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Pd-Catalyzed Dehydrogenative Oxidation of Alcohols to Functionalized Molecules

Takamichi Mori,*[,†] Chihiro Ishii,[‡] and Masanari Kimura*[,‡]

[†]Department of Applied Chemistry, Faculty of Engineering, Sanyo-Onoda City University, 1-1-1 Daigakudori, Sanyo-Onoda, Yamaguchi 756-0884, Japan

[‡]Graduate School of Engineering, Nagasaki University, 1-14 Bunkyo machi, Nagasaki 852-8521, Japan

Supporting Information

ABSTRACT: A dehydrogenative oxidation reaction of primary alcohols to aldehydes catalyzed by a simple Pd/Xantphos catalytic system was developed under an argon or nitrogen atmosphere without oxidizing agents or hydrogen acceptors. The reaction product could be easily changed: under aerobic conditions, esters were obtained in aprotic solvents, whereas the corresponding carboxylic acids were produced in aqueous media. These oxidizing processes were applicable to the efficient synthesis of useful nitrogen-containing heterocyclic compounds such as indole, quinazoline, and benzimidazole via intramolecular versions of this reaction from amino alcohols.

KEYWORDS: *oxidation, hydrogen transfer, palladium, aldehyde, ester, carboxylic acid*

INTRODUCTION

The selective oxidation of alcohols to the corresponding carbonyl compounds is one of the most fundamental and useful transformations in both organic synthesis and industrial chemistry.[1] Various classical methods for the oxidation of alcohols have been well-developed to date, for example, the use of stoichiometric amounts of oxidizing agents such as chromium salts or MnO_2,[2] Swern oxidizing agents,[3] and the Dess−Martin reagent,[4] all of which produce large amounts of inorganic or organic toxic waste as byproducts.[5] Hydrogen transfer oxidation reactions without any oxidizing reagents are among the most straightforward and superior protocols from a green chemistry viewpoint.[6] Although dehydrogenative oxidations of alcohols to aldehydes,[7−10] esters,[11,12] and carboxylic acids catalyzed by homogeneous transition metals (e.g., ruthenium, rhodium, and iridium; Figure 1) are known,[13] each product requires its own catalytic system. From this point of view, it would be worthwhile to develop a new industrially relevant catalytic system that can control the selective oxidation of alcohols.

We recently found that Pd/Xantphos catalysts can be used for efficient dehydrogenative carbonyl−ene-type reactions of aldehydes in the presence of conjugated dienes to provide dienyl alcohols.[14] In that case, the Pd/Xantphos catalytic system promotes the dehydrogenative coupling reaction between the aldehyde and the conjugated diene via β-hydride elimination of the key oxapalladacycle intermediate. Thus, the

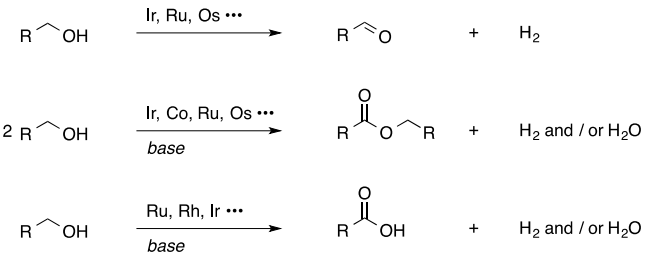

Figure 1. Dehydrogenation reactions of alcohols to aldehydes, esters, and carboxylic acids.

formed Pd/Xantphos complex seems to achieve dehydrogenation from the alkylpalladium intermediate.

Herein we disclose a Pd/Xantphos catalytic system that accelerates the transformation of primary alcohols to aldehydes via dehydrogenative oxidation processes. A similar catalytic system under aerobic conditions also provides an easy route to esters and carboxylic acids (Figure 2). Furthermore, these

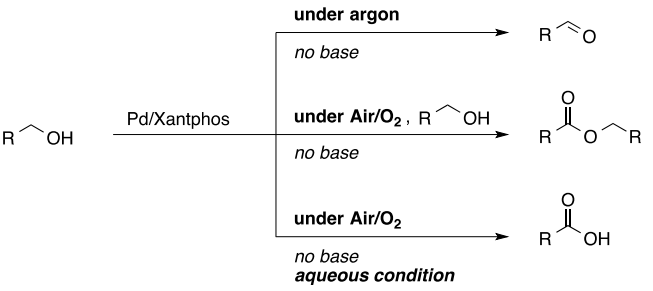

Figure 2. Pd/Xantphos-catalyzed selective oxidation reactions of alcohols.

oxidizing reactions are amenable to the efficient synthesis of useful nitrogen-containing heterocyclic compounds such as indole, quinazoline, and benzimidazole via acceptorless dehydrogenative condensation from the corresponding amino alcohols.

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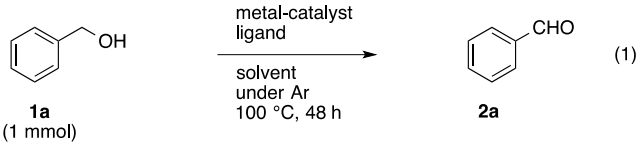
RESULTS AND DISCUSSION

The dehydrogenative oxidations of benzyl alcohol (**1a**) to benzaldehyde (**2a**) using various kinds of palladium catalysts, solvents, and ligands under argon were investigated, and the results are shown in Table 1. $Pd(OAc)_2$ was used as a catalyst

Table 1. Optimization of the Reaction Conditions for the Oxidation of Alcohols under Ar[a]



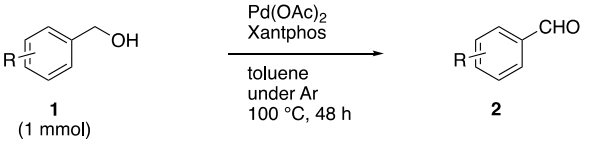
entry	metal catalyst	ligand (mmol)	solvent	yield of **2a** (%)[b]
1	none	none	toluene	0
2	$Pd(OAc)_2$	none	toluene	6
3	$Pd(OAc)_2$	PPh_3 (0.1)	toluene	3
4	$Pd(OAc)_2$	PCy_3 (0.1)	toluene	13
5	$Pd(OAc)_2$	$(n\text{-Bu})_3P$ (0.1)	toluene	17
6	$Pd(OAc)_2$	Xphos (0.1)	toluene	52
7	$Pd(OAc)_2$	dppb (0.05)	toluene	35
8	$Pd(OAc)_2$	dppf (0.05)	toluene	74
9	$Pd(OAc)_2$	DPEphos (0.05)	toluene	33
10	$Pd(OAc)_2$	Xantphos (0.05)	toluene	90
11	$PdCl_2$	Xantphos (0.05)	toluene	9
12	$Pd_2(dba)_3$	Xantphos (0.05)	toluene	42
13	$Pd(acac)_2$	Xantphos (0.05)	toluene	25
14	$Pd(PPh_3)_2Cl_2$	Xantphos (0.05)	toluene	13
15	$Pd(OAc)_2$	Xantphos (0.05)	DMF	23
16	$Pd(OAc)_2$	Xantphos (0.05)	DMA	12
17	$Pd(OAc)_2$	Xantphos (0.05)	1,4-dioxane	trace
18[c]	$Pd(OAc)_2$	Xantphos (0.05)	THF	50

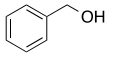
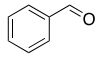
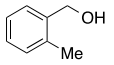
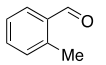
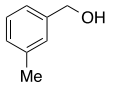
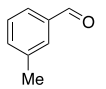
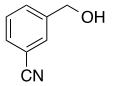
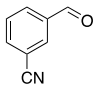
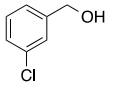
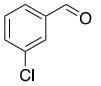
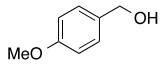
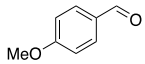
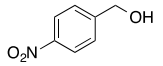
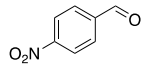
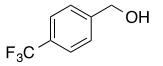
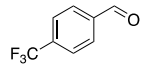
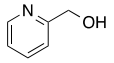
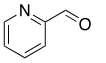
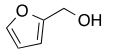
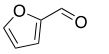
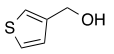
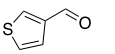
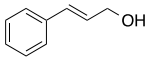
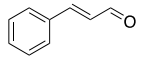
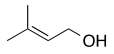
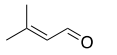
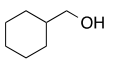
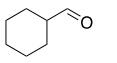
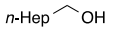
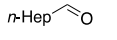
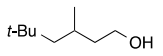
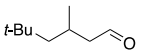
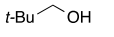
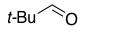
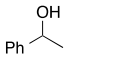
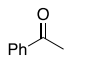
[a]The reaction was undertaken in the presence of alcohol **1a** (1.0 mmol), transition-metal catalyst (0.05 mmol) and ligand (0.05–0.1 mmol) in solvent (3 mL) at 100 °C for 48 h under argon. [b]Determined by NMR analysis using ferrocene as an internal standard. [c]The reaction temperature was 60 °C.

in the absence of a ligand or in the presence of a wide variety of ligands. In the presence of monodentate phosphine ligands such as PPh_3, PCy_3, $(n\text{-Bu})_3P$, and Xphos, low to moderate catalytic formation of benzaldehyde occurred (3–52% yield; Table 1, entries 3–6). Bidentate phosphine ligands such as dppp, dppf, DPEphos, and Xantphos tended to show higher reactivity than the monodentate phosphine ligands (Table 1, entries 7–10). In the presence of 0.05 mmol of $Pd(OAc)_2$ with 0.05 mmol of Xantphos under an argon atmosphere, benzaldehyde was obtained in 90% yield (Table 1, entry 10). Next, we examined the reactions with various kinds of palladium catalysts under argon at atmospheric pressure (Table 1, entries 11–14). It became clear that a combination of $Pd(OAc)_2$ and a Xantphos ligand was the most effective catalytic system for these dehydrogenative oxidation processes. Various solvents such as toluene, DMF, DMA, 1,4-dioxane, and THF were used, and it was found that toluene at 100 °C provided the most efficient dehydrogenative oxidation of benzyl alcohol to benzaldehyde (Table 1, entries 15–18).

Using these optimized catalytic conditions, we studied the dehydrogenative oxidation reactions of different benzyl alcohol derivatives **1** to give the corresponding aldehydes **2**, and these results are summarized in Table 2. As the oxidation of **1a** in the

Table 2. Pd/Xantphos-Catalyzed Dehydrogenation Reaction under Ar[a,b]



entry	alcohols		products	yield (%)
1		**1a**		**2a**: 90
2		**1b**		**2b**: 76
3		**1c**		**2c**: 67
4		**1d**		**2d**: 76
5		**1e**		**2e**: 33
6		**1f**		**2f**: 80
7		**1g**		**2g**: 91
8		**1h**		**2h**: 61
9		**1i**		**2i**: 85
10		**1j**		**2j**: 85
11		**1k**		**2k**: 84
12		**1l**		**2l**: 76
13		**1m**		**2m**: 93
14		**1n**		**2n**: 57
15		**1o**		**2o**: 40
16		**1p**		**2p**: 35
17		**1q**		**2q**: 27
18		**1r**		**2r**: 99

[a]The reactions were undertaken in the presence of alcohols **1** (1.0 mmol), $Pd(OAc)_2$ catalyst (0.05 mmol), and Xantphos (0.05 mmol) in toluene (3 mL) at 100 °C for 48 h under argon. [b]Yields were determined by NMR analysis using ferrocene as an internal standard.

presence of Pd/Xantphos in toluene afforded **2a** in 90% yield (Table 2, entry 1), we also performed experiments with benzyl alcohol derivatives bearing electron-donating and electron-withdrawing groups. The reaction of the sterically demanding alcohol 2-methylbenzyl alcohol (**1b**) proceeded to give the corresponding aldehyde **2b** in 76% yield (Table 2, entry 2). The reactions of 2-pyridinemethanol (**1i**), furfuryl alcohol (**1j**), and 3-thiophenemethanol (**1k**) proceeded to afford **2i**, **2j**, and

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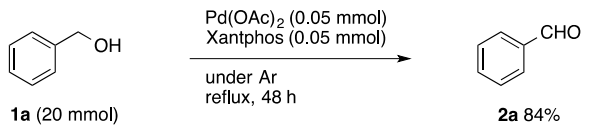
2k, respectively, in high yields (Table 2, entries 9−11). The oxidation of cinnamyl alcohol (**1l**) and 3-methyl-2-buten-1-ol (**1m**) also provided the corresponding α,β-unsaturated aldehydes **2l** and **2m**, respectively (Table 2, entries 12 and 13). Moreover, aliphatic primary alcohols were tolerated and provided the expected aldehydes, albeit in modest yields (Table 2, entries 14−17). A *sec*-alkyl alcohol, 1-methylbenzyl alcohol, afforded the desired ketone in quantitative yield (Table 2, entry 18). Furthermore, we succeeded in extending the reaction to a multigram scale for the efficient synthesis of aldehydes from alcohols (Scheme 1).

Scheme 1. Multigram-Scale Synthesis of Aldehyde 2a[a]

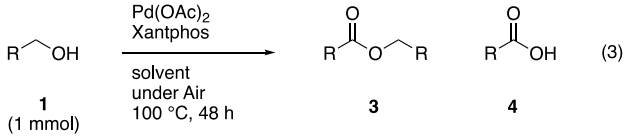


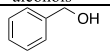
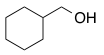
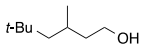
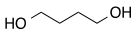
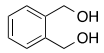
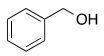
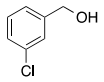
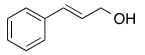
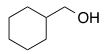
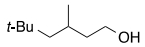
[a]The reaction was undertaken in the presence of alcohol **1a** (2.16 g, 20.0 mmol), $Pd(OAc)_2$ catalyst (0.05 mmol), and Xantphos (0.05 mmol) at reflux for 48 h under an argon atmosphere without solvent. Aldehyde **2a** was isolated in 84% yield (1.78 g, 16.8 mmol), and distilled using a Kugelrohr apparatus (bp 80 °C, 30 mmHg).

The products of the oxidation of alcohols promoted by Pd/Xantphos could be changed to favor the formation of esters by performing the reaction under aerobic conditions instead of an argon atmosphere (Table 3). Esters were obtained as the main products with 2 equiv of the alcohols. The esterification reactions of benzyl alcohol, cyclohexylmethanol, and 3,5,5-trimethyl-1-hexanol gave the corresponding esters in good yields (Table 3, entries 1−3). The oxidation reactions of 1,4-butanediol and 1,2-benzenedimethanol under aerobic conditions proceeded to provide the expected lactones via intramolecular oxidative cyclization (Table 3, entries 4 and 5). When water was used as the solvent instead of an aprotic solvent, carboxylic acids were readily produced exclusively. The reactions of the benzyl alcohol derivatives proceeded to give the corresponding benzoic acids (Table 3, entries 6 and 7). Oxidation of cinnamyl alcohol provided cinnamic acid (**4l**) in 59% yield, and aliphatic primary alcohols also participated in a similar oxidation process to afford the corresponding aliphatic carboxylic acids **4n** and **4p** in 88% and 47% yield, respectively (Table 3, entries 8−10).

A series of these oxidation reactions were applicable to the synthesis of nitrogen-containing heterocycles such as indoles and quinazolines via acceptorless dehydrogenative condensation of amino alcohols (Tables 4 and 5).[15] When 2-(2-aminophenyl)ethanol (**5a**) was treated with Pd/Xantphos under argon at atmospheric pressure, indole (**6a**) was obtained via an intramolecular cyclization in high yield. We examined the scope of the reaction with various 2-(2-aminophenyl)-ethanol derivatives under similar catalytic conditions, and substrates bearing an electron-donating or electron-withdrawing group were also tolerated (Table 4). Furthermore, when 2-aminobenzylamine and benzyl alcohols were treated under similar catalytic conditions, quinazoline frameworks were constructed via intermolecular oxidative condensation in a single operation. Some representative examples of the oxidative coupling reactions of substituted benzyl alcohols and 2-aminobenzylamine are summarized in Table 5. Irrespective of the electronic nature of the benzyl alcohol, substituted benzyl alcohols such as 4-methoxybenzyl alcohol

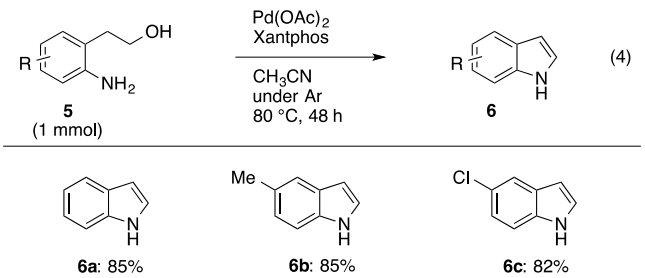
Table 3. Pd/Xantphos-Catalyzed Oxidation Reactions under Aerobic Conditions[a,b]



entry	alcohols		solvent	product: **3** (%)	product: **4** (%)
1		**1a**	toluene	**3a**: 85	nd
2		**1n**	PhCl	**3n**: 86	nd
3		**1p**	PhCl	**3p**: 82	nd
4		**1s**	toluene	**3s**: 57	nd
5		**1t**	toluene	**3t**: 90	nd
6[c]		**1a**	H_2O	nd	**4a**: 70
7[c]		**1e**	H_2O	nd	**4e**: 65
8[c]		**1l**	H_2O	nd	**4l**: 59
9[c]		**1n**	H_2O	nd	**4n**: 88
10[c]		**1p**	H_2O	nd	**4p**: 47

[a]The reactions were undertaken in the presence of alcohols **1** (1.0 mmol), $Pd(OAc)_2$ catalyst (0.05 mmol), and Xantphos (0.05 mmol) in the solvent (3 mL) at 100 °C for 48 h under aerobic conditions. [b]Yields were determined by NMR analysis using ferrocene as an internal standard. [c]The reaction was performed at reflux temperature.

Table 4. Synthesis of Indoles via Oxidation of Alcohols Catalyzed by Pd/Xantphos[a,b]



[a]The reactions were undertaken in the presence of amino alcohols **5** (1.0 mmol), $Pd(OAc)_2$ catalyst (0.05 mmol), and Xantphos (0.05 mmol) in CH_3CN (3 mL) at 80 °C for 48 h under argon. [b]Isolated yields are shown.

and 4-nitrobenzyl alcohol provided the desired heterocyclic compounds **8b** and **8c** (Table 5). Although 4-trifluoromethyl-substituted benzyl alcohol did not give the corresponding product in high yield, this procedure is clearly useful for the simple synthesis of fluorinated nitrogen-containing heterocyclic compounds.

The dehydrogenative coupling reaction of 1,2-phenylenediamine with benzyl alcohol is also a straightforward synthetic route to benzimidazole (Scheme 2). This coupling reaction proceeds via three-steps: dehydrogenation of the alcohol,

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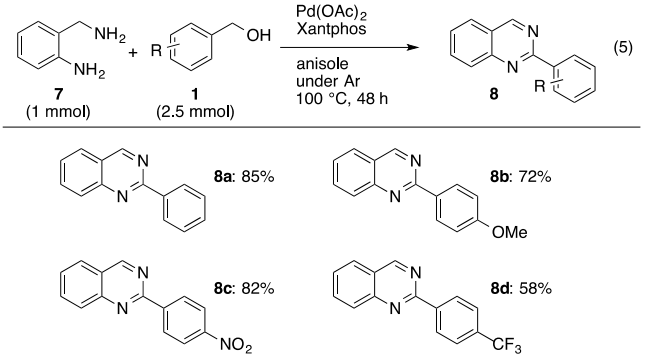
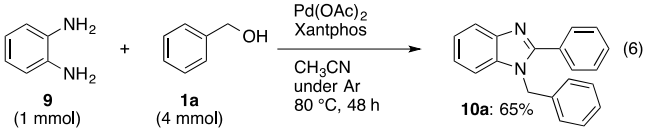
Table 5. Synthesis of Quinazolines via Oxidation of Alcohols Catalyzed by Pd/Xantphos[a,b]



[a]The reactions were undertaken in the presence of **7** (1.0 mmol), alcohols **1** (2.5 mmol), $Pd(OAc)_2$ catalyst (0.05 mmol), and Xantphos (0.05 mmol) in anisole (3 mL) at 100 °C for 48 h under argon. [b]Isolated yields are shown.

Scheme 2. Synthesis of Benzimidazole 10a via Oxidation of Alcohol 1a Catalyzed by Pd/Xantphos[a,b]



[a]The reaction was undertaken in the presence of **9** (1.0 mmol), **1a** (4.0 mmol), $Pd(OAc)_2$ catalyst (0.05 mmol), and Xantphos (0.05 mmol) in CH_3CN (3 mL) at 80 °C for 48 h under argon. [b]The isolated yield is shown.

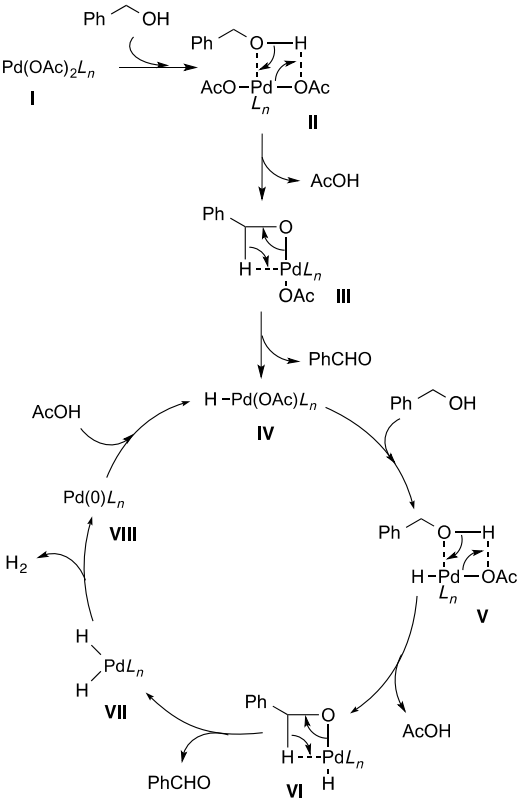
condensation of the diamine with the aldehyde, and dehydrogenation of the hemiaminal. It is noteworthy that the Pd/Xantphos catalytic system promotes the consecutive dehydrogenation and dehydration processes to provide important nitrogen-containing heterocycles such as quinazolines and benzimidazoles in a single manipulation (Table 5 and Scheme 2).

A plausible reaction mechanism for the dehydrogenative oxidation of benzyl alcohol to benzaldehyde is shown in Scheme 3. The $Pd(OAc)_2$/Xantphos complex might add to benzyl alcohol to provide coordinated benzyloxypalladium acetate **III** via σ-bond metathesis with the liberation of AcOH. This benzyloxypalladium acetate would readily undergo β-hydride elimination to form benzaldehyde along with palladium hydride complex **IV**.[11g] Bidentate phosphine ligands with a large bite angle, such as Xantphos, seem to prefer the β-hydride elimination to the reductive elimination.[16] Thus, the formed palladium hydride complex **IV** would undergo the exchange reaction with benzyl alcohol followed by a second σ-bond metathesis from intermediate **V** to afford dihydropalladium complex **VII** with the formation of benzaldehyde. The reductive elimination of hydrogen gas from dihydropalladium complex **VII** might proceed to give rise to Pd(0)/Xantphos.[11h,17] Oxidative addition of the generated AcOH to the Pd(0) species seems to provide palladium hydride complex **IV** as an active catalyst.[18]

■ CONCLUSION

We have developed a simple hydrogen transfer oxidation reaction that oxidizes primary alcohols to aldehydes and is

Scheme 3. Plausible Mechanism for the Oxidation of Benzyl Alcohol Catalyzed by Pd/Xantphos



promoted by Pd/Xantphos catalytic system under an argon or nitrogen atmosphere without oxidizing agents. Under aerobic conditions, esters are obtained in aprotic solvents, whereas the corresponding carboxylic acids are produced in aqueous media. These oxidizing processes can be applied to the efficient synthesis of useful nitrogen-containing heterocyclic compounds such as indoles, quinazolines, and benzimidazoles via intramolecular acceptorless dehydrogenative condensation from amino alcohols. All of the methods described herein would be convenient and straightforward synthetic methodologies toward the synthesis of physiologically active molecules and medicinal compounds.

■ EXPERIMENTAL SECTION

Reactions employed oven-dried glassware unless otherwise noted. Distillations were carried out in a Kugelrohr apparatus (SIBATA GTO-350RG glass tube oven). Boiling points are meant to refer to the oven temperature (±1 °C). Microanalyses were performed by the Instrumental Analysis Center of Nagasaki University. Thin-layer chromatography employed glass 0.25 mm silica gel plates with UV indicator (silica gel 60 F_{254}, Merck). Flash chromatography columns were packed with 230−400 mesh silica gel as a slurry in hexane. Gradient flash chromatography was conducted by elution with a continuous gradient from hexane to the indicated solvent. ^1H and ^{13}C NMR data were obtained with a JEOL GX400 NMR spectrometer using tetramethylsilane as an internal standard. Chemical shift values are given in parts per million downfield from the internal standard.

General Procedure 1: Pd/Xantphos-Catalyzed Oxidation of Alcohols to Aldehydes under Argon (Table 1, entry 10). To a solution of $Pd(OAc)_2$ (11.2 mg, 0.05 mmol)

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and Xantphos (28.9 mg, 0.05 mmol) in dry toluene (3 mL) was added benzyl alcohol (**1a**) (108.1 mg, 1.0 mmol) via syringe under an argon atmosphere. The mixture was stirred at 100 °C for 48 h, and the reaction was monitored by gas chromatography. The mixture was then dried ($MgSO_4$) and concentrated in vacuo. The NMR yield of benzaldehyde (**2a**) (90%) was determined using ferrocene as an internal standard.

*Benzaldehyde (**2a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (td, J = 6.8, 1.6 Hz, 2H), 7.63 (tt, J = 6.8, 1.6 Hz, 1H), 7.88 (dt, J = 6.8, 1.6 Hz, 2H), 10.02 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.9, 129.6, 134.4, 136.3, 192.3; MS (EI) m/z (relative intensity) 106 (M^+, 82), 105 (80), 77 (100), 51 (61).

*2-Methylbenzaldehyde (**2b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 3H), 7.25 (dd, J = 7.6, 1.4 Hz, 1H), 7.35 (td, J = 7.6, 1.4 Hz, 1H), 7.47 (td, J = 7.6, 1.4 Hz, 1H), 7.79 (dd, J = 7.6, 1.4 Hz, 1H), 10.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 126.3, 131.7, 132.0, 133.6, 134.1, 140.5, 192.7; MS (EI) m/z (relative intensity) 120 (M^+, 70), 119 (75), 91 (100), 65 (28).

*3-Methylbenzaldehyde (**2c**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.40−7.44 (m, 2H), 7.67−7.69 (m, 2H), 9.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 127.2, 128.9, 130.0, 135.3, 136.5, 138.9, 192.6; MS (EI) m/z (relative intensity) 120 (M^+, 75), 119 (85), 91 (100), 65 (32).

*m-Formylbenzonitrile (**2d**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (t, J = 7.8 Hz, 1H), 7.92 (dt, J = 7.8, 1.4 Hz, 1H), 8.13 (dt, J = 7.8, 1.4 Hz, 1H), 8.18 (t, J = 1.4 Hz, 1H), 10.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.8, 117.5, 130.1, 133.2, 133.3, 136.9, 137.2, 189.9; MS (EI) m/z (relative intensity) 131 (M^+, 70), 130 (100), 102 (58), 76 (30), 50 (25).

*m-Chlorobenzaldehyde (**2e**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (t, J = 7.8 Hz, 1H), 7.59 (dt, J = 7.8, 1.2 Hz, 1H), 7.76 (dt, J = 7.8, 1.2 Hz, 1H), 7.85 (t, J = 1.2 Hz, 1H), 9.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.9, 129.2, 130.3, 134.3, 135.4, 137.7, 190.8; MS (EI) m/z (relative intensity) 140 (M^+, 82), 139 (100), 111 (70), 75 (40), 50 (42).

*p-Anisaldehyde (**2f**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 7.00 (dd, J = 7.8, 1.8 Hz, 2H), 7.84 (dd, J = 7.8, 1.8 Hz, 2H), 9.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 114.2, 129.8, 131.9, 164.5, 190.7; MS (EI) m/z (relative intensity) 136 (M^+, 78), 135 (100), 107 (25), 92 (25), 77 (48).

*p-Nitrobenzaldehyde (**2g**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, J = 7.5, 2.0 Hz, 2H), 8.41 (dd, J = 7.5, 2.0 Hz, 2H), 10.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.2, 130.4, 140.0, 151.0, 190.3; MS (EI) m/z (relative intensity) 151 (M^+, 100), 150 (86), 105 (25), 77 (76), 51 (98).

*4-(Trifluoromethyl)benzaldehyde (**2h**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, J = 7.2, 1.6 Hz, 2H), 8.02 (dd, J = 7.2, 1.6 Hz, 2H), 10.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.1, 126.1, 129.9, 135.6, 138.6, 191.1; MS (EI) m/z (relative intensity) 174 (M^+, 73), 145 (100), 125 (20), 95 (25), 75 (25), 50 (35).

*2-Pyridinecarbaldehyde (**2i**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 1H), 7.89 (td, J = 5.2, 0.8 Hz, 1H), 7.98 (dd, J = 8.0, 0.8 Hz, 1H), 8.81 (dd, J = 5.2, 0.8 Hz, 1H), 10.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.6, 127.8, 137.0, 150.1, 152.6, 193.3; MS (EI) m/z (relative intensity) 107 (M^+, 25), 79 (100), 78 (47), 52 (83), 51 (77).

*Furfural (**2j**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (dd, J = 3.4, 1.2 Hz, 1H), 7.26 (dd, J = 3.4, 0.8 Hz, 1H), 7.70 (d, J = 1.2 Hz, 1H), 9.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.6, 120.9, 148.0, 1530, 177.9; MS (EI) m/z (relative intensity) 96 (M^+, 100), 95 (87), 39 (63), 29 (20).

*3-Thiophenecarbaldehyde (**2k**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 1H), 7.55 (dd, J = 5.0, 1.4 Hz, 1H), 8.13 (dd, J = 3.0, 1.4 Hz, 1H), 9.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 125.3, 127.4, 136.7, 143.0, 184.9; MS (EI) m/z (relative intensity) 112 (M^+, 97), 111 (100), 83 (38), 45 (36).

*trans-Cinnamaldehyde (**2l**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (dd, J = 16.0, 7.6 Hz, 1H), 7.42−7.49 (m, 4H), 7.55−7.57 (m, 2H), 9.71 (dd, J = 7.6, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.4, 128.5, 129.0, 131.2, 133.9, 152.7, 193.6; MS (EI) m/z (relative intensity) 132 (M^+, 72), 131 (100), 103 (48), 77 (55), 51 (60).

*3-Methyl-2-butenal (**2m**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99 (d, J = 0.8 Hz, 3H), 2.18 (d, J = 0.8 Hz, 3H), 5.89 (dqq, J = 8.4, 0.8, 0.8 Hz, 1H), 9.96 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 26.9, 127.8, 160.3, 190.8; MS (EI) m/z (relative intensity) 84 (M^+, 100), 55 (76), 41 (43), 29 (37).

*Cyclohexanecarbaldehyde (**2n**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.43 (m, 5H), 1.65−1.82 (m, 3H), 1.85−1.91 (m, 2H), 2.21−2.26 (m, 1H), 9.62 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 25.9, 49.9, 205.0; MS (EI) m/z (relative intensity) 112 (M^+, 10), 83 (27), 68 (25), 55 (100), 41 (50).

*Octanal (**2o**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (m, 3H), 1.30 (m, 8H), 1.63 (m, 2H), 2.42 (m, 2H), 9.77 (t, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.1, 22.6, 29.0, 29.1, 31.6, 43.9, 202.9; MS (EI) m/z (relative intensity) 128 (M^+, 1), 110 (10), 84 (50), 69 (25), 56 (55), 43 (100).

*3,5,5-Trimethylhexanal (**2p**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 9H), 1.02 (d, J = 7.2 Hz, 3H), 1.16−1.27 (m, 2H), 2.13−2.21 (m, 1H), 2.23−2.30 (m, 1H), 2.37−2.41 (m, 1H), 9.74 (t, J = 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 24.7, 29.9, 31.2, 50.8, 53.2, 203.1; MS (EI) m/z (relative intensity) 142 (M^+, 1), 109 (15), 98 (23), 83 (40), 57 (100), 41 (25).

*Pivaldehyde (**2q**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 9H), 9.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 42.5, 206.1; MS (EI) m/z (relative intensity) 86 (M^+, 32), 57 (100), 41 (80).

*Acetophenone (**2r**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59 (s, 3H), 7.44 (td, J = 7.8, 0.8 Hz, 2H), 7.55 (tt, J = 7.8, 0.8 Hz, 1H), 7.94 (dt, J = 7.8, 0.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 128.2, 128.4, 133.0, 137.0, 198.0; MS (EI) m/z (relative intensity) 120 (M^+, 46), 105 (100), 77 (90), 51 (50), 43 (25).

General Procedure 2: Pd/Xantphos-Catalyzed Oxidation of Alcohols to Esters/Carboxylic Acids under Aerobic Conditions (Table 3, entry 1). To a solution of $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and Xantphos (28.9 mg, 0.05 mmol) in dry toluene (3 mL) was added **1a** (108.1 mg, 1.0 mmol) via syringe under aerobic conditions. The mixture was stirred at 100 °C for 48 h, and the reaction was monitored by gas chromatography. The reaction mixture was dried ($MgSO_4$) and concentrated in vacuo, and the residual oil was subjected to column chromatography over silica gel (hexane/EtOAc = 4/1 v/v) to give **3a** (90.3 mg, 85% yield, R_f = 0.8).

*Benzyl Benzoate (**3a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (s, 2H), 7.26−7.57 (m, 8H), 8.08 (dd, J = 6.6, 1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 66.8, 128.2, 128.3, 128.5, 128.7, 129.8, 130.0, 133.1, 136.1, 166.5; MS (EI) m/z (relative

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intensity) 212 (M^+, 23), 194 (11), 105 (100), 91 (50), 77 (27), 65 (13), 51 (20).

*Cyclohexylmethyl Cyclohexanecarboxylate (**3n**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90−1.03 (m, 2H), 1.11−1.34 (m, 6H), 1.40−1.49 (m, 2H), 1.58−1.78 (m, 9H), 1.84−1.92 (m, 2H), 2.26−2.32 (m, 1H), 3.87 (d, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 25.7, 26.4, 29.1, 29.7, 37.2, 43.3, 69.3, 176.2; MS (EI) m/z (relative intensity) 224 (M^+, 1), 129 (13), 111 (15), 96 (100), 81 (76), 67 (25), 55 (90).

*3,5,5-Trimethylhexyl 3,5,5-Trimethylhexanoate (**3p**).* Diastereomeric mixture, **3p**/**3p′** = 60/40 as estimated by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$, major isomer) δ 0.89 (s, 9H), 0.91 (s, 9H), 0.95 (d, J = 6.4 Hz, 3H), 0.98 (d, J = 6.4 Hz, 3H), 1.01−1.12 (m, 2H), 1.21 (t, J = 4.0 Hz, 2H), 1.42−1.48 (m, 1H), 1.56−1.68 (m, 2H), 2.01−2.15 (m, 2H), 2.27−2.29 (m, 1H), 4.03−4.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer) δ 22.4, 22.7, 26.2, 26.6, 27.0, 29.9, 31.0, 31.1, 37.9, 44.1, 50.5, 62.7, 173.3; ^{1}H NMR (400 MHz, $CDCl_3$, minor isomer) δ 0.89 (s, 9H), 0.91 (s, 9H), 0.95 (d, J = 6.4 Hz, 3H), 0.98 (d, J = 6.4 Hz, 3H), 1.01−1.12 (m, 2H), 1.25 (t, J = 4.0 Hz, 2H), 1.42−1.48 (m, 1H), 1.56−1.68 (m, 2H), 2.01−2.15 (m, 2H), 2.30−2.32 (m, 1H), 4.03−4.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, minor isomer) δ 22.5, 22.7, 26.2, 26.6, 27.0, 29.9, 31.0, 31.1, 37.9, 44.1, 51.0, 62.7, 173.3; MS (EI) m/z (relative intensity) 284 (M^+, 1), 269 (5), 159 (23), 141 (25), 126 (32), 115 (42), 70 (83), 57 (100).

*γ-Butyrolactone (**3s**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (dquin, 2H), 2.50 (td, 2H), 4.36 (td, J = 7.6, 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 27.5, 68.3, 177.6; MS (EI) m/z (relative intensity) 86 (M^+, 50), 56 (42), 42 (100).

*Phthalide (**3t**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (s, 2H), 7.51 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.70 (t, J = 7.6 Hz, 1H), 7.92 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.6, 122.1, 125.7, 129.0, 146.5, 171.1; MS (EI) m/z (relative intensity) 134 (M^+, 43), 105 (100), 77 (69), 51 (30).

*Benzoic Acid (**4a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (td, J = 8.0, 2.0 Hz, 2H), 7.63 (tt, J = 8.0, 2.0 Hz, 1H), 8.13 (dt, J = 8.0, 2.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.5, 129.3, 130.2, 133.8, 172.4; MS (EI) m/z (relative intensity) 122 (M^+, 83), 105 (100), 77 (82), 51 (60).

*m-Chlorobenzoic Acid (**4e**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (td, J = 7.6, 1.6 Hz, 1H), 7.60 (dt, J = 7.6, 1.6 Hz, 1H), 8.01 (dt, J = 7.6, 1.6 Hz, 1H), 8.10 (t, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.3, 129.8, 130.3, 130.9, 133.9, 134.7, 170.9; MS (EI) m/z (relative intensity) 156 (M^+, 82), 139 (100), 111 (52), 75 (35), 50 (29).

*trans-Cinnamic Acid (**4l**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (d, J = 16.0 Hz, 1H), 7.25−7.43 (m, 3H), 7.56 (dd, J = 7.2, 2.0 Hz, 2H), 7.81 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 117.3, 128.4, 128.9, 130.7, 134.0, 147.1, 172.5; MS (EI) m/z (relative intensity) 148 (M^+, 75), 147 (100), 131 (25) 103 (47), 77 (50), 51 (62).

*Cyclohexanecarboxylic Acid (**4n**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22−1.34 (m, 3H), 1.41−1.48 (m, 2H), 1.63−1.66 (m, 1H), 1.75−1.77 (m, 2H), 1.92−1.96 (m, 2H), 2.30−2.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 25.7, 28.8, 42.9, 182.5; MS (EI) m/z (relative intensity) 128 (M^+, 22), 83 (50), 73 (62), 55 (100), 41 (70).

*3,5,5-Trimethylhexanoic Acid (**4p**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (s, 9H), 1.02 (d, J = 6.4 Hz, 3H), 1.12−1.34 (m, 2H), 2.06−2.40 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 26.8, 29.9, 31.0, 43.7, 50.5, 179.4; MS (EI) m/z (relative intensity) 158 (M^+, 1), 125 (7), 103 (10), 83 (25), 57 (100), 41 (33).

General Procedure 3: Pd/Xantphos-Catalyzed Oxidation Reaction for the Synthesis of Nitrogen-Containing Heterocycles under Argon (Table 4, entry 1). To a solution of $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and Xantphos (28.9 mg, 0.05 mmol) in dry CH_3CN (3 mL) was added amino alcohol **5a** (137.2 mg, 1.0 mmol) via syringe under argon. The mixture was stirred at 80 °C for 48 h, and the reaction was monitored by gas chromatography. The reaction mixture was dried ($MgSO_4$) and concentrated in vacuo, and the residual oil was subjected to column chromatography over silica gel (hexane/EtOAc = 4/1 v/v) to give **6a** (99.6 mg, 85% yield, R_f = 0.3).

*Indole (**6a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (d, J = 1.2 Hz, 1H), 7.12−7.22 (m, 3H), 7.36 (d, J = 8.2 Hz, 1H), 7.66 (d, J = 8.2 Hz, 1H), 8.01 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.0, 119.8, 120.7, 121.9, 124.1, 127.8, 135.7; MS (EI) m/z (relative intensity) 117 (M^+, 100), 90 (50), 89 (41), 58 (28).

*5-Methylindole (**6b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 6.47 (d, J = 1.6 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 2.6 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.44 (s, 1H), 7.96 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 102.0, 110.6, 120.3, 123.6, 124.2, 128.1, 129.0, 134.0; MS (EI) m/z (relative intensity) 131 (M^+, 78), 130 (100), 103 (11), 77 (22), 65 (47), 51 (18).

*5-Chloroindole (**6c**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (d, J = 3.6 Hz, 1H), 7.15 (dd, J = 8.8, 1.6 Hz, 1H), 7.21 (d, J = 3.6 Hz, 1H), 7.29 (dd, J = 8.8, 1.6 Hz, 1H), 7.61 (s, 1H), 8.14 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 102.4, 111.9, 120.1, 122.3, 125.5, 128.9, 134.1; MS (EI) m/z (relative intensity) 151 (M^+, 100), 124 (11), 116 (23), 89 (30), 76 (17), 58 (15).

General Procedure 4: Pd/Xantphos-Catalyzed Oxidative Synthesis of Quinazolines from Diamine 7 and Alcohols (Table 5). To a solution of $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and Xantphos (28.9 mg, 0.05 mmol) in dry anisole (3 mL) were successively added **1a** (270.3 mg, 2.5 mmol) and diamine **7** (122.2 mg, 1.0 mmol) via syringe under argon. The mixture was stirred at 100 °C for 48 h, and the reaction was monitored by gas chromatography. The reaction mixture was dried ($MgSO_4$) and concentrated in vacuo, and the residual oil was subjected to column chromatography over silica gel (hexane/EtOAc = 50/1 v/v) to give **8a** (175.4 mg, 85%, R_f = 0.4).

*2-Phenylquinazoline (**8a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.59 (m, 4H), 7.89−7.91 (m, 2H), 8.07 (dd, J = 8.2, 0.8 Hz, 1H), 8.62 (dd, J = 8.2, 2.0 Hz, 2H), 9.45 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.6, 127.1, 127.2, 128.5, 128.6, 130.6, 134.0, 138.0, 150.7, 160.4, 161.0; MS (EI) m/z (relative intensity) 206 (M^+, 100), 179 (56), 103 (30), 76 (34), 50 (25).

*2-(4-Methoxyphenyl)quinazoline (**8b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 7.03 (dd, J = 6.8, 2.0 Hz, 2H), 7.52 (td, J = 6.8, 1.6 Hz, 1H), 7.83 (td, J = 6.8, 2.0 Hz, 2H), 8.02 (dd, J = 6.8, 2.0 Hz, 1H), 8.87 (dd, J = 6.8, 2.0 Hz, 2H), 9.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 113.9, 123.2, 126.7, 127.0, 128.3, 130.1, 130.7, 133.9, 150.7, 160.3, 160.8, 161.8; MS (EI) m/z (relative intensity) 236 (M^+, 100), 221 (17), 193 (13), 166 (12), 118 (14), 96 (15).

*2-(4-Nitrophenyl)quinazoline (**8c**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (t, J = 7.6 Hz, 1H), 8.00 (t, J = 7.6 Hz, 2H),

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8.13 (dd, J = 7.6, 1.2 Hz, 1H), 8.37 (dd, J = 7.2, 2.0 Hz, 2H), 8.82 (dd, J = 7.2, 2.0 Hz, 2H), 9.51 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.7, 123.9, 127.2, 128.3, 128.8, 129.4, 134.6, 143.8, 149.2, 150.6, 158.8, 160.7; MS (EI) m/z (relative intensity) 251 (M^+, 70), 221 (30), 207 (52), 194 (100), 77 (25), 44 (32).

*2-(4-Trifluoromethylphenyl)quinazoline (**8d**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (t, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.95−7.98 (m, 2H), 8.13 (dd, J = 8.4, 1.2 Hz, 1H), 8.76 (dd, J = 8.4, 1.2 Hz, 2H), 9.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.9, 125.4, 125.5, 127.2, 127.9, 128.8, 128.8, 132.0, 134.4, 141.3, 150.7, 159.7, 160.7; MS (EI) m/z (relative intensity) 274 (M^+, 100), 247 (32), 76 (31), 50 (26).

General Procedure 5: Pd/Xantphos-Catalyzed Oxidative Synthesis of Benzimidazoles from Diamine 9 and Alcohols (Scheme 2). To a solution of $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and Xantphos (28.9 mg, 0.05 mmol) in dry CH_2CN (3 mL) were successively added **1a** (432.5 mg, 4.0 mmol) and diamine **9** (108.1 mg, 1.0 mmol) via syringe under argon. The mixture was stirred at 80 °C for 48 h, and the reaction was monitored by gas chromatography. The reaction mixture was dried ($MgSO_4$) and concentrated in vacuo, and the residual oil was subjected to column chromatography over silica gel (hexane/EtOAc = 10/1 v/v) to give **10a** (184.9 mg, 65%, R_f = 0.3).

*1-Benzyl-2-phenyl-1H-benzimidazole (**10a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 (s, 2H), 7.06 (d, J = 6.4 Hz, 2H), 7.18−7.30 (m, 6H), 7.37−7.46 (m, 3H), 7.67 (dd, J = 7.6, 1.4 Hz, 2H), 7.87 (dd, J = 7.6, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.2, 110.4, 119.8, 122.5, 122.9, 125.8, 127.6, 128.6, 128.9, 129.1, 129.7, 129.9, 135.9, 136.2, 143.0, 154.0; MS (EI) m/z (relative intensity) 284 (M^+, 64), 207 (7), 193 (4), 180 (4), 166 (4), 152 (2), 91 (100).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.9b00207.

Experimental procedures, plausible mechanism for oxidation of alcohols, and ^{1}H and ^{13}C NMR spectra of products (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: tmori@rs.socu.ac.jp (T. Mori).
*E-mail: masanari@nagasaki-u.ac.jp (M. Kimura).

ORCID

Masanari Kimura: 0000-0003-2900-9554

Notes

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■ ABBREVIATIONS

dppb, 1,4-bis(diphenylphosphino)butane; dppf, 1,1′-bis(diphenylphosphino)ferrocene; Xantphos, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; DMF, *N*,*N*-dimethylformamide; DMA, *N*,*N*-dimethylacetamide; THF, tetrahydrofuran

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(17) The evolution of hydrogen gas was observed by GC analysis (see the Supporting Information). Although it is premature to rationalize the mechanism by qualitative analysis, a dehydrogenative oxidation mechanism seems to be probable.
(18) A possible mechanism involving the generation of hydrogen peroxide with a palladium hydride complex under aerobic conditions is proposed in Scheme SI-1.

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