Graphical Abstract

Carbon–carbon bond formations at the benzylic positions of *N*-benzylxanthone imines and *N*-benzyldi-1-naphthyl ketone imine

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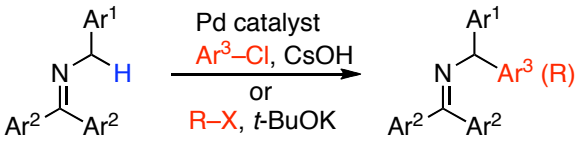

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Carbon–carbon bond formations at the benzylic positions of *N*-benzylxanthone imines and *N*-benzyldi-1-naphthyl ketone imine

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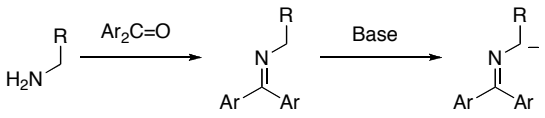
Abstract—Two *N*-benzyl imines are designed to allow for carbon–carbon bond formations at the aminated benzylic positions. Direct benzylic arylation reactions of *N*-benzylxanthone imine with aryl chlorides proceed under palladium catalysis in the presence of cesium hydroxide, yielding the corresponding benzhydrylamine derivatives. Alkylation reactions of *N*-benzyldi-1-naphthyl ketone imine with alkyl halides in the presence of potassium *tert*-butoxide afford the corresponding 1-phenylalkylamines in high yields. Conjugate addition of *N*-benzyldi-1-naphthyl ketone imine is also described.

1. Introduction

Functionalizations of amines are important in organic synthesis. Among possible transformations, generation of carbanions adjacent to nitrogen is interesting and represents umpolung of the customary reactivity of amines. A nitrogen atom bearing an electron-withdrawing group enables the adjacent C–H bond to be readily metalated.[1] As a method for the activation, formation of imine with aromatic ketone is promising (Scheme 1). Deprotonation becomes facile due to the formation of highly delocalized azaallyl anion.

Here we report carbon–carbon bond formations by using two *N*-benzyl imines. *N*-Benzylxanthone imine proved to react with aryl chloride in the presence of cesium hydroxide and a palladium catalyst to lead to benzylic arylation of the imine.[2] The other imine, *N*-benzyldi-1-naphthyl ketone imine, is found to be suitable for benzylic alkylation and conjugate addition by means of potassium *tert*-butoxide.



Scheme 1. Preparation of imine for base-mediated activation of C–H bond adjacent to nitrogen.

2. Result and discussion

2.1. Palladium-catalyzed benzylic arylation of *N*-benzylxanthone imine with aryl chloride

Transition-metal-catalyzed arylation of a C(sp^3)–H bond with aryl halide via deprotonation of the acidic hydrogen is a recently developed powerful carbon–carbon bond forming strategy.[3–7] We envisioned that the strategy would be applicable to direct arylation of *N*-benzyl ketimine at the benzylic position (Scheme 2). Imine **1**, readily prepared from benzylamine and aromatic ketone, has acidic benzylic hydrogens.[8] Palladium-catalyzed arylation of **1** with aryl halide would afford **2**, which is then subjected to hydrolysis to yield **3**. The overall transformation represents a formal cross-coupling reaction of aryl halide with an α-aminobenzyl metal.

Keywords: benzylic arylation, palladium, deprotonation, benzylic alkylation, *N*-benzylimines.

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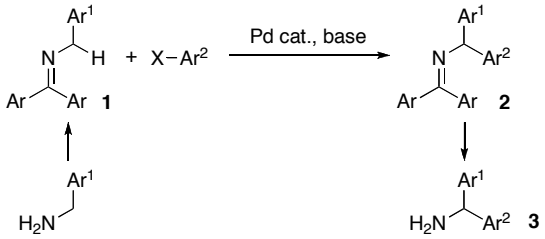
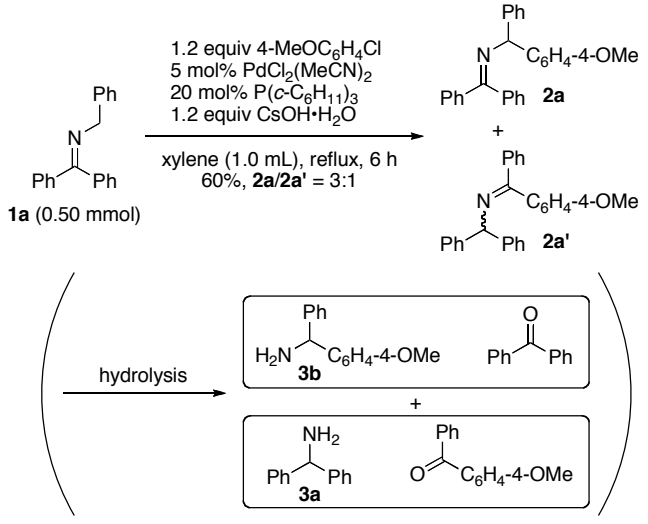


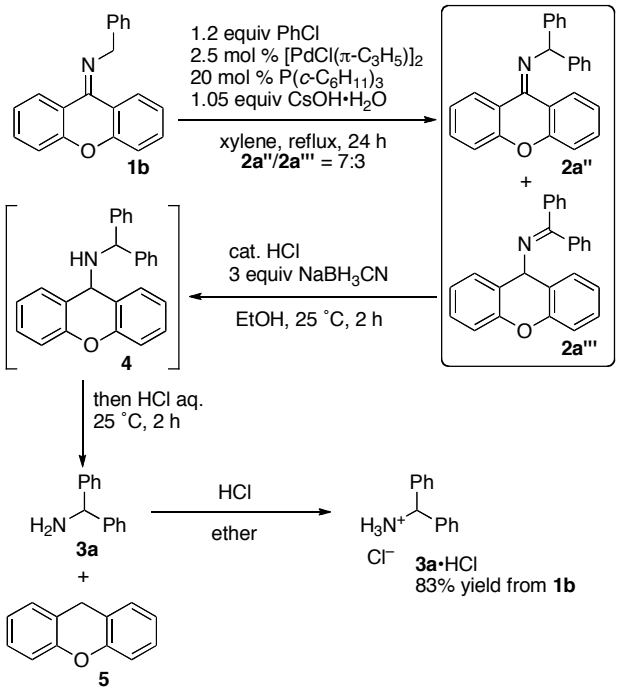
Scheme 2. Concept of formal benzylic arylation of benzylamine.

Our initial attempt employed *N*-benzylbenzophenone imine (**1a**) as a substrate (Scheme 3). Treatment of **1a** with 4-chloroanisole in the presence of cesium hydroxide and catalytic amounts of $PdCl_2(MeCN)_2$ and $P(c\text{-}C_6H_{11})_3$ in refluxing xylene provided the corresponding arylated product **2a**. However, unexpected isomer **2a'** was obtained as a byproduct. Cesium-hydroxide-mediated benzylic deprotonation of initially formed **2a** readily took place in situ to form the corresponding azaallylic anion. The azaallylic anion was protonated in situ to form **2a** or **2a'**. Iterations of the deprotonation/protonation sequence would afford the 3:1 mixture. Apparently, hydrolysis of the mixture would yield a mixture of benzhydrylamines **3a** and **3b**. To achieve the formal benzylic arylation of benzylamine as outlined in Scheme 2, the isomerization had to be precluded. After many attempts, we concluded that the isomerization was inevitable.



Scheme 3. Palladium-catalyzed benzylic arylation of *N*-benzylbenzophenone imine (**1a**).

The inevitable isomerization eventually led us to design *N*-benzylxanthone imine (**1b**). Treatment of **1b** with chlorobenzene in the presence of cesium hydroxide under palladium catalysis afforded the corresponding coupling product **2a''** and its isomer **2a'''** in a ratio of 7:3 (Scheme 4). The mixture of **2a''** and **2a'''** was then reduced by means of sodium cyanoborohydride and a catalytic amount of hydrochloric acid in ethanol to afford secondary amine **4** in the reaction flask. Further addition of an excess of hydrochloric acid resulted in the formation of benzhydrylamine (**3a**) and xanthene (**5**). The oxygen-bridged xanthene moiety is the suitable scaffold of *N*-benzyl imine because of the exclusive formations of **3a** and highly delocalized and thus stable 9-xanthenyl cation. Reduction of the xanthenyl cation took place with the remaining sodium cyanoborohydride in the same pot to form xanthene (**5**). After simple acid/base extraction in a separatory funnel, the product **3a** was isolated as its hydrochloride salt **3a**•HCl in 83% overall yield. It is worth noting that each step was high yielding and that no chromatographic purification was required during the overall process.



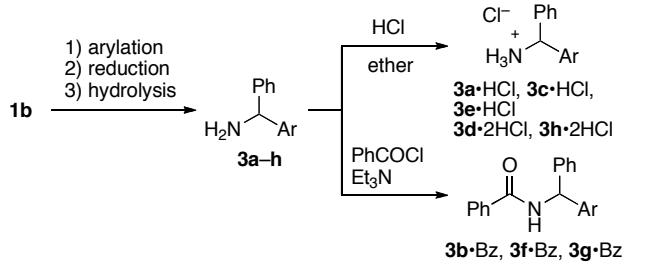
Scheme 4. Palladium-catalyzed benzylic arylation of *N*-benzylxanthone imine (**1b**).

Although the reaction of **1b** with iodobenzene afforded a complex mixture, that with bromobenzene yielded **3a**•HCl in 80% yield under otherwise the same reaction conditions. Other trialkylphosphines, such as PMe_3, $P(c\text{-}C_5H_9)_3$, $P(n\text{-}Bu)_3$, and $P(t\text{-}Bu)_3$, were inferior to $P(c\text{-}C_6H_{11})_3$, and 30–50% combined yields of **2a''** and **2a'''** were obtained along with mixtures of unidentified byproducts. Use of triarylphosphines including PPh_3 and $P(o\text{-}Tol)_3$ resulted in low combined yields of **2a''** and **2a'''** (30–50%), which were accompanied by byproducts and recovered **1a** (10–30%). The 1:4 molar ratio of $Pd/P(c\text{-}C_6H_{11})_3$ is important. The combined yield of **2a''** and **2a'''** was less than 20% when a $Pd/P(c\text{-}C_6H_{11})_3$ ratio was 1:3. As the precursor of the catalyst, other palladium complexes, including $Pd(acac)_2$, $PdCl_2(PhCN)_2$, and $Pd(OAc)_2$, showed comparable yet slightly lower catalytic activity. A temperature as high as 140 °C was essential. A similar reaction in refluxing toluene led to very low conversion. Cesium hydroxide is the only effective base among the

bases tested. The use of KOH, *t*-BuOK, and Cs_2CO_3 gave only traces of **2a''** and **2a'''**.

Table 1 shows the scope of aryl chlorides. The electronic properties of aryl chlorides have little influence on the efficiency of the reaction. Electron-rich aryl chlorides (entries 2–4) as well as an electron-deficient one (entry 7) reacted smoothly. However, neither acetyl nor alkoxycarbonyl moieties survived under the basic conditions. 2-Chlorotoluene underwent the reaction similarly, irrespective of the steric hindrance of the 2-methyl group (entry 5). The reaction of 4-chlorostyrene provided the desired product **3f**•Bz in moderate yield (entry 6), although the aryl chloride can alternatively undergo polymerization via intermolecular Mizoroki–Heck reaction,[9] forming oligo(4-phenylenevinylene). Installation of a 2-pyridyl ring at the benzylic position was facile (entry 8).

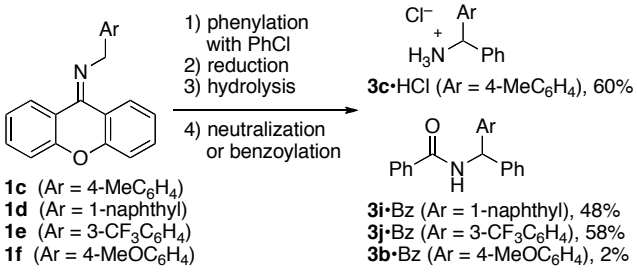
Table 1. Arylation of **1b** with ArCl and isolation of benzhydrylamine derivatives[a,b]



entry	ArCl	product	yield /%
1	C_6H_5Cl	**3a**•HCl	83
2	4-$MeOC_6H_4Cl$	**3b**•Bz	75
3	4-MeC_6H_4Cl	**3c**•HCl	73
4	4-$Me_2NC_6H_4Cl$	**3d**•2HCl	82
5	2-MeC_6H_4Cl	**3e**•HCl	73
6	4-CH_2=CHC_6H_4Cl	**3f**•Bz	47[c]
7	4-$Me_2NC(=O)C_6H_4Cl$	**3g**•Bz	71
8	2-chloropyridine	**3h**•2HCl	80

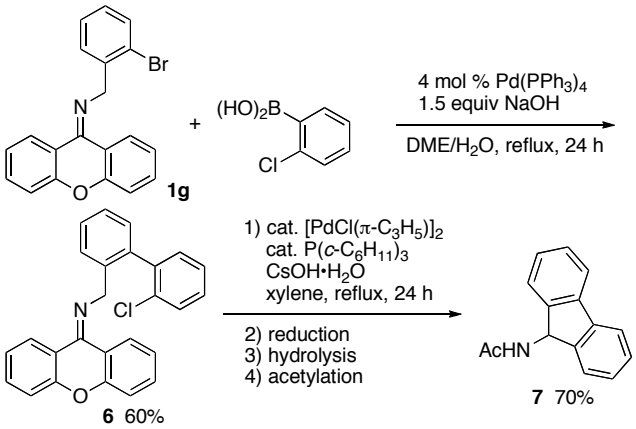
[a] The reaction conditions are the same as shown in Scheme 4. [b] Instead of treatment with HCl, benzoylation of **3b**, **3f**, and **3g** was performed for purification (entries 2, 6, and 7). [c] Formic acid was used instead of hydrochloric acid to remove the xanthenyl group.

The scope of the aryl group of *N*-(arylmethyl)xanthone imines was not satisfactorily wide (Scheme 5). For instance, **1f** having an electron-donating methoxy group suffered from very low conversion, probably due to the slower deprotonation.



Scheme 5. Scope of *N*-(arylmethyl)xanthone imines

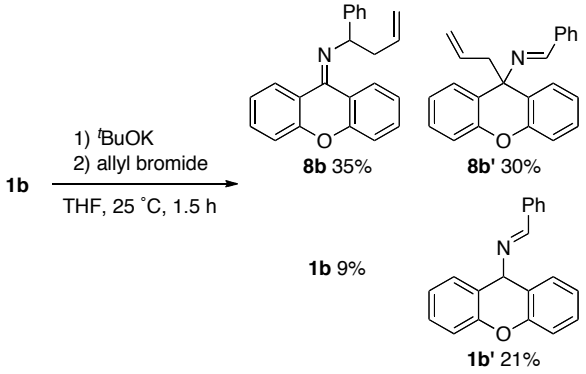
The benzylic arylation offers a new route to 9-fluorenylamine derivatives (Scheme 6). The palladium-catalyzed cross-coupling reaction of **1g** with *o*-chlorophenylboronic acid yielded biaryl **6**. The intramolecular benzylic arylation of **6** constructed fluorenylamine skeleton, eventually affording **7**.



Scheme 6. Synthesis of fluorenylamine

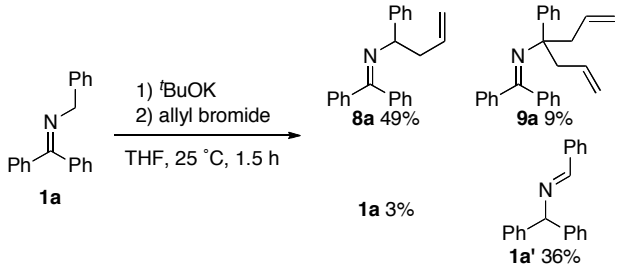
2.2. Benzylic alkylation of *N*-benzyldi-1-naphthyl ketone imine with alkyl halides or acrylamides

We next examined allylation of **1b** with allyl bromide in the presence of a base. Treatment of **1b** with potassium *tert*-butoxide in THF at 25 ˚C followed by addition of allyl bromide afforded the desired allylated product **8b** in only 35% yield (Scheme 7). Product **8b** was contaminated with its isomer **8b'**, starting material **1b**, and **1b'** that is the regioisomer of **1b**.



Scheme 7. Allylation of **1b**

There is a report of the efficient reaction of *N*-benzylbenzophenone imine (**1a**) with allyl bromide under similar reaction conditions to yield allylated product **8a** in high yield selectively.[10] However, we could not reproduce the result, and the reaction resulted in formation of a mixture of **8a** and diallylated **9a** as well as moderate conversion (Scheme 8).

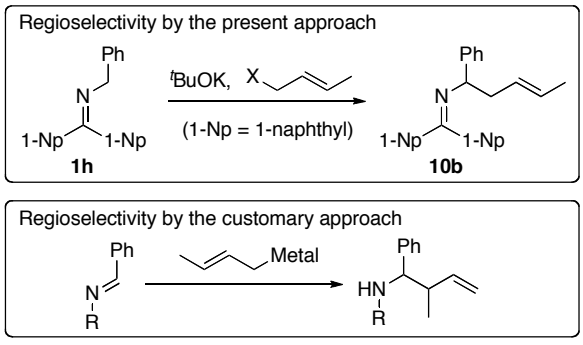


Scheme 8. Allylation of **1a**

We thought that increasing the steric hindrance at the ketimine scaffold led to cleaner allylation, avoiding the second allylation. Finally, di-1-naphthyl ketone imine **1h** proved to be converted to monoallylated product **10a** exclusively (Table 2, entry 1). Removal of the di-1-naphthylmethylene moiety was successful upon treatment of **10a** with hydroxylamine in aqueous ethanol at 150 ˚C under microwave irradiation. It is worth noting that heating **10a** conventionally for 24 h at reflux afforded a complex mixture containing none of **11a**. The amine **11a** was isolated as its benzamide derivative **11a**•Bz.

The reaction of **1h** with crotyl chloride occurred at the chlorinated carbon of crotyl chloride in an S_N2 manner (entry 2). Cinnamyl bromide and prenyl bromide also underwent S_N2 reaction similarly (entries 3 and 4). On the other hand, the reaction with 3-chloro-1-butene took place in an S_N2' mode to yield **11b**•Bz exclusively (entry 6). The potassium salt of **1h** is bulky enough to react with allylic electrophiles selectively at the less hindered position. The regioselectivity of the reaction complements that of the reaction of benzaldehyde imine with allylic nucleophiles (Scheme 9).

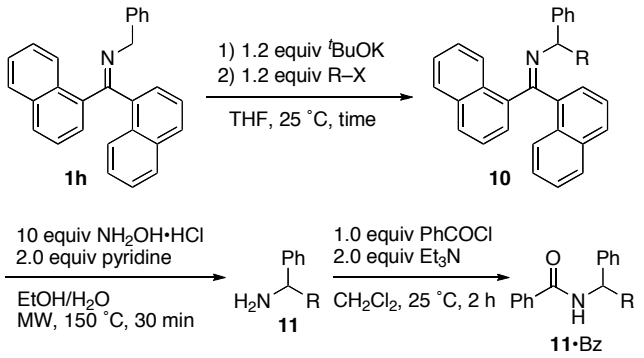
Not only allylic electrophiles but also alkyl halides underwent nucleophilic substitution (entries 7–10). Primary alkyl bromides reacted smoothly, although 2-bromobutane was less reactive to afford the corresponding amide **11i**•Bz in 50% yield.

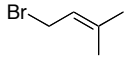
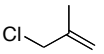
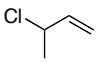
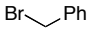
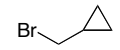
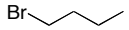
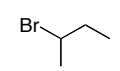


Scheme 9. Regioselectivity in synthesizing homoallylamines.

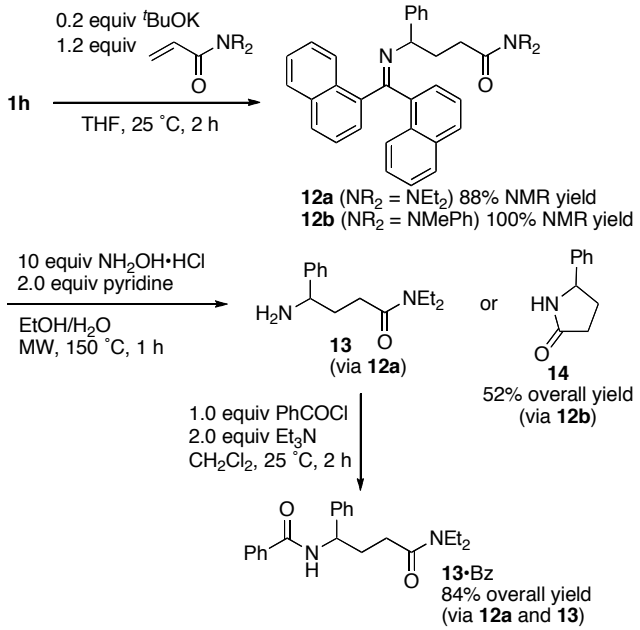
Acrylamides are good Michael acceptors that underwent conjugate addition of **1h** with the aid of potassium *tert*-butoxide (Scheme 10). The resulting 1,4-adducts **12a** and **12b** were then treated with hydroxylamine to release the corresponding amines. Imine **12a** was converted to the anticipated amine **13** in excellent yield. In contrast, γ-phenyl-γ-butyrolactam (**14**) was exclusively obtained from **12b** under the same reaction conditions. The difference would be due to the ability of the NR_2 group as a leaving group.

Table 2. Alkylation of **1h**



entry	R–X	time /h	**10** /%[a]	**11**•Bz /%[b]
1		2.5	**10a**, 100	**11a**•Bz, 90
2[c]		5.0	**10b**, 89[d]	**11b**•Bz, 71[e,f]
3		2.5	**10c**, 90[d,g]	**11c**•Bz, 61[f]
4		2.0	**10d**, 100[d]	**11d**•Bz, 62[f]
5		1.5	**10e**, 89	**11e**•Bz, 78
6		1.0	**10b**, 73[d]	**11b**•Bz, 77[f,h]
7		1.0	**10f**, 89[d]	**11f**•Bz, 78
8		4.5	**10g**, 91	**11g**•Bz, 87
9		6.0	**10h**, 82	**11h**•Bz, 71
10		24	**10i**, ND[d,i]	**11i**•Bz, 50

[a] NMR yield. [b] Isolated yield based on **1h**. [c] *E*/*Z* = 83:17. [d] Microwave irradiation was performed for 1.0 h to complete the liberation of **11**. [e] *E*/*Z* = 85:15. [f] Linear product, $PhCONHCH(Ph)CH_2CH{=}CR^1R^2$, was exclusively obtained without contamination by the corresponding branched isomer, $PhCONHCH(Ph)CR^1R^2CH{=}CH_2$. [g] A larger amount of ^{t}BuOK (2.0 equiv) was used. [h] *E*/*Z* = 90:10. [i] Not determined.



Scheme 10. Conjugate addition of **1h** to acrylamides

3. Conclusion

Two *N*-benzyl imines are designed to allow for carbon–carbon bond formations at the aminated benzylic positions, which represent umpolung of the customary reactivity of amines. Direct benzylic arylation reactions of *N*-benzylxanthone imine with aryl chlorides proceed under palladium catalysis in the presence of cesium hydroxide, yielding the corresponding benzhydrylamine derivatives. As for nucleophilic alkylation and conjugate addition, *N*-benzyldi-1-naphthyl ketone imine is the suitable imine to react with alkyl halides and acrylamides in the presence of potassium *tert*-butoxide.

4. Experimental

4.1. General

4.1.1. Instrumentation

^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra were taken on a Varian Unity INOVA 500 spectrometer and were recorded in $CDCl_3$ [using tetramethylsilane (for ^{1}H, δ = 0.00 ppm) and $CDCl_3$ (for ^{13}C, δ = 77.2 ppm) as an internal standard] or DMSO-d_6 [using DMSO (for ^{1}H, δ = 2.50 ppm) and DMSO-d_6 (for ^{13}C, δ = 39.7 ppm) as an internal standard]. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. Mass spectra were determined on a JEOL Mstation 700 spectrometer. Melting points were determined on Yanaco micro melting point apparatus. TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck Silica gel 60F_{254}. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

The reactions under microwave conditions were carried out using a focused microwave unit (Biotage Initiator™). The maximum irradiation power is 400 W. Each reaction was run in a 5-mL glass pressure vial, which is a commercially available vial special for the Biotage Initiator™. It took 4 min to reach 150 ˚C. After reaching the indicated temperatures, controlled microwave irradiation started and continued for 30 (or 60) min, keeping the reaction temperature constant.

4.1.2. Materials

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Toluene and xylene were purchased from Wako Pure Chemical Co. and stored over slices of sodium. Cesium hydroxide monohydrate was purchased from Nacalai Tesque. Tricyclohexylphosphine was purchased from Strem. Allylpalladium(II) chloride dimer was obtained from Aldrich Chemicals. Preparations of imines are shown below. Acrylamides were prepared by reactions of acryloyl chloride with secondary amine.

4.2. Experimental procedures

4.2.1. Synthesis of *N*-benzyl imines

The synthesis of **1b** is representative. A solution of titanium(IV) chloride (4.1 mL, 37.5 mmol) in toluene (50 mL) was slowly added to a solution of xanthone (9.8 g, 50 mmol) and benzylamine (24.6 mL, 225 mmol) in toluene (150 mL) at 0 °C. The resulting mixture was stirred for 30 min at ambient temperature, and then for 6 h at reflux. Diethyl ether (200 mL) was added, and the reaction mixture was passed through a pad of Celite and the precipitate was washed with diethyl ether (40 mL × 3). The solvent was removed under reduced pressure. *N*-Benzylxanthone imine (**1b**) was recrystallized from hexane/toluene as a white solid (13.1 g, 46 mmol) in 92% yield. Other imines were prepared in a similar fashion.

4.2.2. Typical procedure for synthesis of benzhydrylamine hydrochlorides (Table 1)

Synthesis of benzhydrylamine hydrochloride (**3a•HCl**) is representative. Cesium hydroxide monohydrate (0.18 g, 1.05 mmol) and allylpalladium chloride dimer (9.1 mg, 0.025 mmol) were placed in a 20-mL two-necked reaction flask equipped with a Dimroth condenser under argon atmosphere. Tricyclohexylphosphine (0.5 M in toluene, 0.40 mL, 0.20 mmol), xylene (2.0 mL), *N*-benzylxanthone imine (**1b**) (285 mg, 1.0 mmol), and chlorobenzene (0.12 mL, 1.2 mmol) were sequentially added at ambient temperature. The resulting mixture was heated at reflux for 24 h. After the mixture was cooled to room temperature, a saturated aqueous ammonium chloride solution (5 mL) was added. The product was extracted with chloroform (10 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. The residue included a

mixture of imines **2a''** and **2a'''** (7 : 3), which was used for the next step without further purification.

A drop of hydrochloric acid (12 M) was added to a solution of the crude mixture of **2a''** and **2a'''** and sodium cyanoborohydride (189 mg, 3.0 mmol) in ethanol (5 mL). The resulting mixture was stirred at 25 ˚C for 2 h. Hydrochloric acid (12 M, 5 mL) and water (1 mL) were then added, and the resulting mixture was stirred at 25 ˚C for 2 h. The reaction was quenched with water (10 mL), and diethyl ether (10 mL) was then added. The product was extracted with hydrochloric acid (1 M, 5 mL × 3). The combined aqueous layer was neutralized with sodium hydroxide and extracted with chloroform (5 mL × 3). The combined organic layer was dried over sodium sulfate, and concentrated in vacuo. The residue containing amine **3a** was used for the next step without further purification.

Hydrochloride in ether (1.0 M, 2.0 mL, 2.0 mmol) was added to a solution of the crude amine **3a** in methanol (5 mL). After the mixture was stirred for 2 h at room temperature, the solvent was removed in vacuo. Anhydrous ether (20 mL) was added to the resulting mixture. Insoluble materials were collected by filtration to yield benzhydrylamine hydrochloride (**3a•HCl**) (183 mg, 0.83 mmol, 83% overall yield).

4.2.3. Procedure for synthesis of *N*-benzhydrylbenzamides (Table 1)

The synthesis of **3f** is representative. Cesium hydroxide monohydrate (0.18 g, 1.05 mmol) and allylpalladium chloride dimer (9.1 mg, 0.025 mmol) were placed in a 20-mL two-necked reaction flask equipped with a Dimroth condenser under argon atmosphere. Tricyclohexylphosphine (0.5 M in toluene, 0.40 mL, 0.20 mmol), xylene (2.0 mL), *N*-benzylxanthone imine (**1b**) (285 mg, 1.0 mmol), and *p*-chlorostyrene (0.14 mL, 1.2 mmol) were sequentially added at ambient temperature. The resulting mixture was heated at reflux for 24 h. After the mixture was cooled to room temperature, a saturated aqueous ammonium chloride solution (5 mL) was added. The product was extracted with chloroform (10 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. The residue included a mixture of the corresponding imines **2f''** and **2f'''**, which was used for the next step without further purification.

A drop of formic acid was added to a solution of the crude mixture of **2f''** and **2f'''** and sodium cyanoborohydride (189 mg, 3.0 mmol) in ethanol (5 mL). The resulting mixture was stirred at 80 ˚C for 2 h. Formic acid (5 mL) and water (1 mL) were then added, and the resulting mixture was stirred at 80 ˚C for 2 h. The reaction was quenched with water (10 mL), and diethyl ether (10 mL) was then added. The product was extracted with hydrochloric acid (1 M, 5 mL × 3). The combined aqueous layer was neutralized with sodium hydroxide, and extracted with chloroform (5 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. The residue containing amine **3f** was used for the next step without further purification.

Benzoyl chloride (0.12 mL, 1.0 mmol) was added to a solution of the crude amine **3f** and triethylamine (0.28 mL, 2.0 mmol) in dichloromethane (5 mL). After the mixture was stirred for 2 h at room temperature, the reaction was quenched with water (10 mL). The product was extracted with chloroform (5 mL × 3). The combined organic layer was dried over sodium sulfate, and concentrated in vacuo. Silica gel column purification (hexane/ethyl acetate = 5 : 1) provided *N*-benzhydrylbenzamide **3f•Bz** (146 mg, 0.47 mmol) in 47% overall yield.

4.2.4. Procedure for Suzuki–Miyaura cross-coupling reaction of imine 1g with *o*-chlorophenylboronic acid

Sodium hydroxide (30 mg, 0.75 mmol), tetrakis(triphenylphosphine)palladium (11.6 mg, 0.01 mmol), *o*-chlorophenylboronic acid (152 mg, 1.0 mmol), and imine **1g** (182 mg, 0.50 mmol) were placed in a 20-mL two-necked reaction flask equipped with a Dimroth condenser under argon atmosphere. Dimethoxyethane (3.0 mL) and water (0.5 mL) were sequentially added at ambient temperature. The resulting mixture was heated at 100 ˚C for 24 h. After the mixture was cooled to room temperature, a saturated aqueous ammonium chloride solution (5 mL) was added. The product was extracted with ethyl acetate (10 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. Chromatographic purification through a short silica gel column (hexane/ethyl acetate = 1 : 1) provided crude product. The yield of the product **6** (60%) was determined by ^{1}H NMR measurement with 1,1,2,2-tetrachloroethane as an internal standard. The residue was used to synthesize **7** without further purification.

4.2.5. Synthesis of *N*-(9-fluorenyl)acetamide (7)

Cesium hydroxide monohydrate (0.88 g, 0.53 mmol) and allylpalladium chloride dimer (4.6 mg, 0.013 mmol) were placed in a 20-mL two-necked reaction flask equipped with a Dimroth condenser under argon atmosphere. Tricyclohexylphosphine (0.5 M in toluene, 0.2 ml, 0.10 mmol), xylene (2.5 mL), and crude imine **6** described above were sequentially added at ambient temperature. The resulting mixture was heated at reflux for 24 h. After the mixture was cooled to room temperature, a saturated aqueous ammonium chloride solution (5 mL) was added. The product was extracted with chloroform (10 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. The residue was used for the next step without further purification.

A drop of hydrochloric acid (12 M) was added to a solution of the crude imine described above and sodium cyanoborohydride (90 mg, 1.5 mmol) in ethanol (2.5 mL). The resulting mixture was stirred at 25 ˚C for 2 h. Hydrochloric acid (12 M, 2.5 mL) and water (0.5 mL) were then added, and the resulting mixture was stirred at 25 ˚C for 2 h. The reaction was quenched with water (5 mL), and diethyl ether (5 mL) was then added. The product was extracted with hydrochloric acid (1 M, 3 mL × 3). The combined aqueous layer was neutralized with sodium hydroxide and extracted with chloroform (5 mL × 3). The combined organic layer was dried over sodium sulfate and

concentrated in vacuo. The residue containing 9-fluorenylamine was used for the next step without further purification.

Acetyl chloride (0.11 mL, 1.5 mmol) was added to a solution of the crude amine and triethylamine (0.21 mL, 1.5 mmol) in dichloromethane (5 mL). After the mixture was stirred for 2 h at room temperature, the reaction was quenched with water (10 mL). The product was extracted with chloroform (5 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. Silica gel column purification (hexane/ethyl acetate = 5 : 1) provided *N*-(9-fluorenyl)acetamide (**7**, 47 mg, 0.21 mmol) in 70% isolated yield starting from **6**.

4.2.6. Typical procedure for alkylation with allyl/alkyl halides (Table 2)

Synthesis of *N*-(3-methyl-1-phenyl-3-butenyl)benzamide (**11e**•Bz) is representative. Potassium *tert*-butoxide (1.0 M in tetrahydrofuran, 1.2 mL, 1.2 mmol) was added to a solution of *N*-benzyldi-(1-naphthyl) ketone imine **1h** (372 mg, 1.0 mmol) in tetrahydrofuran (5.0 mL) at 25 ˚C and the reaction mixture was stirred for 10 min. Methallyl chloride (0.12 mL, 1.2 mmol) was then added, and the reaction mixture was stirred for 1.5 h at ambient temperature. A saturated aqueous ammonium chloride solution (5 mL) was added, and the product was extracted with ethyl acetate (5 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. The residue included imine **10e**, which was used for the next step without further purification.

The crude imine and hydroxylamine hydrochloride (700 mg, 10 mmol) were placed in a 5-mL glass pressure vial. The vial was flushed with argon and sealed with a PTFE-silicone septum. Pyridine (0.16 mL, 2.0 mmol), ethanol (2.5 mL), and water (1.0 mL) were added, and the suspension was heated at 150 ˚C with stirring for 30 min in the microwave reactor. The mixture was then cooled to room temperature. Water was added, and the product was extracted with hydrochloric acid (1 M, 5 mL × 3). The combined aqueous layer was neutralized with sodium hydroxide, and extracted with chloroform (5 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. The residue contained the corresponding amine, which was used for the next step without further purification.

Benzoyl chloride (0.12 mL, 1.0 mmol) was added to a solution of the crude amine and triethylamine (0.28 mL, 2.0 mmol) in dichloromethane (5 mL). After the mixture was stirred for 2 h at room temperature, the reaction was quenched with water (10 mL). The product was extracted with chloroform (5 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. Silica gel column purification (hexane/ethyl acetate = 5 : 1) provided *N*-(3-methyl-1-phenyl-3-butenyl)benzamide (**11e**•Bz, 206 mg, 0.78 mmol) in 78% overall yield.

4.2.7. Typical procedure for alkylation with acrylamides (Scheme 10)

Synthesis of 4-benzoylamino-*N*,*N*-diethyl-4-phenylbutanamide (**13**•Bz) is representative. Potassium *tert*-butoxide (1.0 M in tetrahydrofuran, 0.1 mL, 0.1 mmol) was added to a solution of **1h** (186 mg, 0.50 mmol) in tetrahydrofuran (2.5 mL) at 25 ˚C and the reaction mixture was stirred for 10 min. A solution of *N*,*N*-diethylacrylamide (76 mg, 0.60 mmol) in tetrahydrofuran (1.0 mL) was then added, the reaction mixture was stirred for 2 h at ambient temperature. A saturated aqueous ammonium chloride solution (5 mL) was added, and the product was extracted with ethyl acetate (5 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. The residue containing imine **12a** was used for the next step without further purification.

The crude imine and hydroxylamine hydrochloride (350 mg, 5.0 mmol) were placed in a 5-mL glass pressure vial. The vial was flushed with argon and sealed with a PTFE-silicone septum. Pyridine (0.080 mL, 1.0 mmol), ethanol (2.5 mL), and water (1.0 mL) were added, and the suspension was heated at 150 ˚C with stirring for 60 min in the microwave reactor. The mixture was then cooled to room temperature. Water was added, and the product was extracted with hydrochloric acid (1 M, 5 mL × 3). The combined aqueous layer was neutralized with sodium hydrocarbonate and extracted with chloroform (5 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. The resulting mixture was used for the next step without further purification.

Benzoyl chloride (0.070 mL, 0.5 mmol) was added to a solution of the crude amine and triethylamine (0.14 mL, 1.0 mmol) in dichloromethane (2.5 mL). After the mixture was stirred for 2 h at room temperature, the reaction was quenched with water (5 mL). The product was extracted with chloroform (5 mL × 3). The combined organic layer was dried over sodium sulfate and concentrated in vacuo. Silica gel column purification (hexane/ethyl acetate = 5 : 1) provided *N*-(3-methyl-1-phenyl-3-butenyl)benzamide (**13**•Bz, 142 mg, 0.42 mmol) in 84% overall yield.

4.3. Characterization data

Compounds **1a**–**1g**,[2] the hydrochloride salt or benzoylated **3a**–**3j**,[2] **7**,[2] **11a**•Bz,[11] and **14**[12] showed the identical spectra according to the literature.

4.3.1. *N*-(Di-1-naphthylmethylidene)benzylamine (1h). IR (Nujol) 2954, 1686, 1559, 1507, 784, 776 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.56 (d, J = 15.0 Hz, 1H), 4.66 (d, J = 15.0 Hz, 1H), 7.22–7.26 (m, 2H), 7.30–7.38 (m, 6H), 7.43–7.46 (m, 1H), 7.49–7.55 (m, 4H), 7.79–7.87 (m, 3H), 7.92–7.95 (m, 2H), 9.14 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 59.0, 124.7, 125.5, 125.60, 125.64, 126.1, 126.58, 126.64, 126.8, 127.29, 127.34, 128.2, 128.56, 128.60, 128.8, 129.0, 129.2, 130.3, 130.7, 131.3, 133.7, 134.6, 136.7, 137.5, 140.5, 169.2. Found: C, 90.64; H, 5.66%. Calcd for $C_{28}H_{21}N$: C, 90.53; H, 5.70%. m.p.108–110 ˚C.

4.3.2. *N*-[(*E*)-1-Phenyl-3-pentenyl]benzamide (11b•Bz).
IR (Nujol) 3324, 1632, 1528, 1340, 965, 721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6 (ddt, *J* = 6.5, 1.0, 1.0 Hz, 3H), 2.61 (dd, *J* = 6.5, 6.5 Hz, 2H), 5.22 (dt, *J* = 6.5, 6.5 Hz, 1H), 5.35–5.41 (m, 1H), 5.57–5.64 (m, 1H), 6.39 (br d, *J* = 6.5 Hz, 1H), 7.24–7.29 (m, 2H), 7.33–7.36 (m, 3H), 7.42–7.44 (m, 2H), 7.49–7.52 (m, 1H), 7.74–7.77 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 18.2, 39.7, 53.3, 126.5, 126.6, 126.7, 127.1, 127.5, 128.8, 129.4, 131.7, 134.9, 142.1, 166.8. HRMS (DI-FAB$^+$) (*m/z*) Observed: 265.1463 (Δ = 1.4 ppm). Calcd for $C_{18}H_{19}NO$ [M^+]: 265.1467. m.p.107–109 ˚C.

4.3.3. *N*-[(*E*)-1,4-Diphenyl-3-butenyl]benzamide (11c•Bz).
IR (Nujol) 3362, 2953, 2362, 1636, 1522, 1465, 961 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.81–2.91 (m, 2H), 5.37 (dt, *J* = 6.5, 6.5 Hz, 1H), 6.13 (dt, *J* = 15.5, 6.5 Hz, 1H), 6.46 (br d, *J* = 8.0 Hz, 1H), 6.52 (d, *J* = 15.5 Hz, 1H), 7.20–7.23 (m, 1H), 7.26–7.31 (m, 5H), 7.35–7.42 (m, 6H), 7.47–7.50 (m, 1H), 7.75–7.76 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 39.9, 53.4, 125.6, 126.4, 126.7, 127.1, 127.6, 127.7, 128.7, 128.8, 129.0, 131.7, 133.7, 134.7, 137.2, 141.7, 166.9. HRMS (DI-FAB$^+$) (*m/z*) Observed: 327.1617 (Δ = 1.9 ppm). Calcd for $C_{23}H_{21}NO$ [M^+]: 327.1623. m.p.168–170 ˚C.

4.3.4. *N*-(4-Methyl-1-phenyl-3-pentenyl)benzamide (11d•Bz).
IR (Nujol) 3370, 1637, 1525, 1465, 707 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (s, 3H), 1.69 (s, 3H), 2.63 (dd, *J* = 7.0, 7.0 Hz, 2H), 5.09–5.12 (m, 1H), 5.21 (dt, *J* = 7.0, 7.0 Hz, 1H), 6.42 (d, *J* = 7.0 Hz, 1H), 7.24–7.28 (m, 1H), 7.32–7.37 (m, 4H), 7.41–7.44 (m, 2H), 7.48–7.51 (m, 1H), 7.75–7.77 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 18.2, 26.0, 34.9, 53.8, 119.5, 126.7, 127.1, 127.4, 128.8 (× 2), 131.6, 134.9, 135.5, 142.2, 166.9. Found: C, 81.81; H, 7.68%. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58%. m.p.103–105 ˚C.

4.3.5. *N*-(3-Methyl-1-phenyl-3-butenyl)benzamide (11e•Bz).
IR (Nujol) 3360, 1635, 1529, 1490, 1364, 901, 757 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.76 (s, 3H), 2.56–2.65 (m, 2H), 4.82 (s, 1H), 4.86 (s, 1H), 5.30–5.34 (m, 1H), 6.45 (br s, 1H), 7.23–7.27 (m, 1H), 7.31–7.37 (m, 4H), 7.41 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.46–7.50 (m, 1H), 7.75–7.77 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.1, 45.4, 51.7, 114.1, 126.5, 127.1, 127.5, 128.7, 128.8, 131.6, 134.7, 142.4, 142.5, 166.9. Found: C, 81.48; H, 7.27%. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22%. m.p.119–121 ˚C.

4.3.6. *N*-(1,2-Diphenylethyl)benzamide (11f•Bz).
IR (Nujol) 3348, 1635, 1521, 1465, 1082, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.23 (d, *J* = 7.0 Hz, 2H), 5.47 (dt, *J* = 7.0, 7.0 Hz, 1H), 6.48 (br s, 1H), 7.10 (d, *J* = 7.0 Hz, 2H), 7.18–7.33 (m, 8H), 7.38 (dd, *J* = 7.0, 7.0 Hz, 2H), 7.47 (dd, *J* = 7.0, 7.0 Hz, 1H), 7.67 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 42.8, 55.0, 126.8, 126.9, 127.0, 127.6, 128.6, 128.7, 128.8, 129.5, 131.6, 134.7, 137.4, 141.7, 166.9. HRMS (DI-EI$^+$) (*m/z*) Observed: 301.1462 (Δ = 1.6 ppm). Calcd for $C_{21}H_{19}NO$ [M^+]: 301.1467. m.p.173–175 ˚C.

4.3.7. *N*-(2-Cyclopropyl-1-phenylethyl)benzamide (11g•Bz).
IR (Nujol) 3360, 2360, 1631, 1521, 802, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07–0.19 (m, 2H), 0.42–0.50 (m, 2H), 0.62–0.70 (m, 1H), 1.78–1.87 (m, 2H), 5.28 (dt, *J* = 7.0, 7.0 Hz, 1H), 6.58 (br s, 1H), 7.24–7.28 (m, 1H), 7.32–7.38 (m, 4H), 7.40–7.43 (m, 2H), 7.47–7.50 (m, 1H), 7.77–7.79 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 4.6, 4.7, 8.0, 41.4, 54.6, 126.7, 127.1, 127.5, 128.5, 128.8, 131.6, 134.9, 142.5, 166.8. Found: C, 81.34; H, 7.26%. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22%. m.p.127–130 ˚C.

4.3.8. *N*-(1-Phenylpentyl)benzamide (11h•Bz).
IR (Nujol) 3286, 2955, 2374, 1631, 1558, 1325, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, *J* = 7.0 Hz, 3H), 1.26–1.41 (m, 4H), 1.85–1.97 (m, 2H), 5.17 (dt, *J* = 7.0, 7.0 Hz, 1H), 6.31 (br d, *J* = 7.0 Hz, 1H), 7.25–7.28 (m, 1H), 7.33–7.50 (m, 7H), 7.76 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 28.6, 36.2, 54.1, 126.8, 127.1, 127.6, 128.7, 128.9, 131.6, 134.9, 142.6, 166.8. HRMS (DI-EI$^+$) (*m/z*) Observed: 267.1627 (Δ = 1.4 ppm). Calcd for $C_{18}H_{21}NO$ [M^+]: 267.1623. m.p.130–132 ˚C.

4.3.9. *N*-(2-Methyl-1-phenylbutyl)benzamide (11i•Bz).
IR (Nujol) 3281, 2954, 1631, 1558, 1465, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (d, *J* = 7.0 Hz, 3H), 0.95 (t, *J* = 7.5 Hz, 3H), 1.17–1.27 (m, 1H), 1.61–1.69 (m, 1H), 1.90–1.98 (m, 1H), 5.04 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.42 (br s, 1H), 7.23–7.30 (m, 1H), 7.29–7.35 (m, 4H), 7.41–7.45 (m, 2H), 7.47–7.50 (m, 1H), 7.76–7.79 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 11.6, 16.3, 25.6, 40.1, 58.6, 127.1, 127.2, 127.4, 128.7, 128.8, 131.6, 135.0, 141.6, 166.9. HRMS (DI-EI$^+$) (*m/z*) Observed: 267.1626 (Δ = 1.2 ppm). Calcd for $C_{18}H_{21}NO$ [M^+]: 267.1623. m.p.161–162 ˚C.

4.3.10. 4-Benzoylamino-*N*,*N*-diethyl-4-phenylbutanamide (13•Bz).
IR (Nujol) 3325, 1731, 1615, 1528, 1488, 1075, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (t, *J* = 7.0 Hz, 3H), 1.08 (t, *J* = 7.0 Hz, 3H), 2.13–2.19 (m, 1H), 2.35–2.50 (m, 3H), 3.16–3.42 (m, 4H), 5.09–5.13 (m, 1H), 7.22 (dddd, *J* = 7.5, 7.5, 1.0, 1.0 Hz, 1H), 7.30–7.33 (m, 2H), 7.35–7.37 (m, 2H), 7.40–7.43 (m, 2H), 7.45–7.48 (m, 1H), 7.89–7.92 (m, 2H), 8.35 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.2, 14.1, 30.2, 30.4, 40.7, 42.2, 55.0, 126.4, 127.2, 127.3, 128.5, 128.7, 131.4, 134.3, 143.0, 166.6, 172.7. HRMS (DI-EI$^+$) (*m/z*) Observed: 338.1991 (Δ = 0.9 ppm). Calcd for $C_{21}H_{26}N_2O_2$ [M^+]: 338.1994.

Ackknowledgement

This work is supported by Grants-in-Aid for Scientific Research and GCOE Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. T.N. acknowledges JSPS for financial support.

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