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Metal-Free Oxidative Coupling of Benzylamines to Imines under an Oxygen Atmosphere Promoted Using Salicylic Acid Derivatives as Organocatalysts

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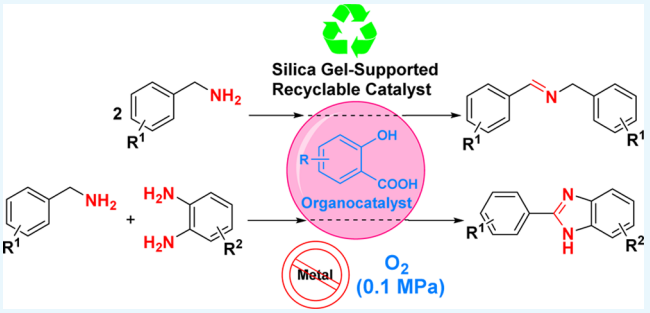
Supporting Information

ABSTRACT: The oxidative coupling of benzylamines proceeds efficiently using salicylic acid derivatives as organocatalysts under an oxygen atmosphere, affording the corresponding *N*-benzylidenebenzylamines in high yields. Electron-rich salicylic acid derivatives such as 4,6-dimethoxysalicylic acid and 4,6-dihydroxysalicylic acid exhibit excellent catalytic activities for the oxidative coupling of benzylamines to give the corresponding imines. This amine oxidation can also be applied to the synthesis of nitrogen-containing heterocycles such as benzimidazole derivatives. Furthermore, to recycle the catalyst, silica gel supported with 4.7 wt % of 4,6-dihydroxysalicylic acid is prepared, which acts as a recyclable catalyst, oxidizing benzylamine to imine four times successfully.



INTRODUCTION

Imines are of great importance for the synthesis of industrial materials and biologically active compounds such as amines, chiral amines, amides, pyrrolines, oxaziridines, hydroxyamines, and nitrones.[1−3] To synthesize imines, many useful oxidation methods have been developed,[4] which include oxidation of primary or secondary amines and oxidative condensation of amines with alcohols. Typical strategies require transition metal catalysts including noble metals[5−9] and non-noble biocompatible metals;[10−14] however, contamination of the final products by these metal residues becomes a serious problem in the synthesis of medicines and functional materials. From the perspective of green chemistry, chemists have shifted their attention to other, more eco-friendly methods. Metal-free catalysts such as graphene oxide,[15] 4-*tert*-butyl-2-hydroxybenzoquinone (TBHBQ),[16] and azobisisobutyronitrile (AIBN)[17] can oxidize benzylic amines to secondary imines. In biology, copper-containing amine oxidases (CuAOs) have high activity and specificity toward the oxidation of primary amines. Thus, bioinspired catalysts, electrogenerated *ortho*-iminoquinone species,[18] *ortho*-quinone,[19] and other mimicry of monoamine oxidase compounds,[20] were used. Visible-light-induced transformation of amines to imines is also an alternative approach; allowing different kinds of photocatalyses to be investigated.[21−24] However, most of these metal-free catalysts are of complex structure and high price. Therefore, the development of more easily available metal-free catalysts for imine synthesis is still desired strongly.

Recently, we have reported a series of eco-friendly oxidations of alcohols and amines using metal catalysts: for example, the vanadium complex-catalyzed oxidation of benzyl alcohols[25] or benzylamines with atmospheric O_2 in water or ionic liquid[26] and the copper sulfate-catalyzed oxidation of amines with H_2O_2 in water[27] (Scheme 1, eqs 1 and 2, respectively). In the former catalytic oxidation, 3-hydroxypicolinic acid (H_2hpic) or its analogues were used as ligands for oxovanadium complexes. During these studies, we were surprised to find that some of the ligands such as salicylic acid and its derivatives themselves functioned as organocatalysts and catalyzed amine oxidation (Scheme 1, eq 3).

Herein, we report a convenient, salicylic acid derivative-catalyzed oxidation of benzylamines to the corresponding imines under an atmosphere of O_2. Furthermore, this new metal-free oxidation method can be applied to the synthesis of nitrogen-containing heterocycles such as benzimidazole derivatives. Moreover, the recyclability of the organocatalyst has been demonstrated successfully by supporting 4,6-dihydroxysalicylic acid on silica gel.

RESULTS AND DISCUSSION

Initially, H_2hpic, which was used as a ligand for the vanadium catalyst in our previous work, was used alone (in the absence of

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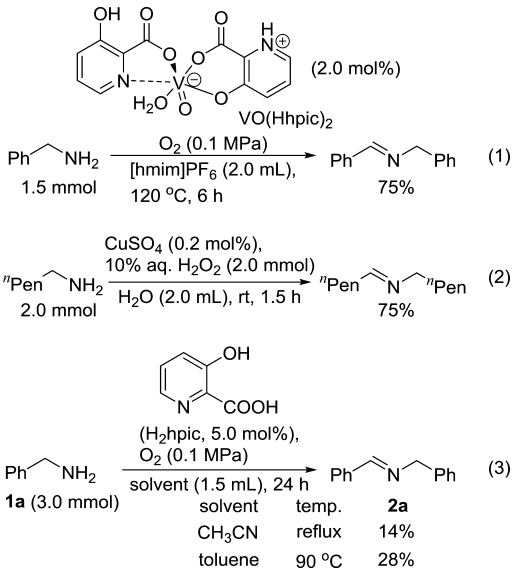
Scheme 1. Catalytic Oxidation of Amines to Imines

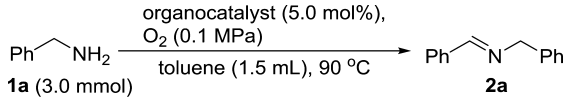


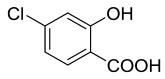
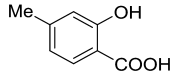
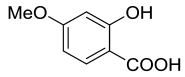
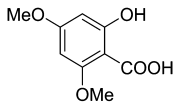
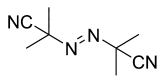
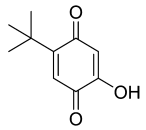
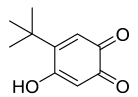
metal catalyst) for the oxidation of benzylamine **1a** under an O_2 atmosphere; interestingly, the formation of the desired product **2a** was observed (Scheme 1, eq 3). Hence, we next explored the functional subunits of H_2hpic, such as the phenol and benzoic acid groups, and their combinations, by using them as catalysts for the amine oxidation (for details, see Table S1). Phenol and benzoic acid are ineffective for the transformation. Surprisingly, salicylic acid is found to have great catalytic activity for the oxidation of benzylamine under O_2, affording *N*-benzylidenebenzylamine **2a** in 80% yield. However, 2-methoxybenzoic acid or methyl 2-hydroxybenzoate is less effective than salicylic acid itself. Introduction of a methylene group between the carboxylic acid and phenyl groups also reduces the yield of **2a**. On the other hand, simple Brønsted acids such as *p*-toluenesulfonic acid and acetic acid, which have recently been reported to promote the oxidation of amines,[28] are ineffective.

To optimize the catalyst for this metal-free oxidation, the amine oxidation was examined using several salicylic acid derivatives (Table 1). 4-Substituted salicylic acids demonstrated almost the same reactivity as nonsubstituted salicylic acid after 24 h (entries 1, 3, and 5). However, at a shorter reaction time (12 h), 4-methoxysalicylic acid **3c** showed higher reactivity than the others (entries 2, 4, and 6). Further optimization revealed that 4,6-dimethoxysalicylic acid **3d** as a catalyst was the most efficient in this metal-free oxidation, affording the desired product in 95% yield (entry 9). To compare with other organocatalysts that have been reported by other research groups, we examined the amine oxidation using AIBN,[17] TBHBQ,[16] and *ortho*-quinone[19] under our optimized reaction conditions. TBHBQ and *ortho*-quinone indicated similar catalytic ability with our catalyst **3d** (entries 12 and 13), whereas a lower yield of the corresponding imine was obtained in the case of AIBN as the catalyst (entry 11).

Using the optimized reaction conditions (Table 1, entry 9), the oxidation of different benzylamine substrates was examined (Table 2). Benzylamine derivatives with electron-donating [**1c** (R = *p*-Me), **1f** (R = *p*-OMe), and **1g** (R = *p*-^{t}Bu)] or electron-withdrawing [**1e** (R = *m*-OMe), **1h** (R = *p*-Cl), and **1i** (R = *p*-CF_3)] groups at the *para*- or *meta*-position can be oxidized to the corresponding imines in high yields. It is noteworthy that sterically hindered *ortho*-substituted benzylic amines **1b** (R = *o*-

Table 1. Oxidation of Benzylamine Catalyzed Using Salicylic Acid Derivatives



entry	organocatalyst		time (h)	yield[a] (%)
1		**3a**	24	81
2		**3a**	12	14
3		**3b**	24	74
4		**3b**	12	15
5		**3c**	24	90
6		**3c**	12	81
7		**3c**	8	43
8		**3d**	12	88
9		**3d**	6	95(87)
10		**3d**	2	65
11		**AIBN**	6	33
12		**TBHBQ**	6	93
13		***ortho*-Q**	6	84

[a]Determined by ^{1}H NMR using 1,3,5-trioxane (isolated yield) as the internal standard; yield of **2a** is based on substrate **1a**.

Me) and **1d** (R = *o*-OMe) undergo oxidative coupling efficiently. Besides, similar oxidation of activated primary amines such as 1-naphthylmethylamine **1j**, furfurylamine **1k**, 2-pyridinemethylamine **1l**, and 2-thiophenemethyamine **1m** was examined. 1-Naphthylmethylamine and 2-thiophenemethylamine can be transformed into the corresponding imines in good yields. By contrast, the oxidation of secondary amines, aliphatic amines, and 4-hydroxybenzylamine was difficult under these conditions. On the other hand, benzylamine featuring primary or secondary alcohol underwent oxidative coupling to

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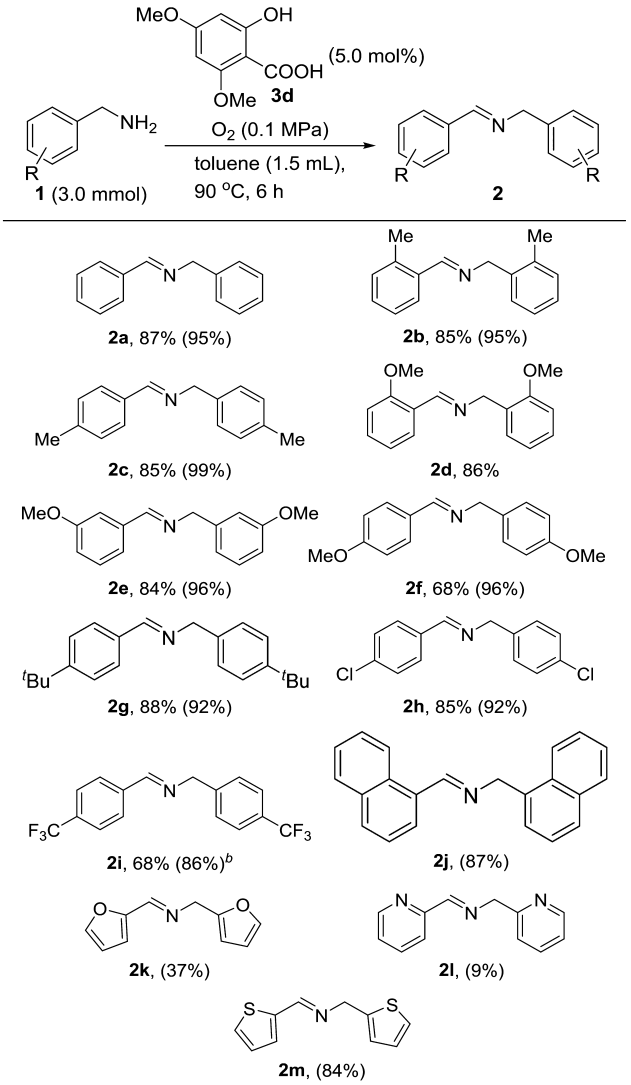
Table 2. Oxidation of Benzylamine Derivatives[a]

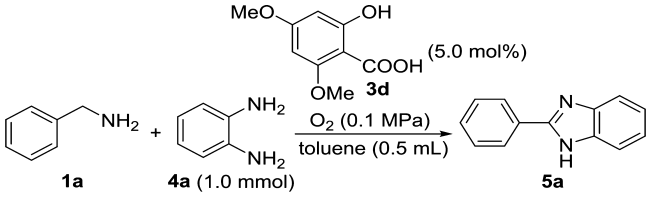


[a]Yield of the isolated product is based on **1** ([1]H NMR yield using 1,3,5-trioxane as the internal standard). [b]Reaction time: 8 h.

afford the corresponding imines in moderate yield (for details, see Scheme S1).[29]

The successful synthesis of imine derivatives prompted us to apply this method to the synthesis of benzimidazole derivatives. The benzimidazole skeleton is an important structural framework found in a large variety of naturally occurring compounds and pharmaceutical agents. Conventionally, numerous methods have been reported for the construction of benzimidazoles. For example, several efficient methods for the synthesis of benzimidazoles from alcohols,[30] benzaldehydes,[31] imines,[32] β-diketones,[33] and carboxylic acids[34] as well as intermolecular condensation of 1,2,4-oxadiazol-5(4*H*)-ones[35] have recently been developed. Besides, examples of benzimidazole synthesis through the cyclization of 1,2-diaminobenzene derivatives with benzylamines under metal[36,37] or metal-free[24,38−42] oxidation conditions have also been reported recently. Owing to the importance of developing a new metal-free oxidative system for the synthesis of benzimidazoles, we applied our oxidation protocol to the synthesis of benzimidazole derivatives (Table 3).

Table 3. Optimization of Conditions for the Oxidative Cyclization of Benzylamine to Benzimidazole[a]



entry	equiv. of **1a**	temp. (°C)	time (h)	yield[a] (%)
1	1	90	12	83
2	1.5	90	12	87
3	1.5	110	12	(93)
4	1.5	110	6	75
5	1.5	110	24	86
6	1.5	60	12	5

[a]Determined by [1]H NMR using 1,3,5-trioxane as the internal standard (isolated yield); yield of **5a** is based on substrate **4a**.

When the reaction of **1a** with 1,2-diaminobenzene **4a** (1 equiv) was performed at 90 °C in the presence of salicylic acid derivative **3d** as the organocatalyst, the desired product **5a** was obtained successfully in 83% yield (Table 3, entry 1). Apparently, the use of 1.5 equiv of **1a** at a higher temperature can slightly improve the yield of **5a** (entries 2 and 3). However, a shorter or longer reaction time resulted in a decrease in the yield of **5a** (entries 4 and 5), and this oxidation reaction could not proceed well at 60 °C (entry 6).

Under the optimized conditions (Table 3, entry 3), the salicylic acid derivative-catalyzed cyclization of several benzylamine derivatives **1** with 1,2-diaminobenzene **4a** was demonstrated and the corresponding benzimidazoles **5** were obtained in high yields (Table 4, **5a−h**). Many substituents on the phenyl group of benzylamine, such as *p*-Me, *o*-MeO, *m*-MeO, *p*-MeO, *m*-Cl, *p*-Cl, and *p*-CF_3, were tolerant to the oxidative cyclization. Moreover, several 1,2-diaminobenzene derivatives **4** were also screened. Electron-donating or electron-withdrawing groups on the aromatic ring of 1,2-diaminobenzenes were well-tolerated under these cyclization reaction conditions, and the desired benzimidazoles **5** were obtained in good yields (Table 4, **5i−n**).

To clarify the mechanism of this oxidation reaction, we performed several control experiments as shown in Scheme 2 (eqs 4−8). At first, as we suspected that the oxidation of benzylamine proceeds following a radical pathway, the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl free radical) was added to the reaction mixture under the standard conditions (Scheme 2, eq 4). As a result, the yield of the desired imine **2a** dramatically decreased to 5%. Moreover, the formation of **6** was confirmed using gas chromatography−mass spectrometry (GC−MS) (m/z = 157 corresponding to **6**). These results strongly suggest that the oxidation involves radical species. The findings in Table 1 clearly indicate that the salicylic acid structure is important for this oxidation. To further clarify the role of the salicylic acid derivatives, compound **7** was prepared from benzylamine **1a** and salicylic acid derivative **3d** (Scheme 2, eq 5) and then subjected to the optimized oxidation conditions. However, the imine product **2a** was generated in only 6% yield (Scheme 2, eq 6). Adding benzylamine **1a** (1 equiv) improved the yield to 43% (Scheme 2, eq 7), suggesting that the oxidation requires free amine **1a**. Furthermore, the catalytic oxidation of **1a** using **7** as a catalyst

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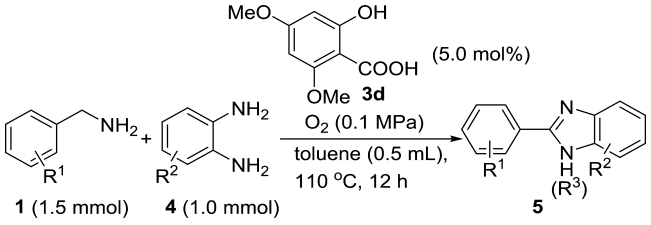
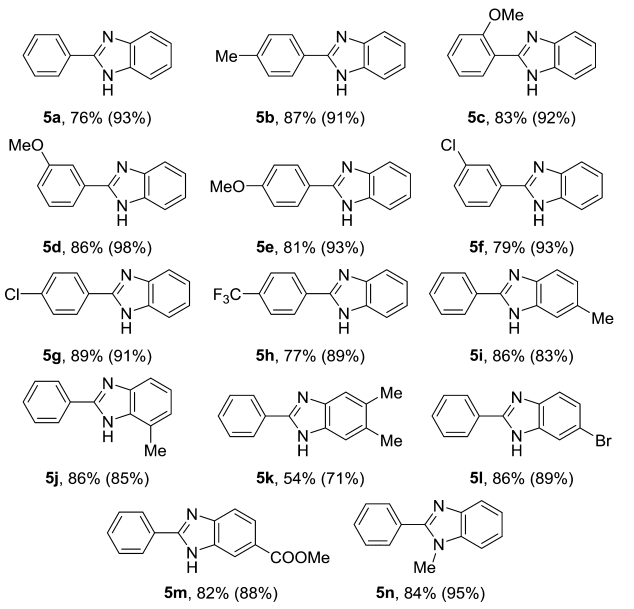
Table 4. Synthesis of Benzimidazoles from Various Benzylamine and 1,2-Diaminobenzene Derivatives[a]





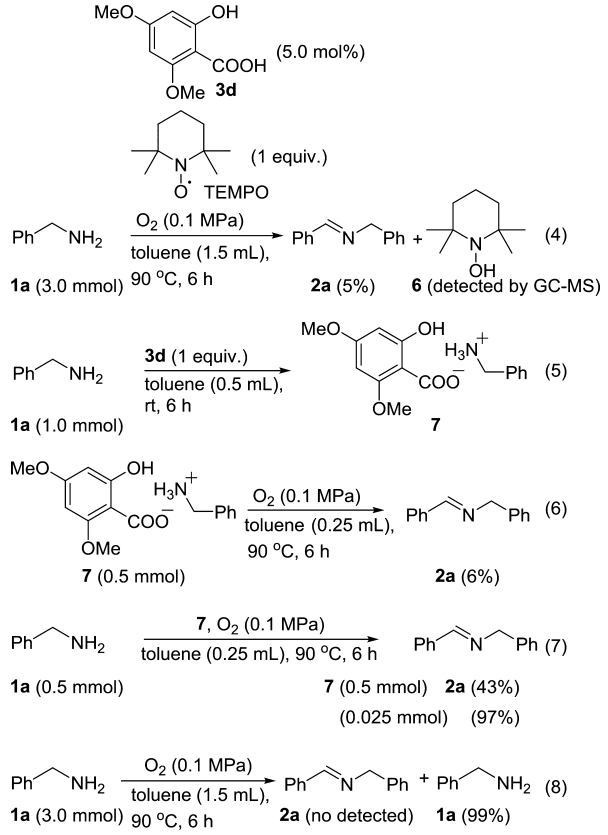
[a]Yield of isolated product is based on **4** (^{1}H NMR yield was determined using 1,3,5-trioxane as the internal standard).

successfully afforded **2a** in 97% yield (Scheme 2, eq 7). In the absence of salicylic acid derivative **3d**, the oxidative coupling of benzylamine to imine could not proceed at all (Scheme 2, eq 8).

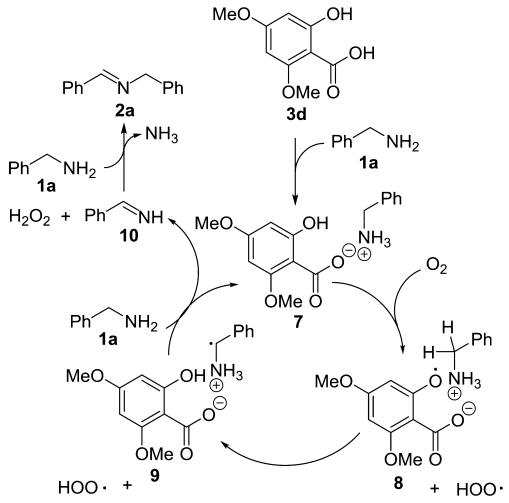
On the basis of these results, a possible catalytic pathway is proposed in Scheme 3. First, benzylamine **1a** and salicylic acid derivative **3d** form the corresponding salt **7**, which may be oxidized by O_2 to generate phenoxy radical **8** and HOO•. The hydrogen abstraction from benzylamine leads to the formation of **9**. Further hydrogen abstraction from the amino group by HOO• affords phenylmethanimine **10** with regeneration of the catalyst **7**; then intermediate **10** undergoes amino group exchange reaction with benzylamine **1a** to afford **2a**.

In view of green chemistry, recyclability of the catalyst is of great importance. Hence, we examined the preparation of silica gel-supported salicylic acid as a recyclable organocatalyst to develop the recyclable amine oxidation method (Scheme 4). To obtain the silica gel-supported 4,6-dimethoxysalicylic acid **3d** catalyst, silica gel was treated with **3d**. However, **3d** could not be supported efficiently on silica gel, and during the washing process of the silica gel with ethyl acetate, most of **3d** was removed from the silica gel (Scheme 4, eq 9). Considering the affinity with silica gel, 4,6-dihydroxysalicylic acid **3e**[43] was chosen as the organocatalyst. As we expected, silica gel supported with 4.7 wt % of **3e** (4.7 wt % **3e** on silica gel) was obtained successfully (Scheme 4, eq 10). Then, the silica gel-supported catalyst (4.7 wt % **3e** on silica gel) was used for the oxidation of benzylamine **1a** to imine **2a** (Table 5).

Scheme 2. Control Experiments



Scheme 3. Possible Pathway for the Catalytic Oxidation of Benzylamine



Compared with 4,6-dihydroxysalicylic acid **3e** itself, the silica gel-supported catalyst (4.7 wt % **3e** on silica gel) showed a similar catalytic activity (entries 1 and 2). On the other hand, the silica gel itself did not indicate any catalytic activity for the imine oxidation (entry 3).

Then, recyclability of the silica gel-supported catalyst (4.7 wt % **3e** on the silica gel) was examined (Table 6). The oxidation of benzylamine **1a** was conducted using silica gel-supported **3e**, and the corresponding imine **2a** was obtained in 84% yield (first run). The resulting silica gel-supported **3e** was recovered by filtration, and reused for the second oxidation. The yield of

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Scheme 4. Preparation of the Silica Gel-Supported Salicylic Acid Catalyst

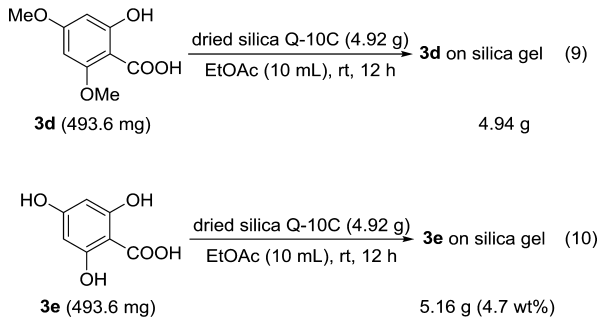
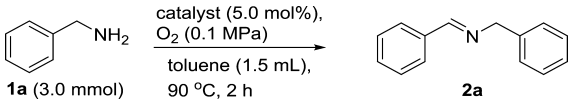
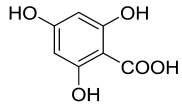


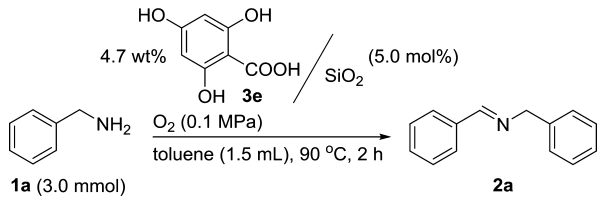
Table 5. Oxidation of Benzylamine by the Silica Gel-Supported Catalyst



entry	catalyst	yield[a] (%)
1	 **3e**	86
2	4.7 wt% **3e** on silica gel	84
3	Silica gel (500 mg)	N.R.

[a]Determined by ^{1}H NMR using 1,3,5-trioxane as the internal standard; yield of **2a** is based on substrate **1a**; N.R.: no reaction.

Table 6. Recycling Study[a]



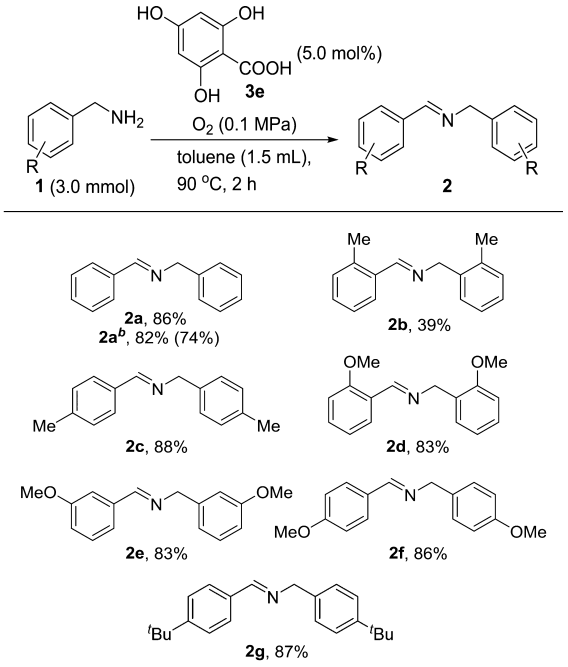
run	first	second	third	fourth
yield of **2a** (%, I)	84	95	64	53
yield of **2a** (%, II)	85	95	66	

[a]Yield of **2a** is based on substrate **1a**, and determined by ^{1}H NMR using 1,3,5-trioxane as the internal standard.

2a was 95% (second run). Similarly, third and fourth oxidations were conducted, and the yields of **2a** were 64% (third run) and 53% (fourth run), respectively. To confirm the reproducibility of this recycling study, the same oxidation and recycling were attempted; similar results were obtained, as indicated in the second row of Table 6. In the second run, imine **2a** was obtained in a higher yield than in the first run. This is probably because some of **1a** and/or **2a** was absorbed by the silica gel in the first run and could not be washed away from the catalyst. After the reaction, the surface of the silica gel-supported catalyst was covered with an unidentified black compound that was hard to clean up. As a result, the catalyst was deactivated to some degree, and the yields of the third and fourth runs gradually decreased.

As can be seen from the recycling experiments (Table 6), 4,6-dihydroxysalicylic acid **3e** is also an effective catalyst for the oxidative coupling of benzylamines to imines. Thus, we further investigate the oxidative coupling of benzylamines using 4,6-dihydroxysalicylic acid **3e** as the catalyst (Table 7). Compared with 4,6-dimethoxysalicylic acid **3d**, 4,6-dihydroxysalicylic acid **3e** indicated further excellent catalytic activity and induced the oxidative coupling in a shorter time (2 h).[44] Although the reason why 4,6-dihydroxysalicylic acid **3e** exhibits a higher catalytic activity compared with 4,6-dimethoxysalicylic acid **3d** is not clear, a better electron-donating ability of the hydroxyl group [Hammett's σ value = −0.37 (p-OH)] compared with that of the methoxyl group [σ value = −0.27 (p-OMe)] might contribute to the efficiency in the present oxidation by increasing the electron density of the organocatalyst. By using the catalyst **3e**, the gram scale synthesis of imine **2a** was examined starting from 10 mmol of **1a** (1.07 g), and 0.72 g (3.7 mmol, 74% isolated yield) of **2a** was obtained successfully, as shown in Table 7.

Table 7. Oxidation of Benzylamine Derivatives Using 4,6-Dihydroxysalicylic Acid as the Organocatalyst[a]



[a]Determined by ^{1}H NMR using 1,3,5-trioxane as the internal standard (isolated yield); yield of **2** is based on substrate **1**. [b]Gram scale: reaction was conducted on 10 mmol of **1a** in 3 mL of toluene using a 50 mL two-neck flask.

CONCLUSIONS

In summary, we have explored a novel metal-free oxidation method to synthesize imines and benzimidazoles from benzylamine derivatives. In this oxidative transformation, the products can be obtained under an atmosphere of oxygen in good to high yields by using salicylic acid derivatives as organocatalysts. Furthermore, the silica gel-supported catalyst realized the oxidative coupling and could attain the recyclability of the catalyst. This oxidation system is cheap, efficient, and

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eco-friendly and can be easily operated. Further investigations of metal-free oxidations are currently under way.

EXPERIMENTAL SECTION

General Remarks. Unless otherwise stated, all benzylamine derivatives, analogues of H_2hpic, salicylic acid derivatives, and silica Q-10C (pore volume = 0.8 cm^3/g; size = 0.85−1.76 mm) were obtained from commercial supplies. All solvents were distilled and degassed with nitrogen before use. ^{1}H NMR spectra were recorded on a JEOL JNM-ECS400 (400 MHz) FT NMR system or a JEOL JNM-ECX400 (400 MHz) FT NMR system in $CDCl_3$ and dimethyl sulfoxide (DMSO)-d_6 with Me_4Si as the internal standard. ^{13}C NMR spectra were recorded on a JEOL JNM-ECX400 (100 MHz) FT NMR system or a JEOL JNM-ECS400 (100 MHz) FT NMR system in $CDCl_3$ and DMSO-d_6.

General Procedure for the Synthesis of Imine Derivatives 2. Benzylamine derivatives **1** (3.0 mmol), 4,6-dimethoxysalicylic acid **3d** (5.0 mol %), and distilled toluene (1.5 mL) were added into a two-neck flask, the reaction vessel was connected to an O_2 balloon at room temperature, and the mixture was stirred at 90 °C under an O_2 atmosphere for 6 h. After the reaction was complete, the resulting mixture was transferred into a round-bottom flask using ethyl acetate and concentrated under reduced pressure. The residue was purified using gel permeation chromatography (eluent: chloroform) to give the product **2**.

N-(Benzylidene)benzylamine (***2a***).[45] Yellow oil, 255 mg, 87% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.79−7.71 (m, 2H), 7.42−7.19 (m, 8H), 4.79 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8, 139.2, 136.0, 130.6, 128.5, 128.4, 128.2, 127.9, 126.9, 64.9.

N-(o-Methylbenzylidene)-o-methylbenzylamine (***2b***).[45] Yellow oil, 284 mg, 85% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (s, 1H), 7.91 (d, J = 7.79 Hz, 1H), 7.32−7.10 (m, 7H), 4.80 (s, 2H), 2.48 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4, 137.6, 137.5, 136.0, 134.1, 130.7, 130.1, 130.0, 128.2, 127.6, 126.9, 126.1, 125.9, 63.2, 19.3, 19.2.

N-(p-Methylbenzylidene)-p-methylbenzylamine (***2c***).[39] White solid, 284 mg, 85% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.65 (d, J = 7.92 Hz, 2H), 7.20 (t, J = 7.52 Hz, 4H), 7.13 (d, J = 8.31 Hz, 2H), 4.75 (s, 2H), 2.36 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6, 140.9, 136.4, 136.3, 133.5, 129.2, 129.1, 128.1, 127.9, 64.7, 21.4, 21.0.

N-(o-Methoxybenzylidene)-o-methoxybenzylamine (***2d***).[39] Yellow oil, 329 mg, 86% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (s, 1H), 8.03 (dd, J = 6.80, 1.81 Hz, 1H), 7.38−7.26 (m, 3H), 7.00−6.81 (m, 4H), 4.82 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 158.2, 156.9, 131.6, 128.9, 128.0, 127.8, 127.3, 124.7, 120.6, 120.3, 110.8, 110.0, 59.5, 55.3, 55.2.

N-(m-Methoxybenzylidene)-m-methoxybenzylamine (***2e***).[46] Yellow oil, 321 mg, 84% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.39−7.38 (m, 1H), 7.33−7.22 (m, 3H), 6.99−6.86 (m, 3H), 6.79 (dd, J = 8.00, 2.50 Hz, 1H), 4.78 (s, 2H), 3.81 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.9, 159.8, 159.7, 140.7, 137.5, 129.5, 129.4, 121.5, 120.2, 117.5, 113.5, 112.3, 111.5, 64.8, 55.3, 55.1.

N-(p-Methoxybenzylidene)-p-methoxybenzylamine (***2f***).[39] Yellow oil, 260 mg, 68% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.68 (d, J = 9.06 Hz, 2H), 7.22 (d, J = 8.61 Hz, 2H), 6.86 (dd, J = 12.23, 8.61 Hz, 4H), 4.68 (s, 2H), 3.75 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5, 160.7, 158.4, 131.5, 129.6, 128.9, 113.8, 113.7, 64.2, 55.1, 55.0.

N-(p-(tert-Butyl)benzylidene)-p-(tert-butyl)benzylamine (***2g***).[46] White solid, 405 mg, 88% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.71 (d, J = 8.70 Hz, 2H), 7.42 (d, J = 8.70 Hz, 2H), 7.35 (d, J = 8.24 Hz, 2H), 7.25 (d, J = 8.24 Hz, 2H), 4.77 (s, 2H), 1.32 (s, 9H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6, 154.10, 149.6, 136.4, 133.5, 128.0, 127.6, 125.4, 125.3, 64.7, 34.8, 34.4, 31.3, 31.2.

N-(p-Chlorobenzylidene)-p-chlorobenzylamine (***2h***).[39] White solid, 335 mg, 85% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1H), 7.68 (d, J = 8.61 Hz, 2H), 7.36 (d, J = 8.61 Hz, 2H), 7.29 (d, J = 9.06 Hz, 2H), 7.23 (d, J = 9.06 Hz, 2H), 4.73 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 137.5, 136.7, 134.3, 132.7, 129.4, 129.2, 128.8, 128.5, 64.0.

N-(p-Trifluoromethylbenzylidene)-p-trifluorobenzylamine (***2i***).[45] Yellow oil, 338 mg, 68% (isolated yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.83 (d, J = 8.31 Hz, 2H), 7.61 (d, J = 7.92 Hz, 2H), 7.56 (d, J = 8.31 Hz, 2H), 7.41 (d, J = 7.92 Hz, 2H), 4.80 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 143.4, 139.3, 132.6 (q, J = 32.1 Hz), 129.4 (q, J = 32.4 Hz), 128.6, 128.2, 125.6 (q, J = 3.9 Hz), 125.5 (q, J = 3.8 Hz), 122.9 (d, J = 35.3 Hz), 120.2 (d, J = 36.2 Hz), 64.3.

General Procedure for the Synthesis of Benzimidazole Derivatives 5. Benzylamine derivatives **1** (1.5 mmol), 1,2-diaminobenzene derivatives **4** (1.0 mmol), 4,6-dimethoxysalicylic acid **3d** (5.0 mol %), and distilled toluene (0.5 mL) were added into a two-neck flask, and the reaction vessel was connected with an O_2 balloon at room temperature. The mixture was stirred at 110 °C under an O_2 atmosphere for 12 h. After the reaction was complete, the resulting mixture was transferred into a round-bottom flask using methanol (MeOH) and concentrated under reduced pressure. The residue was purified using silica gel chromatography [basified by Et_3N (25 wt %)] {eluent: hexane/ethyl acetate [added Et_3N (1.0 v/v %)]} to give the product **5**.

2-Phenyl-1H-benzimidazole (***5a***).[47] Yellowish solid, 147 mg, 76% (isolated yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.93 (br, 1H), 8.22−8.17 (m, 2H), 7.62−7.53 (m, 4H), 7.51−7.46 (m, 1H), 7.23−7.19 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.8, 144.0, 130.7, 130.4, 130.1, 129.6, 129.5, 126.9, 122.6, 119.6, 111.9.

2-(4-Methylphenyl)-1H-benzimidazole (***5b***).[47] Yellow solid, 181 mg, 87% (isolated yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.84 (br, 1H), 8.09 (d, J = 7.99 Hz, 2H), 7.64−7.53 (m, 2H), 7.35 (d, J = 8.39 Hz, 2H), 7.20−7.19 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.9, 144.3, 140.1, 135.5, 130.0, 128.0, 126.9, 122.8, 122.1, 119.2, 111.7, 21.5.

2-(2-Methoxyphenyl)-1H-benzimidazole (***5c***).[47] Yellow solid, 156 mg, 83% (isolated yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.16 (br, 1H), 8.37−8.35 (m, 1H), 7.66−7.63 (m, 2H), 7.49−7.45 (m, 1H), 7.24−7.02 (m, 4H), 4.01 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.3, 149.5, 143.3, 135.3, 131.8, 130.3, 122.6, 122.0, 121.4, 118.9, 118.7, 112.6, 112.5, 56.3.

2-(3-Methoxyphenyl)-1H-benzimidazole (***5d***).[47] Brown solid, 193 mg, 86% (isolated yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.89 (br, 1H), 7.78−7.55 (m, 4H), 7.46 (t, J = 7.59 Hz, 1H), 7.21 (s, 2H), 7.06 (d, J = 8.79 Hz, 1H), 3.86 (s,

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3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.2, 151.6, 132.0, 130.6, 123.1, 119.3, 116.4, 111.9, 55.8.

*2-(4-Methoxyphenyl)-1H-benzimidazole (**5e**).*[47] Yellow solid, 181 mg, 81% (isolated yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.78 (br, 1H), 8.16−8.14 (m, 2H), 7.58 (s, 2H), 7.18−7.10 (m, 4H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.1, 151.9, 128.6, 123.3, 122.4, 118.9, 114.9, 111.5, 55.8.

*2-(3-Chlorophenyl)-1H-benzimidazole (**5f**).*[47] Yellow solid, 180 mg, 79% (isolated yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.04 (br, 1H), 8.24 (s, 1H), 8.17−8.15 (m, 1H), 7.62−7.53 (m, 4H), 7.24−7.22 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.3, 134.3, 132.7, 131.4, 130.0, 126.6, 125.5, 123.4, 122.8, 119.7, 112.1.

*2-(4-Chlorophenyl)-1H-benzimidazole (**5g**).*[47] Yellow solid, 203 mg, 89% (isolated yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.00 (br, 1H), 8.21 (d, J = 6.80 Hz, 2H), 7.67−7.57 (m, 4H), 7.22 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.7, 144.3, 144.2, 135.0, 129.6, 128.7, 123.2, 122.5, 119.5, 111.9.

*2-(4-(Trifluoromethyl)phenyl)-1H-benzimidazole (**5h**).*[48] Yellow solid, 202 mg, 77% (isolated yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.17 (br, 1H), 8.40 (d, J = 7.19 Hz, 2H), 7.92 (d, J = 7.59 Hz, 2H), 7.65 (s, 2H), 7.25 (d, J = 2.80 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.2, 134.5, 130.3, 130.0, 129.7, 128.7, 127.6, 126.5, 126.4, 126.0, 123.3, 119.8, 112.3.

*6-Methyl-2-phenyl-1H-benzimidazole (**5i**).*[47] Yellow solid, 179 mg, 86% (isolated yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.79 (br, 1H), 8.22−8.17 (m, 2H), 7.56−7.36 (m, 5H), 7.02 (d, J = 7.99 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.4, 130.9, 130.2, 129.4, 126.8, 124.0, 119.0, 111.6, 21.9.

*7-Methyl-2-phenyl-1H-benzimidazole (**5j**).*[49] Yellow solid, 178 mg, 86% (isolated yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.86 (br, 0.5H), 12.60 (br, 0.5H), 8.23 (s, 2H), 7.55 (t, J = 7.59 Hz, 2H), 7.49−7.30 (m, 2H), 7.09 (t, J = 7.39 Hz, 1H), 6.99 (d, J = 7.19 Hz, 1H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.9, 143.7, 135.1, 130.9, 130.2, 129.4, 128.9, 127.0, 123.6, 122.9, 122.4, 116.8, 109.3, 17.3.

*5,6-Dimethyl-2-phenyl-1H-benzimidazole (**5k**).*[40] Yellow solid, 120 mg, 54% (isolated yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.67 (br, 1H), 8.16 (d, J = 6.79 Hz, 2H), 7.54−7.31 (m, 5H), 2.32 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.9, 143.1, 134.1, 131.7, 131.0, 130.4, 129.9, 129.4, 126.7, 119.5, 111.9, 20.6.

*6-Bromo-2-phenyl-1H-benzimidazole (**5l**).*[50] Yellow solid, 235 mg, 86% (isolated yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.15 (br, 1H), 8.27−8.17 (m, 2H), 7.81 (s, 1H), 7.57−7.49 (m, 4H), 7.35−7.33 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.0, 130.7, 130.2, 129.5, 127.1, 125.5, 114.8.

*Methyl-2-phenyl-1H-benzimidazole-6-carboxylate (**5m**).*[51] Yellow solid, 206 mg, 82% (isolated yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.15 (br, 1H), 8.27−8.21 (m, 3H), 7.86−7.84 (m, 1H), 7.68−7.66 (m, 1H), 7.59−7.52 (m, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.3, 154.3, 130.9, 130.1, 129.5, 127.3, 123.9, 123.8, 52.5.

*1-Methyl-2-phenyl-1H-benzimidazole (**5n**).*[52] Yellow solid, 175 mg, 84% (isolated yield); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.87−7.85 (m, 2H), 7.71 (d, J = 7.20 Hz, 1H), 7.61−7.56 (m, 4H), 7.33−7.24 (m, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.5, 143.0, 137.1, 130.7, 130.1, 129.8, 129.2, 122.9, 122.4, 119.5, 111.1, 32.2.

Experimental Procedure for the Synthesis of 4.7 wt % 3e on Silica Gel. Silica Q-10C (5.0 g, pore volume = 0.8 cm^3/g, size = 0.85−1.76 mm) was added into a Kugelrohr distillation apparatus and dried at 150 °C (0.5 Torr) for 5 h to give dried silica Q-10C (4.92 g). Then, the dried silica Q-10C was mixed with 4,6-dihydroxy salicylic acid (**3e**, 493.6 mg, 10 wt % of dried silica Q-10C) and 10 mL of ethyl acetate in a round-bottom flask, and the resulting mixture was kept static for 12 h. After concentration by vacuum, the catalyst was dried using the Kugelrohr apparatus at 150 °C (1.1 Torr) for 5 h. The resultant small brown ball was washed using ethyl acetate (10 mL × 3). The filter cake was concentrated by vacuum and further dried using the Kugelrohr apparatus at 150 °C (0.8 Torr) for 6 h to afford 4.7 wt % **3e** on silica gel (5.16 g).

Experimental Procedure for Recycling Study. Benzylamine **1a** (321.4 mg, 3.0 mmol), catalyst 4.7 wt % **3e** on silica gel (542.9 mg, 0.15 mol), and distilled toluene (1.5 mL) were added into a two-neck flask, and the reaction vessel was connected with an O_2 balloon at room temperature. After stirring at 90 °C under an O_2 atmosphere for 2 h, the reaction mixture was filtered. The filter cake was washed using ethyl acetate (5 mL × 3) and dried by vacuum to recover the catalyst 4.7 wt % **3e** on silica gel, which was used for the next run directly. The filtrate was concentrated under reduced pressure and detected using ^{1}H NMR to calculate the yield of product **2a** (84% for the first run).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.6b00235.

^{1}H NMR and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(43) Recovery of 4,6-dihydroxysalicylic acid **3e** was also conducted using acid−base extraction. After the reaction was complete, the reaction mixture was concentrated in vacuo, the residue was added to a 15% NaOH aqueous solution, and the product was extracted with ethyl acetate (EtOAc). Evaporation of the organic layer successfully afforded **2a** in 71% yield. In this treatment, the Na salt of **3e** might be moved to the aqueous layer. Thus, the aqueous layer was acidified with 3 N HCl, and extraction with ethyl acetate (EtOAc) was performed. Unfortunately, however, the organic layer did not contain 4,6-dihydroxysalicylic acid **3e**, most probably due to the decomposition of the catalyst **3e**. Therefore, further detailed optimization of reaction and extraction conditions is required for recovery of the catalyst **3e**.

(44) The oxidative coupling of benzylamine to the corresponding imine was conducted using 4-hydroxybenzoic acid and the related hydroxyl substituted benzoic acids (2,4-dihydroxybonzoic acid, 2,6-dihydroxybonzoic acid, and salicylic acid itself), and the results are shown in Table S2 in the Supporting Information. As can be seen from Table S2, these organocatalysts were all less effective compared with 4,6-dihydroxysalicylic acid **3e**, clearly indicating that the present oxidative coupling of benzylamines requires 4,6-dihydroxysalicylic acid **3e** (or 4,6-dimethoxysalicylic acid **3d**) as organocatalyst.

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