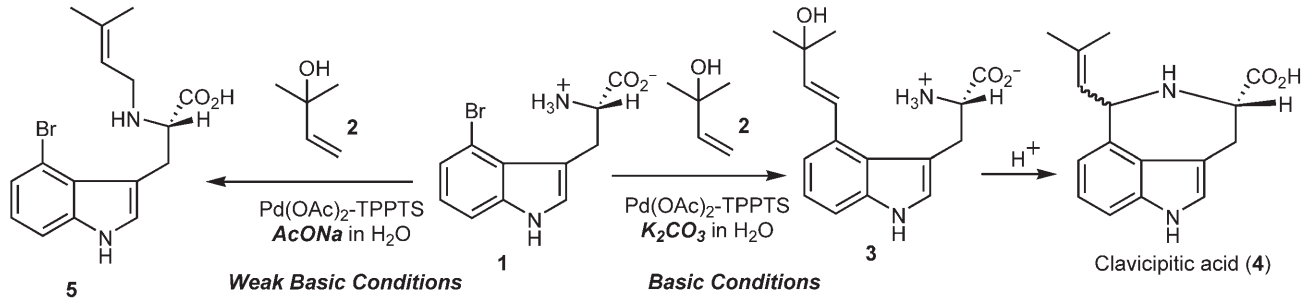
Abstract: Palladium-catalyzed reactions of various haloanilines with 1,1-dimethylallyl alcohol were carried out in the presence of a hydrophilic ligand, 3,3′,3″-phosphinidyne tris(benzenesulfonic acid) trisodium salt (TPPTS), or a lipophilic phosphine ligand, 1,1′-bis(diphenylphosphino)ferrocene (DPPF). The reactions proceeded chemoselectively in aqueous solvent to give *C*-vinylated products under basic conditions or *N*-allylated products under neutral conditions in practical yields (up to 79%). The use of an aqueous solvent played an important role in this chemoselectivity and allowed the development of a one-pot synthesis of 3-methylindole. This chemoselectivity is synthetically useful because the reactive position of haloanilines can be controlled simply by changing the basicity of the reaction medium, which eliminates the need to protect the amino group during the reaction.

Keywords: allylation; chemoselectivity; haloanilines; palladium; synthetic methods; vinylation; water

Introduction

We have been investigating the total synthesis of ergot alkaloids from tryptophan derivatives.[1] During the synthesis of clavicipitic acid (**4**), an interesting chemoselective palladium-catalyzed reaction of unprotected 4-bromotryptophan (**1**) with 1,1-dimethylallylalcohol (**2**) was observed (Scheme 1);[2] *C*-vinylation (Heck reaction) occurred under strong basic conditions to give the C-4-vinylated product **3**, while the *N*-allylated product (**5**) was formed under weakly basic conditions. These results indicate that the reactive site can be controlled by changing the pH in aqueous solution. This is considered to be synthetically useful, because it facilitates the selective introduction of different carbon chains to the amino group and at the bromine-containing carbon atom.

Although numerous palladium-catalyzed vinylations (Heck reactions) have been reported in the literature,[3] there have been few reports on the reaction



Scheme 1. Chemoselective reaction of 4-bromotryptophan (**1**) with 1,1-dimethylallyl alcohol (**2**).

with allyl alcohol,[4] because migration of the double bond during the reaction often gave rise to a mixture of products. However, among the allyl alcohols, 1,1-dimethylallyl alcohol (**2**) gives only the vinylated product.[5] Another report stated that the Heck reaction proceeded more rapidly in aqueous media than in organic solvents.[6] In contrast, palladium-catalyzed allylation with allyl alcohol is difficult[7] because the reactivity of allyl alcohol towards Pd(0) is poor and, compared with allylic carbonate or acetate, the reaction does not easily lead to the formation of the π-allyl complex. For example, *N*-allylation did not proceed without a Lewis acid in organic solvent.[7] Recent studies indicated that palladium-catalyzed *N*- or *C*-allylation with allyl alcohol proceeded in aqueous media without additives and that water played an important role in the activation of allyl alcohol to form π-allyl complexes.[8]

Since unprotected amino acids are scarcely insoluble in organic solvents and possess different properties and reactivities for their zwitterionic form in aqueous solution,[9,10] determining whether this chemoselectivity is observed only for unprotected amino acids such as 4-bromotryptophan is of interest. This prompted us to investigate palladium-catalyzed reactions of various haloanilines **6** with 1,1-dimethylallyl alcohol (**2**) in the presence of either the hydrophilic ligand 3,3′,3″-phosphinidyne tris(benzenesulfonic acid) trisodium salt (TPPTS, **9**), or the lipophilic phosphine ligand 1,1′-bis(diphenylphosphino)ferrocene (DPPF, **10**), in aqueous or organic solvent (Scheme 2). In this paper, we report detailed results, mechanistic considerations, and applications of this chemoselective reaction.[11]

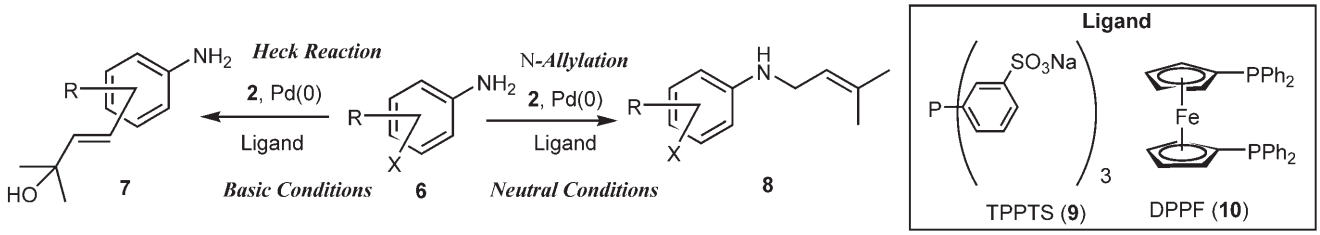
Results and Discussion

A mixture of haloaniline **6**, 1,1-dimethylallyl alcohol (**2**, 5 equiv) was heated in the presence of $Pd(OAc)_2$ (0.1 equiv.) and TPPTS (**9**) or DPPF (**10**) (0.2 equivs.) in various solvents (1 mL) with or without base [K_2CO_3 (3 equivs.)] at 100–130 °C for 4 h under an argon atmosphere in a sealed tube. After work-up, the mixture was subjected to silica gel chromatography to separate the products. The results of the reactions under neutral and basic conditions are summarized in Table 1 and Table 2, respectively.

Under neutral conditions, *N*-allylation occurred selectively to give *N*-allylated products (**12**, **13**, and **14**) without formation of the Heck product. Although a bis-*N*-allylated product (**13**) or regional isomer (**14**) was obtained in some cases, the *N*-mono-allylated product (**12**) was the main product. The reaction had a tendency to proceed more smoothly in water than in toluene or toluene-H_2O to give the *N*-mono-allylated products in good to moderate yields (runs 1 *vs.* 3 or 4, 5 *vs.* 7, and 13), and the water-soluble ligand **9** gave a better yield than the lipophilic ligand **10** (runs 5 *vs.* 6, 9 *vs.* 10, and 11 *vs.* 12). These results reveal that *N*-allylation occurs more smoothly in the aqueous phase than in the organic phase. However, some exceptions were observed: *m*-bromoaniline (**11c**) gave the highest yield (85%) of *N*-allylated product (**12c**) in toluene-H_2O (run 11), and the best yield of **12a** was obtained by the use of DPPF (**10**) (run 2). It is noted that mono-allylated products **12** were obtained in good yields (54–85%), which are sufficient for synthetic purposes. However, formation of the regioisomer **14** limits the utility of the reaction because it was very difficult to separate **14** from the *N*-mono-allylated product **12**. The formation of **13**, which occurred during the reaction of **11c** and **b**, was not as problematic because **13** was easily removed by silica gel chromatography.

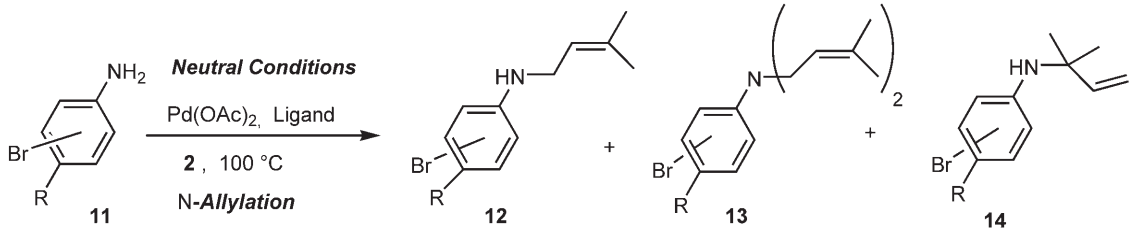
Under basic conditions (3 mol equivs. of K_2CO_3) (Table 2), vinylation occurred selectively without formation of the *N*-allylated products **12**, except for the reaction of **11c**, during which vinylation and *N*-allylation occurred simultaneously when using phosphine ligand **10** in H_2O to give significant amounts of **16** (run 10). A two-phase solvent, toluene-H_2O, was the best for the formation of **15** in greater than 54% yield (runs 4, 8, and 11), and the lipophilic ligand, DPPF (**10**), gave better yields than the water-soluble ligand, TPPTS (**9**) (runs 1 *vs.* 2, 7 *vs.* 8, and 13 *vs.* 14).

These results show that vinylation takes place preferentially in a lipophilic rather than a hydrophilic environment under basic conditions. However, the combination of the two-phase solvent system and DPPF was not always optimal, as shown by the yield from **11a** (run 2) and **11c** (run 11), which involved a combi-



Scheme 2. Palladium-catalyzed chemoselective reaction of haloanilines **6**.

Table 1. Palladium-catalyzed *N*-allylation of haloanilines **11** under neutral conditions.



a: R = CH_3, 2-Br; **b**: R = H, 2-Br; **c**: R = H, 3-Br; **d**: R = Br

Run	**11**	Ligand	Solvent	Time [h]	Product Yield [%] **12**	**13**	**14**[a]	SM (**11**) [%]
1	**11a**	TPPTS	H_2O	4	54	-	11	10
2		DPPF	H_2O	4	70	-	trace	19
3		TPPTS	Toluene-H_2O[b]	4	16	-	2	53
4		TPPTS	Toluene	4	18	-	trace	42
5	**11b**	TPPTS	H_2O	3	65	-	3	-
6		DPPF	H_2O	3	22	-	-	-
7		TPPTS	Toluene-H_2O[b]	3	26	-	-	12
8		DPPF	Toluene-H_2O[b]	3	12	-	-	47
9	**11c**	TPPTS	H_2O	3	65	8	7	-
10		DPPF	H_2O	3	29	1	-	-
11		TPPTS	Toluene-H_2O[b]	3	85	2	-	12
12		DPPF	Toluene-H_2O[b]	3	28	-	-	43
13	**11d**	TPPTS	H_2O	3	71	15	-	-
14		DPPF	H_2O	3	23	3	-	24

[a] The yields were calculated based on integration of the olefinic protons of a mixture of **12** and **14** that was separated by silica gel chromatography.
[b] Toluene:H_2O = 1:1.

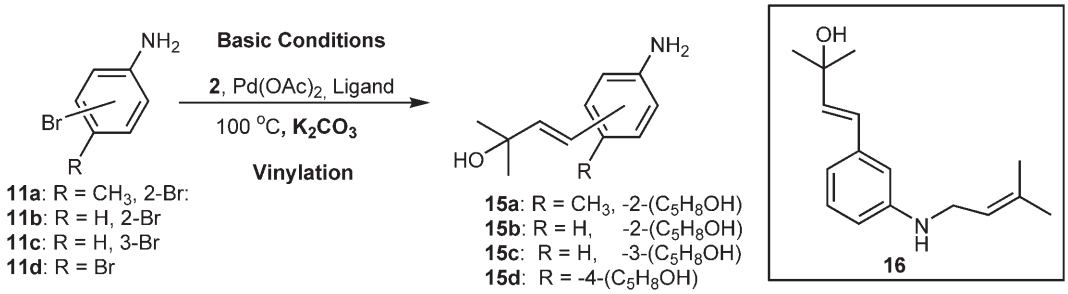
nation of **10** with H_2O and of **9** with toluene-H_2O, respectively. Interestingly, the reaction of 4-bromoaniline (**11d**) resulted in low yields for every combination of ligand and solvent (runs 13, 14 and 15) without recovery of the starting material. Although the reason for the low yield was not clear, the starting material may decompose *via* a σ-complex formed as an intermediate (*vide infra*).

Next, the reaction of iodoaniline **17** with **2** was carried out under neutral and basic conditions. Vinylation of 2- (**17a**) and 3-iodoaniline (**17b**) occurred smoothly to give *C*-vinylated products **15** as shown in Table 3. The use of 2-iodoaniline (**17a**) produced good yields (53–79%) with every combination of ligand and solvent (runs 1–4). These results indicate that the aryl iodide possesses high reactivity toward palladium-catalyzed vinylation. In contrast to **17a** and **17b**, the reaction of 4-iodoaniline (**17c**) resulted in poor yield (20%) (run 6), similarly to 4-bromoaniline. Unfortunately, *N*-allylation proceeded sluggishly under neutral conditions to give the product in low yield from a complex mixture of unknown compounds.[12] This loss of selectivity may be due to the high reactivity of aryl iodide towards Pd(0). The present vinylation, however, is suitable for the preparation of 2- or 3-(1,1-dimethylallyl)anilines (**15a**, **b**, **c**) (run 2 in Table 2, runs 4 and 5 in Table 3).

As reported previously,[2] chemoselectivity for *N*-allylation and *C*-vinylation can be explained by the selective formation of a π-allyl palladium complex (**18**) under neutral conditions or of a σ-aryl palladium complex (**22**) under basic conditions (Scheme 3). But the question remains: how does changing the basicity of the solution control the selectivity of formation of these complexes?

Pd(0) is more reactive towards the Ar–X bond than allyl alcohol in organic solvent because the reaction of aryl halide with Pd(0) selectively forms a σ-complex in the presence of allyl alcohol to give cross-coupled products.[4] In general, allyl alcohol does not react with Pd(0) in an organic solvent; a Lewis acid or highly activated palladium catalyst is required in order to form the π-allyl palladium complex. However, the reactivity of Pd(0) is quite different in aqueous solution.[7] The π-allyl palladium complex is formed directly from allyl alcohol in aqueous solution without any additives, as mentioned in the introduction.[8] Kobayashi also found that carboxylic acid enhanced the formation of the π-allyl complex in aqueous solution.[13] In contrast, the formation of a σ-complex

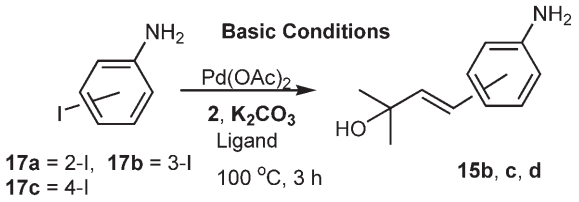
Table 2. Palladium-catalyzed vinylation of haloanilines **11** under basic conditions.



Run	**11**	Ligand	Solvent	Time [h]	**15** [%]	SM (**7**) Recov. [%]
1	**11a**	TPPTS	H_2O	4[a]	34	40
2		DPPF	H_2O	4[a]	61	-
3		TPPTS	Toluene	4	26	-
4		TPPTS	Toluene-H_2O[c]	4	54	-
5	**11b**	TPPTS	H_2O	3	27	-
6		DPPF	H_2O	3	39	-
7		TPPTS	Toluene-H_2O[c]	3	3	49
8		DPPF	Toluene-H_2O[c]	3	67	-
9	**11c**	TPPTS	H_2O	3	57	-
10		DPPF	H_2O	3	31[b]	7
11		TPPTS	Toluene-H_2O[c]	3	74	-
12		DPPF	Toluene-H_2O[c]	3	19	28
13		TPPTS	H_2O	3	17	11
14	**11d**	DPPF	H_2O	3	33	-
15		DPPF	Toluene-H_2O[c]	2	24	-

[a] Temperature: 130 °C.
[b] Compound **16** was formed in 23% yield.
[c] Toluene:H_2O = 1:1.

Table 3. Palladium-catalyzed vinylations of iodoanilines **17** under basic conditions.



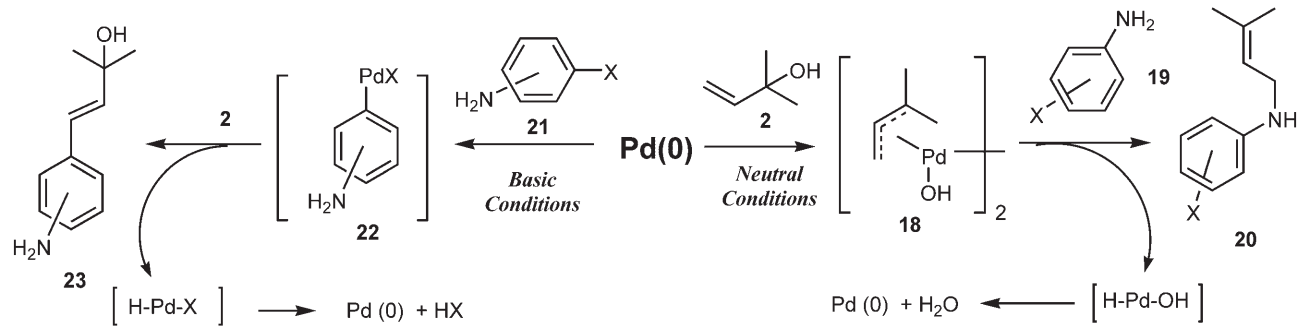
Run	**17**	Ligand	Solvent	Product **15** [%]
1	2-I (**17a**)	TPPTS	H_2O	61
2		DPPF	H_2O	53
3		DPPF	Toluene-H_2O[a]	62
4		TPPTS	EtOH-H_2O[b]	79
5	3-I (**17b**)	TPPTS	H_2O	74
6	4-I (**17c**)	TPPTS	H_2O	20

[a] Toluene:H_2O = 1:1.
[b] EtOH:H_2O = 1:1.

might be inhibited under neutral conditions by suppression of Pd(0) regeneration due to the absence of base, which neutralizes HX formed through decomposition of [H–Pd–X] during the reaction. Therefore, under neutral conditions, formation of the *N*-allylated product **20** is favored over that of the *C*-vinylated product **23**. To find out whether the reactivity of *N*-allylation was changed by the basicity of the aqueous solution, the reaction of aniline (**24**) with **2** was selected as a model (Table 4). Palladium-catalyzed allylation proceeded smoothly under neutral to weakly acidic conditions to give a mixture of mono- (**25**) and diallylaniline (**26**) in excellent yields (71–86%) (runs 1–3); however, the yield was significantly reduced under basic conditions (run 4). These results demonstrate that the rate of *N*-allylation is reduced by the presence of base.

If the chemoselective reaction of *ortho*-haloanilines (**11b** or **17a**) proceeded successively, a convenient synthesis of heterocyclic compounds might be possible (Scheme 4); *N*-allylation followed by vinylation would give a 3-alkylindole (**28**) (Route A), while the reverse would give the quinoline derivative **29** (Route B).

First, the palladium-catalyzed intramolecular cyclization of **27** (X = I or Br) was attempted to investigate the possibility of a one-pot synthesis *via* route A. Unfortunately, the reaction did not give **28** and was accompanied by recovery of starting material. Since this low reactivity was thought to be due to steric hin-

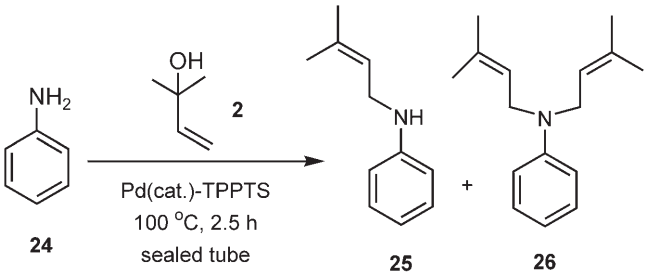


Scheme 3. Pathway of the palladium-catalyzed reaction of haloaniline **21**.

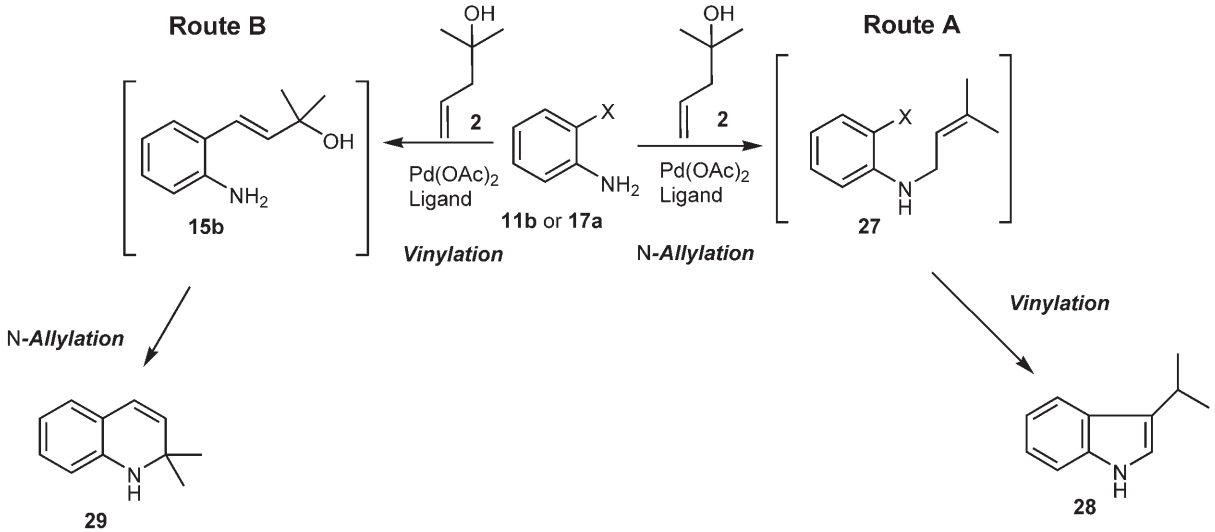
drance by the dimethyl group during intramolecular cyclization of **27**, a one-pot reaction of 2-iodoaniline (**17a**) with a less hindered allyl alcohol (**30**) was attempted (Scheme 5). During the reaction of **17a** with **30** under neutral conditions, formation of **31** was observed by TLC. Et_3N in EtOH was then added to the mixture,[14] which was kept at 70 °C for 3 h. 3-Methylindole (**32**) was formed smoothly in 63 % overall yield from **17a**.

Next, a one-pot synthesis of a quinoline derivative was attempted (Scheme 6). After the reaction of **17a** with **2** under basic conditions, the reaction mixture was neutralized to pH 7 by the addition of AcOH and heated at 100 °C for 3 h. However, only starting material was recovered (**17a**, 21 %) without formation of the cyclized product **29**. Therefore, the intramolecular *N*-allylation of pure **15b** under neutral conditions was carried out. The desired cyclized product **29** was obtained in moderate yield (42 %). We then attempted the one-pot reaction again with a different combination of ligand and solvent, but all of these attempts failed.[15] The highest yield of **15b** was 79 % (Table 3, run 4), and so the best overall yield of cyclized product **29** from **17a** was 33 % in a two-step synthesis.

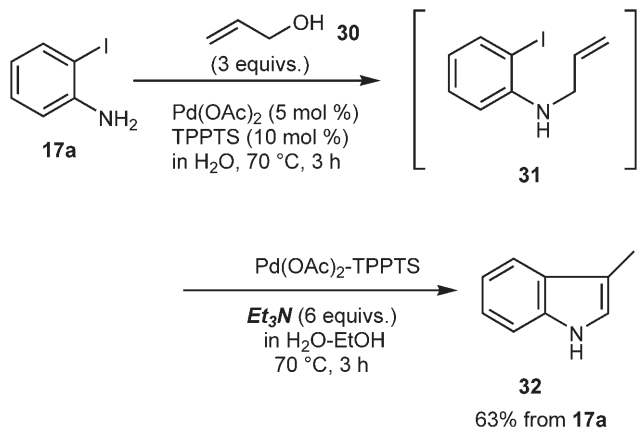
Table 4. Palladium-catalyzed allylation of aniline **24** under neutral conditions.



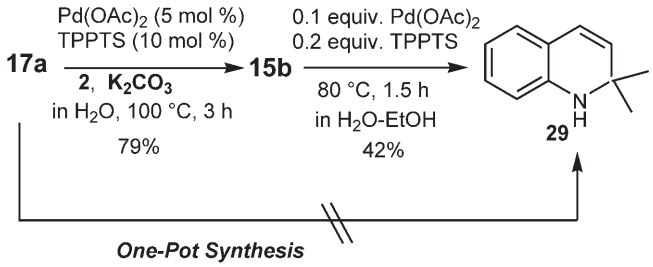
Run	Solvent	Base	Yield [%] (**25**:**26**)
1	H_2O	-	89 (56:44)
2	H_2O:AcOEt (2:1)	-	71 (88:12)
3	H_2O	KH_2PO_4 (3 equivs.)	86 (40:60)
4	H_2O	K_2CO_3 (3 equivs.)	37 (84:16)



Scheme 4. Synthetic plan for heterocycles.



Scheme 5. One-pot synthesis of 3-methylindole **32**.



Scheme 6. One-pot synthesis of 2,2-dimethylquinoline **29**.

Conclusions

The present study clearly demonstrates that palladium-catalyzed reactions of haloanilines (**11** or **17**) with 1,1-dimethylallyl alcohol (**2**) show complete chemoselectivity in aqueous media; *C*-vinylation occurs under basic conditions and *N*-allylation occurs under neutral conditions to give the products in practical yields (up to 79%), with the exception of the vinylation of 4-haloanilines (**11d** and **17c**). The results also indicate that H_2O plays an important role in this chemoselectivity, allowing a one-pot synthesis of 3-methylindole (**31**). The chemoselectivity demonstrated here is synthetically useful because the reactive position of haloanilines could be controlled by simply changing the basicity of the reaction medium, eliminating the need for protection of the amino group during the reaction.

Experimental Section

General Remarks

All reagents and solvents were obtained commercially and used as received unless otherwise indicated. All melting points were determined on a Yanagimoto micro-melting hot stage apparatus and are uncorrected. All reactions were carried out under argon atmosphere. IR spectra were recorded as KBr tablets (unless otherwise stated) on a JASCO FT/IR-230 spectrometer. NMR spectra were recorded on a JEOL GX-400 (400 MHz) spectrometer (unless otherwise stated) with tetramethylsilane as the internal reference. The following abbreviations were used: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; br, broad; dif, diffused; Ar, aromatic. EI-mass spectra and high resolution mass spectra were measured with a JEOL JMS-01SG-2 or JMS-AM-II-50 spectrometer using a direct inlet system. FAB-mass spectra were measured with a JEOL JMS-600H spectrometer using a direct inlet system.

Typical Procedure for Palladium-Catalyzed Reaction of Haloanilines (11a–d and 17a– c) with 1,1-Dimethylallyl Alcohol (2)

A mixture of haloaniline (1.0 mmol), 1,1-dimethylallyl alcohol (5.0 mmol), $Pd(OAc)_2$ (0.10 mmol), and ligand (0.20 mmol) [with K_2CO_3 (1.5 mmol) in the case of basic conditions] in H_2O (4 mL) was heated with stirring in a sealed tube at the temperatures and reaction times indicated in the tables. Then the mixture was poured into water and saturated with K_2CO_3, and the whole was extracted with benzene three times. The combined organic layer was washed with saturated NaCl and dried over $MgSO_4$. After evaporation of the solvent, the resulting oil was purified by silica gel chromatography (hexane:AcOEt). Yields are given in Table 1, Table 2, and Table 3, and the analytical details of the products **12a–d**, **13c**, **d**, **15a–d**, and **16** are listed in the Supporting Information.

Typical Procedure for Palladium Catalyzed Reaction of Aniline (24) with 1,1-Dimethylallyl Alcohol (2)

A mixture of aniline (**24**, 0.25 mmol), 1,1-dimethylallyalcohol (**2**, 0.75 mmol), $Pd(OAc)_2$ (0.025 mmol), and TPPTS (**9**) (0.05 mmol) [with additives (0.38 mmol) as indicated in Table 4] in H_2O (0.20 mL) was heated with stirring in a sealed tube at 100 °C for 2.5 h. Then the mixture was directly subjected to silica gel chromatography (hexane:AcOEt) for purification. The yields were given in Table 4, and the spectral data of **25** and **26** are identical with reported data.[7g]

On-Pot Synthesis of 3-Methylindole (32) from 2-Iodoaniline (17a) and Allyl Alcohol (30)

A mixture of 2-iodoaniline (**17a**, 55 mg, 0.25 mmol), allyl alcohol (**30**, 50 μL, 0.75 mmol), $Pd(OAc)_2$ (5.5 mg, 0.025 mmol), and TPPTS (**9**, 28 mg, 0.05 mmol) in H_2O (0.20 mL) was heated with stirring in a sealed tube at 70 °C for 3 h. Then Et_3N (210 μL, 2.0 mmol) and EtOH (1.5 mL) were added to the reaction mixture and the mixture was stirred for 3 h at 70 °C. AcOEt was added to the reaction mixture and the organic layer was washed with saturated NaCl and dried over $MgSO_4$. After evaporation of the solvent, the resulting residue was purified by silica-gel chromatography to give 3-methylindole (**32**) as a pale brown solid; yield: 21 mg (63%).

Synthesis of 1,1-Dimethyldihydroquinoline (29) by Palladium-Catalyzed Cyclization of 15b

A mixture of **15b** (45 mg, 0.26 mmol), $Pd(OAc)_2$ (6 mg, 0.027 mmol), and TPPTS (**9**, 30 mg, 0.053 mmol) in EtOH-

H_2O (1:1, 1.2 mL) was heated with stirring in a sealed tube at 80 °C for 1.5 h. Then the mixture was poured into saturated $NaHCO_3$, and the whole was extracted with AcOEt three times. The combined organic layer was washed with saturated NaCl and dried over $MgSO_4$. After evaporation of the solvent, the resulting oil (0.179 g) was purified by silica gel chromatography (hexane:AcOEt) to give pure 2,2-dimethyldihydroquinoline (**29**) as an pale yellow oil; yield: 0.017 g (42 %).

Supporting Information

Analytical details of the products **29** and **32** are given in the Supporting Information.

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