

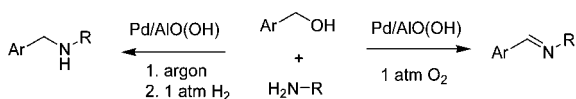
One-Pot Synthesis of Imines and Secondary Amines by Pd-Catalyzed Coupling of Benzyl Alcohols and Primary Amines

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Imines and secondary amines were synthesized selectively by controlling reaction conditions for the Pd-catalyzed one-pot reactions of benzyl alcohols with primary amines. The reactions did not require any additives and were effective for a wide range of alcohols and amines.

The carbon–nitrogen bond-forming reaction is one of the significant transformations in organic synthesis.¹ In particular, imines are highly desirable, owing to their applications as electrophiles in many organic reactions such as reduction, addition, condensation, and cycloaddition.² Traditionally, imines are synthesized via the addition of amines and carbonyl compounds with azeotropic distillation to expel the liberated water.³ Furthermore, condensation reactions carried out in the presence of Lewis acids have also been documented in the literature.⁴ As a related C–N coupling reaction, Taylor and co-

workers have reported the direct conversion of activated alcohols into imines and amines using stoichiometric amounts of MnO₂ (oxidizing agent) and polymer-supported cyanoborohydride (reducing agent).⁵ On the other hand, the borrowing hydrogen approach is a strategy for the *N*-alkylation of amines since there is no net hydrogen gain or loss.⁶ In this regard ruthenium⁷ and iridium⁸ catalysts have been successfully employed to achieve this oxidation, imination, and reduction sequence. However, these methods are mainly focused on the synthesis of amines even though imines are the intermediates. We have recently developed a heterogeneous palladium catalyst, Pd/AIO(OH) (**1**),^{9a} that is composed of palladium nanoparticles entrapped in boehmite nanofibers. The catalyst has shown high activity and excellent efficiency in the aerobic oxidation of alcohols and racemization of amines for chemoenzymatic dynamic kinetic resolution and α -alkylation of ketones with alcohols.⁹ During the course of our investigation, we found that this system could be effective for the C–N coupling reaction of various alcohols with amines to couple imines or amines without any additives. Moreover, this reaction promises an attractive green chemistry, as water is the only byproduct. We first examined the reaction of benzyl alcohol (1.0 mmol) with 2-phenylethylamine (1.2 mmol) in the presence of **1** (2.0 mol % of Pd) for 20 h at 90 °C under oxygen atmosphere and obtained *N*-benzylidene-2-phenylethylamine in 90% yield.¹⁰ Meanwhile, the same reaction under argon gave a 80:20 mixture of *N*-benzyl-2-phenylethylamine and *N*-benzylidene-2-phenylethylamine after 12 h. Subsequently, we could convert the mixture to pure *N*-benzyl-2-phenylethylamine (92% yield) at 25 °C under hydrogen atmosphere (Scheme 1).

The efficacy of **1** for the coupling of benzyl alcohol with 2-phenylethylamine was compared with those of various commercial catalysts (Table 1). The catalyst **1** exhibited the highest activity among the commercial palladium catalysts such as Pd/C, Pd/Al₂O₃, Pd/CaCO₃, Pd/BaCO₃, and PdEnCat (entries 2–6). Other metal catalysts such as Ru/Al₂O₃ and Rh/Al₂O₃ were found to be feeble under the same conditions (entries 7 and 8).

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(1) (a) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742. (b) Balraju, V.; Iqbal, J. *J. Org. Chem.* **2006**, *71*, 8954. (c) Djakovitch, L.; Dufaud, V.; Zaidi, R. *Adv. Synth. Catal.* **2006**, *348*, 715. (d) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (e) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23.

(2) (a) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikaiya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916. (b) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102. (c) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889. (d) Murahashi, S. I.; Komiya, N.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312. (e) Drury, W. J.; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 11006. (f) Sandhu, J. S. *Heterocycles* **1987**, *26*, 777. (g) Shi, M.; Xu, Y.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4507. (h) Balan, D.; Adolffson, H. *J. Org. Chem.* **2001**, *66*, 6498. (i) Hattori, K.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 3264. (j) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407.

(3) (a) Schiff, H. *Annals* **1864**, *131*, 118. (b) Moffett, R. B. In *Organic Syntheses*; Rabjohn, N., Ed.; John Wiley & Sons, Inc: New York, 1963; Collect. Vol. IV, pp 608–611. (c) Castellano, J. A.; Goldmacher, J. E.; Barton, L. A.; Kane, J. S. *J. Org. Chem.* **1968**, *33*, 3501. (d) Taguchi, K.; Westheimer, F. H. *J. Org. Chem.* **1971**, *36*, 1570.

(4) (a) Billman, J. H.; Tai, K. M. *J. Org. Chem.* **1958**, *23*, 535. (b) White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213. (c) Weingarten, H.; Chupp, J. P.; White, W. A. *J. Org. Chem.* **1967**, *32*, 3246. (d) Moretti, I.; Torre, G. *Synthesis* **1970**, 141. (e) Jennings, W. B.; Lovely, C. J. *Tetrahedron Lett.* **1988**, *29*, 3725. (f) Branchaud, B. P. *J. Org. Chem.* **1983**, *48*, 3531. (g) Texier-Boulet, F. *Synthesis* **1986**, 679. (h) Armstrong, J. D.; Wolfe, C. N.; Keller, J. L.; Lynch, J.; Bhupathy, M.; Volante, R. P. *Tetrahedron Lett.* **1997**, *38*, 1531. (i) Liu, G.; Gogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278. (j) Chakraborti, A. K.; Bhagat, S.; Rudrawar, S. *Tetrahedron Lett.* **2004**, *45*, 7641.

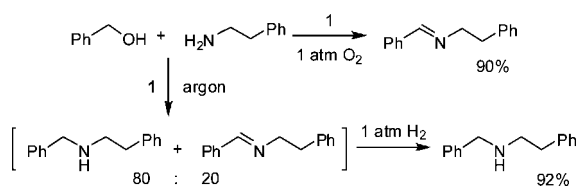
(5) Blackburn, L.; Taylor, R. J. K. *Org. Lett.* **2001**, *11*, 1637.
(6) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555.

(7) Tillack, A.; Hollmann, D.; Michalik, D.; Beller, M. *Tetrahedron Lett.* **2006**, *47*, 8881.

(8) Fujita, K.-i.; Enoki, Y.; Yamaguchi, R. *Tetrahedron* **2008**, *64*, 1943, and references cited therein.

(9) (a) Kwon, M. S.; Kim, N.; Park, C. M.; Lee, J. S.; Kang, K. Y.; Park, J. *Org. Lett.* **2005**, *7*, 1077. (b) Kwon, M. S.; Kim, N.; Seo, S. H.; Park, I. S.; Cheedra, R. K.; Park, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6913. (c) Kim, M. J.; Kim, W. H.; Han, K.; Choi, Y. K.; Park, J. *Org. Lett.* **2007**, *9*, 1157. (d) Kim, S.; Bae, S. W.; Lee, J. S.; Park, J. *Tetrahedron* **2009**, *65*, 1461.

(10) The reaction of benzyl alcohol (1.0 mmol) with 2-phenylethylamine (1.2 mmol) was carried out in toluene, ethyl acetate, and dichloromethane in the presence of **1** (2.0 mol % of Pd) for 12 h at 90 °C under argon to give the products in 90% (amine:imine = 80:20), 63% (70:30), and 0% yield, respectively.

SCHEME 1. Palladium-Catalyzed Coupling of Benzyl Alcohol and 2-Phenylethylamine

TABLE 1. Comparison of Catalytic Activities^a

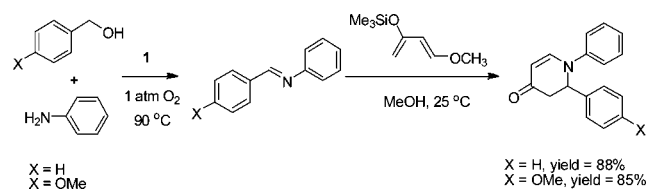
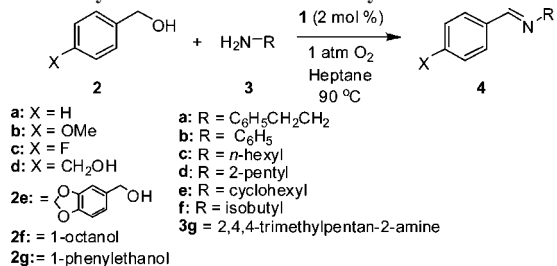
entry	catalyst	yield (%) ^b
1	1	90 (57) ^c
2	5% Pd/C	19
3	5% Pd/Al ₂ O ₃	42
4	5% Pd/CaCO ₃	3
5	5% Pd/BaCO ₃	13
6	4.3% PdEnCat	5
7	5% Ru/Al ₂ O ₃	8
8	5% Rh/Al ₂ O ₃	0

^a A solution of benzyl alcohol (1.0 mmol) and 2-phenylethylamine (1.2 mmol) in heptane (5.0 mL) was heated in the presence of catalyst (2.0 mol % of Pd or Ru) at 90 °C under 1 atm of O₂ for 20 h. ^b Determined by ¹H NMR with an internal standard. ^c After 10 h.

The generality of this methodology has been investigated with different types of benzyl alcohols and amines to produce corresponding imines under oxygen atmosphere (Table 2). The electronic effect on the aromatic ring was not significant; the reactions of benzyl alcohol were similar to those of 4-methoxybenzyl alcohol and 4-fluorobenzyl alcohol (entries 1–6). However, the reactions with aniline required more catalyst than those with aliphatic amines (entries 4–6). Meanwhile, the reactions with primary aliphatic amines were not affected by the steric bulkiness of the alkyl groups (entries 7–11); even 2,4,4-trimethylpentan-2-amine was reacted successfully with a benzyl alcohol to give the expected imine in high yield (entry 11). A diimine was obtained also successfully when 1,4-phenylenedimethanol was employed (entry 10). However, the reactions employing 1-octanol and 1-phenylethanol were not successful. The expected imine was produced only in about 8% in the reaction of 1-octanol with 2-phenylethylamine (entry 12). In the reaction of 1-phenylethanol, acetophenone was formed in 11%, but the corresponding imine was not detected.

Having established conditions for the in situ oxidation–imine-formation, we envisaged the one-pot production of secondary amines from primary alcohols and amines through oxidation–imine formation and imine hydrogenation (Table 3). The initial investigation on benzyl alcohol (1.0 mmol) and 2-phenylethylamine (1.2 mmol) with **1** (2.0 mol % of Pd) in *n*-heptane at 90 °C under argon for 12 h, followed by hydrogen atmosphere for 6 h at room temperature, led to *N*-benzyl-2-phenylethanamine in 84% yield. The hydrogenation was carried out after checking the complete consumption of benzyl alcohol by TLC. Secondary amines, which correspond to the imines in Table 2, were isolated in 75–92% yield by column chromatography.

We also attempted the one-pot aza Diels–Alder reaction of imines (Scheme 2). After the coupling reaction of primary benzyl alcohols and aniline under aerobic conditions, Danishefsky's dienes were reacted with the resulting imines. Purification of the aza Diels–Alder products by column chromatography provided 1,2-diphenyl-2,3-dihydropyridin-4-one and 2-(4-methoxyphenyl)-1-phenyl-2,3-dihydro-1*H*-pyridin-4-one through desilylation in 88% and 85% yields, respectively.

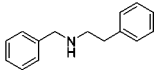
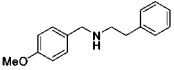
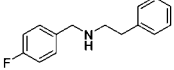
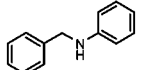
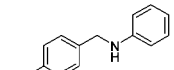
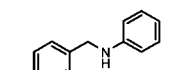
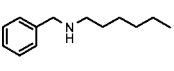
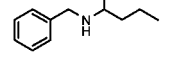
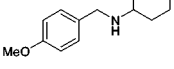
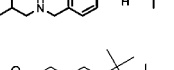
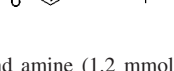
SCHEME 2. One-Pot Aza Diels–Alder Reaction.

TABLE 2. Synthesis of Imines from Benzyl Alcohols and Amines^a


Entry	Alcohol	Amine	Time (h)	Product	Yield (%) ^b
1	2a	3a	20		90
2	2b	3a	20		92
3	2c	3a	24		92
4 ^c	2a	3b	20		90
5 ^c	2b	3b	24		91
6 ^c	2c	3b	24		92
7	2a	3c	20		93
8	2a	3d	20		90
9	2b	3e	20		93
10 ^d	2d	3f	24		82
11	2e	3g	24		98
12	2f	3a	24		8
13	2g	3b	24		0

^a A solution of alcohol (1.0 mmol) and amine (1.2 mmol) in heptane (5.0 mL) was heated in the presence of **1** (2.0 mol % of Pd) at 90 °C under 1 atm of O₂. ^b Determined by ¹H NMR with an internal standard. ^c 4.0 mol % of Pd was used. ^d Excess of isobutylamine (4.8 mmol) was used.

In conclusion, we have demonstrated a simple and efficient one-pot synthesis of imines and secondary amines from benzyl alcohols and amines highly selectively using a heterogeneous palladium catalyst without any additives under aerobic and

TABLE 3. One-Pot Synthesis of Secondary Amines^a

Entry	Alcohol	Amine	Time (h) ^b	Product	Yield (%) ^c
1	2a	3a	12		84
2	2b	3a	12		92
3	2c	3a	16		81
4 ^d	2a	3b	20		84
5 ^d	2b	3b	24		84
6 ^d	2c	3b	20		75
7	2a	3c	12		82
8	2a	3d	12		88
9	2b	3e	20		86
10 ^e	2d	3f	24		80
11	2e	3g	20		84

^a A solution of alcohol (1.0 mmol) and amine (1.2 mmol) in heptane (5.0 mL) was heated in the presence of **1** (2.0 mol % of Pd) at 90 °C under argon followed by 1 atm of H₂ for 6 h at 25 °C. ^b Reaction time for the coupling of amine and alcohol. ^c Isolation yield. ^d 4.0 mol % of Pd was used. ^e Excess of isobutylamine (4.8 mmol) was used.

anaerobic conditions, respectively. Extrapolation of this study to other reactions involving imines will enhance the opportunity of discovering new avenues.

Experimental Section

Reaction of Benzyl Alcohol with 2-Phenylethylamine under 1 atm of O₂. Benzyl alcohol (108 mg, 1.00 mmol),

2-phenylethylamine (146 mg, 1.20 mmol), **1** (2 mol % Pd), and *n*-heptane (5 mL) were placed in a 50 mL flask (glass tube) and allowed to react under an O₂ balloon at 90 °C for 20 h (**Caution:** be cautious in the use of oxygen with the catalyst and organic solvents). The catalyst was separated by filtration and the filtrate was concentrated under reduced pressure. Cyclohexene (102 μL, 1.01 mmol) as an internal standard was added in the reaction mixture and analyzed by ¹H NMR spectroscopy. The peak at 5.66 ppm was selected as the standard. ¹H NMR (300 MHz, CDCl₃, ppm) δ 3.00 (t, 2H, *J* = 7.5 Hz), 3.86 (t, 2H, *J* = 6.3 Hz), 7.17–7.38 (m, 10H), 8.2 (s, 1H).

Reaction of Benzyl Alcohol with 2-Phenylethylamine under Argon Atmosphere. Benzyl alcohol (108 mg, 1.00 mmol), 2-phenylethylamine (146 mg, 1.20 mmol), **1** (2 mol % of Pd), and *n*-heptane (5 mL) were placed in a 50 mL flask (glass tube) and allowed to react under argon at 90 °C for 12 h. After purging argon gas, the reaction mixture was stirred at 25 °C for 6 h under a hydrogen balloon. The catalyst was separated by filtration, and the filtrate was purified by column chromatography to give *N*-benzyl-2-phenylethanamine (178 mg) in 84% yield. ¹H NMR (300 MHz, CDCl₃, ppm) δ 1.4 (br, 1H), 2.77–2.92 (m, 4H), 3.78 (s, 2H), 7.14–7.34 (m, 10H); ¹³C (75 MHz, CDCl₃, ppm) δ 36.5, 50.7, 54.0, 126.3, 127.1, 128.2, 128.6, 128.6, 128.9, 140.2, 140.3.

One-Pot Synthesis of 1,2-Diphenyl-2,3-dihydropyridin-4-one. Benzyl alcohol (108 mg, 1.00 mmol), aniline (112 mg, 1.20 mmol), **1** (4 mol % of Pd), and *n*-heptane (5 mL) were placed in a 50 mL flask (glass tube) and allowed to react under argon at 90 °C for 20 h. After the solution had cooled to room temperature, *trans*-1-methoxy-3-trimethylsiloxy-1,3-butadiene (400 μL, 2.0 mmol) and methanol (2 mL) were added and the mixture was stirred for 6 h at 25 °C. The catalyst was separated by filtration, and the filtrate was purified by column chromatography to give 1,2-diphenyl-2,3-dihydropyridin-4-one (220 mg, 88% yield). ¹H NMR (300 MHz, CDCl₃, ppm) δ 2.79 (ddd, 1H, *J*₁ = 16.4 Hz, *J*₂ = 3.0 Hz, *J*₃ = 1.0 Hz), 3.30 (dd, 1H, *J*₁ = 16.4 Hz, *J*₂ = 7.2 Hz), 5.30 – 5.27 (m, 2H), 7.13–7.00 (m, 3H), 7.32–7.26 (m, 7H), 7.68 (dd, 1H, *J*₁ = 7.8 Hz, *J*₂ = 1.0 Hz); ¹³C (75 MHz, CDCl₃, ppm) δ 43.6, 61.9, 103.2, 118.7, 124.6, 126.3, 128.0, 129.2, 129.7, 138.1, 144.9, 148.4, 190.4.

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

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