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Palladium-Catalyzed Mono-*N*-allylation of Unprotected Anthranilic Acids with Allylic Alcohols in Aqueous Media

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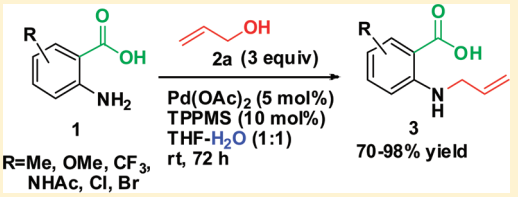
Supporting Information

ABSTRACT: Palladium-catalyzed *N*-allylation of anthranilic acids **1a**−**j** with allyl alcohol **2a** in the presence of $Pd(OAc)_2$, sodium diphenylphosphinobenzene-3-sulfonate (TPPMS) in THF−H_2O at room temperature gave only mono-*N*-allylated anthranilic acids **3a**−**j** in good yields (70−98%). The reactions of 4-bromoanthranilic acid **1i** with 2-methyl-3-buten-2-ol **2b** showed complete chemoselectivity in *N*-allylation (neutral conditions) and *C*-vinylation (basic conditions). In our catalytic system, the keys to success are use of an unprotected anthranilic acid as a starting material and the presence of water in the reaction medium. The carboxyl group of anthranilic acid and water may play important roles for the smooth generation of the π-allyl palladium species by activation of the hydroxyl group of the allylic alcohol.



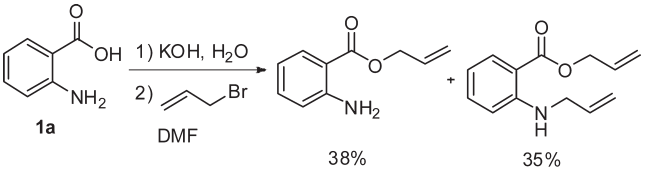
INTRODUCTION

Protection of reactive functional groups such as amino, hydroxyl, or carboxyl groups is essential in organic synthesis, not only for suppressing side reactions but also for easy handling by decreased polarity.[1] However, protection sometimes causes serious problems, e.g., increasing the number of synthetic steps and difficulty in deprotecting unstable compounds. Therefore, the development of unprotected syntheses should lead to a breakthrough in organic synthesis. One of the most effective ways for achieving such a concept is the development of selective reactions toward various reactive functional groups.

During the total synthesis of clavicipitic acids, we found that the reactivity of an unprotected amino acid could be controlled by changing the pH in aqueous media. A palladium-catalyzed allylation of free 4-bromotryptophan with 1,1-dimethylallyl alcohol occurred at the amino group under weakly basic or neutral conditions, whereas vinylation (Heck reaction) occurred selectively at the C-4-position (bromine-substituted carbon atom) under strongly basic conditions.[2] It should be emphasized that pH plays a critical role in the chemoselectivity of palladium-catalyzed reactions.

Palladium-catalyzed allylations with allylic alcohols are especially interesting, because it is known that the reactivity of allylic alcohols toward Pd(0) is poor compared with that of allylic carbonates or acetates. Although palladium-catalyzed *N*-allylation with allylic alcohols occurred in organic solvents by adding Lewis acids,[3] cationic Pd^{II} catalysts,[4] Pt catalysts,[5] or Pd-$P(OPh)_3$ catalysts[6] as additives, the same reaction proceeded smoothly in aqueous media without such additives, in which water played an important role in the activation of the allylic alcohol to form the π-allyl complex.[7] This finding was applied by us to the *N*-allylation of water-soluble free amino acids to give the *N*-monoallylated products selectively in good yields.[7f] Furthermore, halo-anilines, which are soluble in organic solvents, showed pH-controlled chemoselectivity only in the presence of water.[7c] On the basis of these works, we became interested in further expanding the substrate scope of this methodology to anthranilic acids, aromatic amino acids that are also soluble in organic solvents. Anthranilic acids are not only biologically important compounds as metabolites of tryptophan but also key units in a wide range of relevant pharmacophores with a broad spectrum of activities.[8] Herein, we report a palladium-catalyzed mono-*N*-allylation of anthranilic acids with allylic alcohols in aqueous media.

Scheme 1. Reaction of Anthranilic Acid 1a with Allylbromide



To the best of our knowledge, the allylation of unprotected anthranilic acids with allylic alcohols has not been described before. Reductive amination,[9] *N*-alkylation,[10] and palladium-catalyzed allylation[11] of anthranilic acid ester have been reported. In contrast, there are few examples of direct *N*-allylation of anthranilic acids. The reaction of anthranilic acid **1a** with allylbromide gives the corresponding allyl esters (Scheme 1).[12]

RESULTS AND DISCUSSION

When a mixture of anthranilic acid **1a** and allyl alcohol **2a** was stirred in the presence of $Pd(OAc)_2$ (5 mol %) and sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 10 mol %) in

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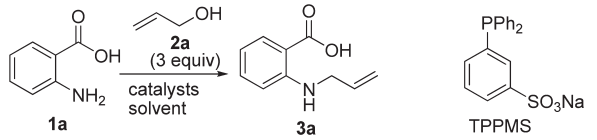
Table 1. Effects of Catalysts and Solvent on *N*-Allylation of 1a[a]



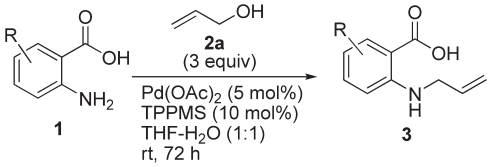
entry	catalyst	solvent	conditions	yield [%]
1	$Pd(OAc)_2$/TPPMS	H_2O	rt, 48 h	0
2	$Pd(OAc)_2$/TPPMS	H_2O	70 °C, 16 h	73
3	none	H_2O	70 °C, 16 h	0
4	$Pd(OAc)_2$/TPPMS	THF−H_2O (1:1)	rt, 48 h	92
5	$Pd(OAc)_2$/TPPMS	$CHCl_3$−H_2O (1:1)	rt, 48 h	92
6	$Pd(OAc)_2$/TPPMS	toluene−H_2O (1:1)	rt, 48 h	87
7	$Pd(OAc)_2$/TPPMS	THF[b]	rt, 48 h	66
8	$Pd(OAc)_2$/TPPMS	THF	rt, 48 h	0
9	$Pd(OAc)_2/PPh_3$	THF−H_2O (1:1)	rt, 48 h	47
10	$Pd_2(dba)_3$[c]/PPh_3	THF−H_2O (1:1)	rt, 48 h	72
11	$Pd(PPh_3)_4$	THF−H_2O (1:1)	rt, 48 h	73
12	$Pd(OAc)_2/PPh_3$	THF	rt, 48 h	0
13	$[PdCl(\pi\text{−allyl})]_2$/TPPMS	THF−H_2O (1:1)	rt, 48 h	72
14	$Pd_2(dba)_3$[c]/TPPMS	THF−H_2O (1:1)	rt, 48 h	81
15	$PdCl_2$/TPPMS	THF−H_2O (1:1)	rt, 48 h	28

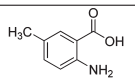
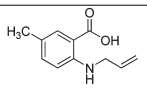
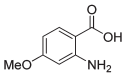
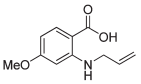
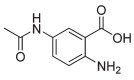
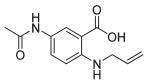
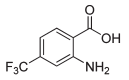
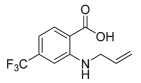
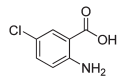
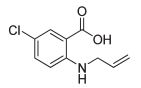
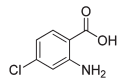
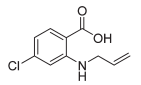
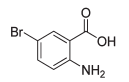
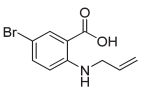
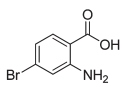
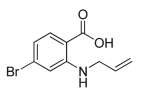
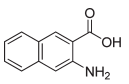
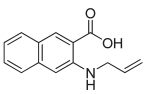
[a] Anthranilic acid **1a** (1 mmol), Pd catalyst (5 mol %), ligand (10 mol %), and allyl alcohol **2a** (3 equiv). [b] H_2O (1 equiv) was added. [c] 2.5 mol %.

H_2O at room temperature for 48 h, no reaction occurred (entry 1 in Table 1). The reaction did proceed at 70 °C to give the desired product **3a** in 73% yield (entry 2). Only mono-*N*-allylated product **3a** was obtained in good yield despite the possibility of forming the diallylated product or allyl ester. Since the reaction did not proceed without the palladium catalyst (entry 3), a S_N2'-type reaction mechanism was excluded in the formation of the *N*-allylated product. In a THF−water biphasic system, the reaction proceeded even at room temperature to give the product **3a** in high yield (entry 4, 92%). With regard to the organic solvent in the biphasic system, $CHCl_3$ (entry 5, 92%) and toluene (entry 6, 87%) also gave good results. The presence of only 1 equiv of water is enough to promote the reaction smoothly (entry 7, 66%), but no reaction occurred in only THF (entry 8). These results clearly show that the reaction proceeded smoothly in organic solvents only in the presence of water (at least 1 equiv). Since the reaction also proceeded in water at high temperature (entry 2), *N*-allylation might occur in both the organic and aqueous phases. This consideration was supported by the use of a water-insoluble ligand, PPh_3, for the reaction, which proceeded smoothly in the biphasic system (entries 9−11) but did not proceed in the absence of water (entry 12). Water might be required for the smooth generation of the π-allyl palladium species by hydration of the hydroxyl group. With regard to the palladium catalyst, the use of zero- or divalent palladium, $[PdCl(\pi\text{-allyl})]_2$ or $Pd_2(dba)_3$, also gave the product in good yields (entry 13, 72%; entry 14, 81%), although the use of $PdCl_2$ resulted in a poor yield (entry 15).

Results for the *N*-allylation of a number of anthranilic acids substituted by electron-withdrawing and electron-donating groups **1b**−**j** with allyl alcohol **2a** using $Pd(OAc)_2$ and TPPMS

Table 2. *N*-Allylation of Various Anthranilic Acids 1[a]



Entry	Anthranilic acid **1**		Product **3**		Yield [%]
1		**1b**		**3b**	73
2		**1c**		**3c**	98
3		**1d**		**3d**	79
4[b]		**1e**		**3e**	71
5		**1f**		**3f**	82
6[b]		**1g**		**3g**	70
7		**1h**		**3h**	90
8		**1i**		**3i**	75
9		**1j**		**3j**	81

[a] Anthranilic acid **1** (1 mmol), $Pd(OAc)_2$ (5 mol %), TPPMS (10 mol %), and allyl alcohol **2a** (3 equiv) in THF (2 mL) and H_2O (2 mL), rt, 72 h. [b] 80 °C, 5 h.

are summarized in Table 2. All of the anthranilic acids examined underwent mono-*N*-allylation smoothly to give the corresponding mono-*N*-allyl anthranilic acids in overall yields ranging from 70% to 98% (entries 1−9). It is noted that bromoanthranilic acids (**1h** and **1i**) gave only *N*-allylated products (**3h** and **3i**) in good yield despite the possible formation of a *C*-vinylated product by the Heck reaction (entries 7 and 8). These results are consistent with our previous report that the Pd-catalyzed allylations of bromoanilines with 2-methyl-3-buten-1-ol gave *N*-allylated products selectively under neutral conditions, whereas vinylation occurred at the bromine-substituted carbon atom selectively under basic conditions. Therefore, we next attempted the palladium-catalyzed reaction of 4-bromoanthranilic acid **1i** with 2-methyl-3-buten-1-ol **2b** under neutral and basic conditions (Scheme 2). Since *N*-allylation of **1i** with sterically hindered allylic alcohol **2b** did not proceed at room temperature in THF−water, we investigated the reaction at 100 °C in water. Under neutral conditions, *N*-allylation occurred selectively to give *N*-allylated product **3l**

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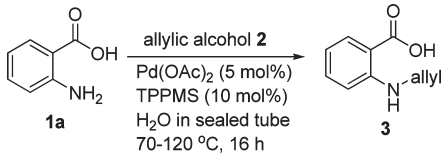
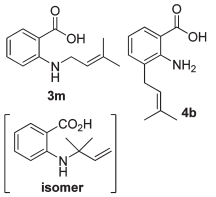
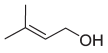
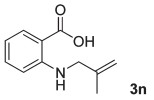
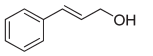
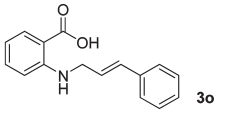
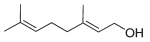
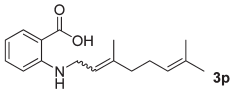
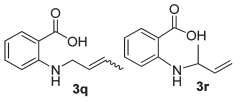
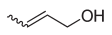
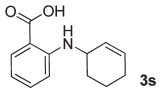
Table 3. *N*-Allylation with Various Allylic Alcohols 2[a]



Entry	Allylic alcohol 2	(equiv)	Temp (°C)	Products 3	Yield
1		**2b** (4)	100		**3m**: 78% **4b**: 6%
2		**2c** (4)	100		**3m**: 74%, **4b**: trace
3		**2d** (5)	120		**3n**: 51%
4		**2e** (1.3)	70		**3o**: quant
5		**2f** (5)	120		**3p**: 77%[b]
6[c]		**2g** (3)	70		41% (**3q**:**3r**=88:12), **3q** (*E*:*Z*=85:15)
7[c]		**2h** (3)[d]	70		61% (**3q**:**3r**=88:12), **3q** (*E*:*Z*=84:16)
8		**2i** (4)	100		**3s**: 30%

[a] Anthranilic acid **1a** (2 mmol), Pd catalyst (5 mol %), ligand (10 mol %), and allyl alcohol **2a** (3 equiv). [b] *E*/*Z* mixture. [c] The regio- and stereoisomeric ratios of **3** were determined by ^{1}H NMR spectroscopy. [d] *E*/*Z* mixture of **2g** (*E*/*Z* = 95/5) was used.

(76%) along with *C*-allylated product **4a** (11%), which was formed by aromatic amino-Claisen rearrangement of regioisomer **3k**. Cooper[13] reported that *N*-(1,1-dimethylallyl)aniline was rearranged to 2-(3,3-dimethylallyl)aniline using a catalytic amount of *p*-toluenesulfonic acid in acetonitrile−water (10:1) in 70% yield. In contrast, under basic conditions (4 equiv of NaOH), the Heck reaction occurred selectively to give *C*-vinylated product **5** in 98% yield. Since the carbon side chain could be introduced to the bromine-substituted carbon atom, trisubstituted benzene derivatives might be easily prepared regioselectively. As reported previously,[7c] chemoselectivity for *N*-allylation and *C*-vinylation can be explained by the selective formation of a π-allyl palladium complex under neutral conditions or of a σ-aryl palladium complex under basic conditions. The formation of a σ-complex might be inhibited under neutral conditions by suppression of Pd(0) regeneration due to the absence of base, which neutralizes HBr formed through decomposition of H-Pd^{II}-Br during the reaction.

We next investigated the scope of different allylic alcohols **2** in water at various temperatures, which was optimized on the basis of TLC analysis (Table 3). The reaction of 2-methyl-3-buten-2-ol **2b** afforded the mono-*N*-allylated product **3m** in 78% yield along with rearrangement product, 2-amino-3-(3-methylbut-2-enyl)benzoic acid **4b**, from the corresponding isomer in 6% yield (entry 1). Prenyl alcohol **2c** also gave the same product **3m** in good yield (entry 2, 74%). The reaction of β-methallyl alcohol **2d** proceeded slowly (entry 3, 51%). Hydrophobic allylic alcohols such as cinnamyl alcohol **2e**, which are not soluble in water, gave *trans* product **3o** selectively in quantitative yield (entry 4), whereas geraniol **2f** gave an *E*/*Z* mixture of allylated product **3p** (entry 5). Thus, this reaction should be applicable to the *N*-allylation with various aliphatic allylic alcohols. When α-substituted

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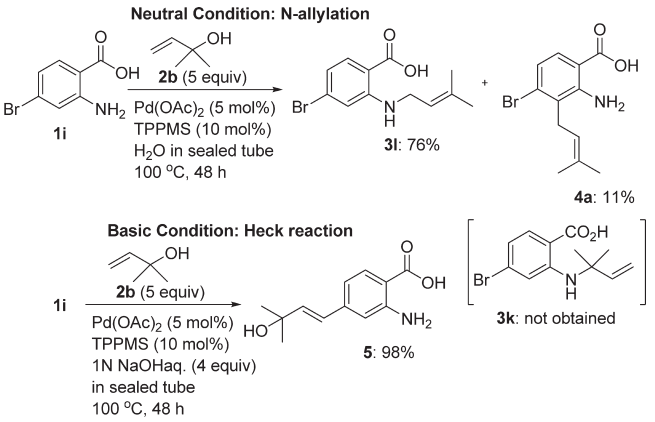
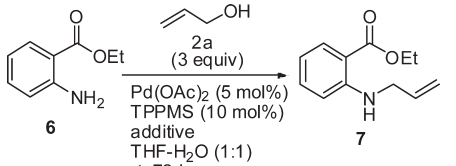
Scheme 2. Chemoselective Palladium-Catalyzed Reaction: Selectivity in the Reaction of 4-Bromoanthranilic Acid 1i with 2-Methyl-3-buten-1-ol 2b

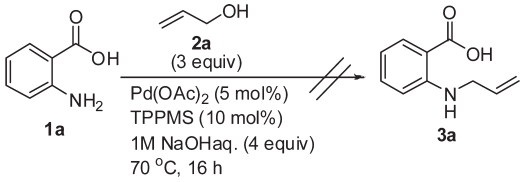


Scheme 3. *N*-Allylation of Anthranilic Acid Ethyl Ester 6



additive	yield (%) 7
None	26
AcOH (1 equiv)	62

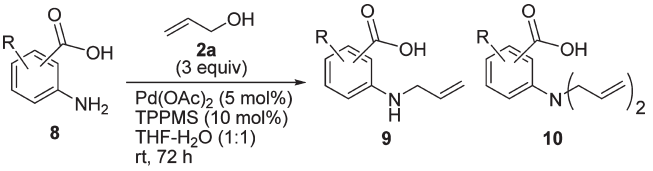
Scheme 4. *N*-Allylation of Anthranilic Acid 1a in Aqueous NaOH

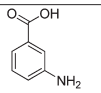
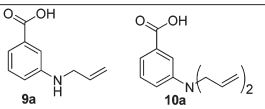
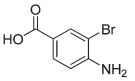
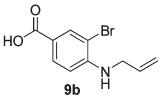


allylic alcohol **2g** was used, the inseparable mixture of regio- and stereoisomer **3q** and **3r** were obtained in 41% yield. The substitution occurred mainly at less sterically hindered primary carbon atom to give *E*/*Z* mixture. The obtained regio- and stereoselectivities were almost the same as that using γ-substituted allylic alcohol **2h**, suggesting that the reaction proceeds via the same π-allyl palladium intermediate (entries 6 and 7). The sterically demanding secondary alcohol **2i** gave lower yield (entry 8, 30%).

Manabe[14] and Yang[7b] reported that carboxylic acids enhanced the formation of the π-allyl complex in aqueous media. To evaluate the effect of the carboxyl group of anthranilic acid in our catalytic system, *N*-allylation of anthranilic acid ethyl ester **6** was carried out. *N*-Allylation of **6** with allyl alcohol **2a** using Pd(OAc)$_2$ and TPPMS in THF−H$_2$O (1:1) gave mono-*N*-allylated **7** in only 26% yield (Scheme 3). To our surprise, use of acetic

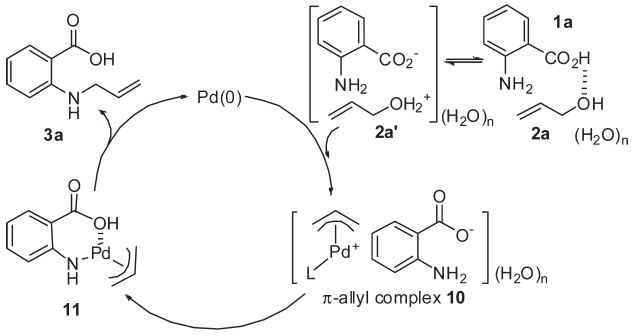
Table 4. *N*-Allylation of Aminobenzoic Acid 8[a]



Entry	Aminobenzoic acid **8**		Product		Yield
1		**8a**		**9a** / **10a**	**9a**: trace **10a**: 71%
2		**8b**		**9b**	**9b**: 75%

[a] Aminobenzoic acid **8** (1 mmol), Pd(OAc)$_2$ (5 mol %), TPPMS (10 mol %), and allyl alcohol **2a** (3 equiv) in THF (2 mL) and H$_2$O (2 mL), rt, 72 h.

Scheme 5. Possible Mechanism for the Formation of *N*-Allyl Anthranilic Acid 3a



acid (1 equiv) as an additive greatly improved the yield to 62%, whereas NaOH suppressed the *N*-allylation of anthranilic acid **1a** (Scheme 4). These results suggested that the carboxyl group of anthranilic acid may play a key role as an activator in our catalytic system. In addition, the reaction of 3-aminobenzoic acid **8a** gave di-*N*-allylated **10a** in 71% yield (Table 4, entry 1). In contrast, 4-amino-3-bromobenzoic acid **8b** afforded only mono-*N*-allylated **9b** in 75% yield (entry 2). Thus, *N*-allylation of anthranilic acids can give only mono-*N*-allylated product by the steric effect of carboxyl group at the *ortho* position.

A possible mechanism for the formation of *N*-allyl anthranilic acid **3a** from anthranilic acid **1a** and allyl alcohol **2a** in water is illustrated in Scheme 5. First, oxidative addition of alcohol **2a** to a Pd(0) species affords the π-allyl palladium complex **10**. The carboxyl group of anthranilic acid may play an important role for the smooth generation of **10** by activation of the hydroxyl group. Next, ligand exchange of the π-allyl system with the amino group of **10** takes place at the π-allyl system to generate intermediate **11**, followed by reductive elimination to give the mono-*N*-allylated product **3a** exclusively. Since the reaction did not occur without water, water may activate the allyl alcohol via hydration of the hydroxyl group for the smooth generation of the π-allyl

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palladium intermediate.[7a] Furthermore, concerning the role of the carboxylic acid, water molecules play an important role in the ionization of acids. Therefore, water assists proton transfer from the carboxyl group to the hydroxyl group of allyl alcohol **2a** and also stabilizes the charged form **2a′** by solvation. Overall, the carboxyl group of anthranilic acid and water may play important roles for the smooth generation of the π-allyl palladium species by activation of the hydroxyl group of allylic alcohols in our catalytic system.

Our method also succeeds under neutral conditions in good yield. In contrast, NaOH suppressed the *N*-allylation. Therefore, pH plays a critical role in the palladium-catalyzed *N*-allylation, and the outcome of the *N*-allylation can be controlled simply by changing the basicity of the reaction media.

CONCLUSION

In summary, we have developed a methodology for achieving a palladium-catalyzed mono-*N*-allylation of unprotected anthranilic acids **1** with allylic alcohols **2** in aqueous media. This methodology offers a new synthetic strategy for the chemical modification of anthranilic acids into *N*-allylated derivatives using the Tsuji−Trost reaction without additives for activation of allylic alcohols in aqueous media. In our catalytic system, the key is the use of an unprotected anthranilic acid, which accelerates the palladium-catalyzed *N*-allylation. In addition, water also plays a key role as a solvent. Recently, organic reactions in water have attracted attention not only for their environmental and economical advantages but also for their unique reactivity. Therefore, development of reactions in water is an important goal of synthetic methodology. We are currently working on the development of new reactions involving water-soluble compounds in aqueous media.

EXPERIMENTAL SECTION

General Procedure for *N*-Allylation (Method A). A mixture of anthranilic acid **1** (1 mmol), palladium(II) acetate (12 mg, 0.05 mmol), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 36 mg, 0.1 mmol), and prop-2-en-1-ol **2a** (204 μL, 3 mmol) in THF (2 mL) and H_2O (2 mL) was stirred at room temperature for 48 h. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes−EtOAc) to give desired product **3a**−**d**, **3f**, **3h**−**j**, and **7**.

General Procedure for *N*-Allylation (Method B). A mixture of anthranilic acid **1** (1 mmol), palladium(II) acetate (12 mg, 0.05 mmol), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 36 mg, 0.1 mmol), and prop-2-en-1-ol **2a** (204 μL, 3 mmol) in THF (2 mL) and H_2O (2 mL) was heated at 80 °C for 5 h. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes−EtOAc) to give desired product **3e** and **3g**.

General Procedure for *N*-Allylation (Method C). A mixture of anthranilic acid **1** (1 mmol), palladium(II) acetate (12 mg, 0.05 mmol), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 36 mg, 0.1 mmol), and allylic alcohol **2** (1.3−5 mmol) in H_2O (4 mL) was heated for 16−48 h. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes−EtOAc) to give desired product **3l**−**s** and **4a,b**.

2-(Allylamino)benzoic Acid 3a[15] (Table 1). Following the general procedure (method A), **3a** was obtained as a white solid. Mp 119−120 °C; IR (KBr) (cm^{-1}) 3378, 3300−2500, 1671; ^1H NMR (400 MHz, DMSO-d_6) δ 3.80−3.90 (m, 2H), 5.15 (dd, J = 10.4, 1.6 Hz, 1H), 5.23 (dd, J = 17.2, 1.6 Hz, 1H), 5.85−6.00 (m, 1H), 6.57 (dd, J = 7.2, 7.2 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 7.30−7.40 (m, 1H), 7.80 (dd, J = 7.2, 1.6 Hz, 1H), 7.99 (brs, 1H), 12.6 (brs, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 44.4, 110.0, 111.5, 114.3, 115.5, 131.6, 134.4, 135.3, 150.7, 170.0; MS-EI m/z (%) 177 (M^+, 100).

2-(Allylamino)-5-methylbenzoic Acid 3b (Entry 1 in Table 2). Following the general procedure (method A), **3b** was obtained as a white solid. Mp 103−105 °C; IR (KBr) (cm^{-1}) 3376, 3300−2500, 1666; ^1H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 3.80−3.90 (m, 2H), 5.18 (dd, J = 10.2, 1.4 Hz, 1H), 5.28 (dd, J = 17.1, 1.4 Hz, 1H), 5.89−6.00 (m, 1H), 6.60 (d, J = 8.8 Hz, 1H), 7.21 (dd, J = 8.8, 2.2 Hz, 1H), 7.78 (d, J = 2.0 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 20.1, 45.4, 108.6, 111.9, 116.1, 123.9, 132.2, 134.7, 136.7, 149.8, 173.5; MS-EI m/z (%) 191 (M^+, 100).

2-(Allylamino)-4-methoxybenzoic Acid 3c (Entry 2 in Table 2). Following the general procedure (method A), **3c** was obtained as a white solid. Mp 136−137 °C; IR (KBr) (cm^{-1}) 3363, 3300−2500, 1655; ^1H NMR (400 MHz, DMSO-d_6) δ 3.76 (s, 3H), 3.80−3.90 (m, 2H), 5.16 (d, J = 10.2 Hz, 1H), 5.24 (d, J = 17.3 Hz, 1H), 5.88−6.00 (m, 1H), 6.13 (d, J = 2.2 Hz, 1H), 6.17 (ddd, J = 8.8, 2.2, 1.0 Hz, 1H), 7.72 (dd, J = 8.8, 1.0 Hz, 1H), 8.07 (brs, 1H), 12.3 (brs, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 44.5, 55.0, 95.3, 101.8, 103.5, 115.6, 133.5, 135.3, 152.6, 164.2, 169.6; MS-EI m/z (%) 207 (M^+, 87), 189 (100); HRMS-EI m/z (M^+) calcd for $C_{11}H_{13}NO_3$ 207.0895, found 207.0893.

5-Acetamido-2-(allylamino)benzoic Acid 3d (Entry 3 in Table 2). Following the general procedure (method A), **3d** was obtained as an yellow solid. Mp 127−130 °C; IR (KBr) (cm^{-1}) 3378, 3279, 3300−2500, 1665; ^1H NMR (400 MHz, DMSO-d_6) δ 1.97 (s, 3H), 3.80−3.90 (m, 2H), 5.14 (dd, J = 10.2, 1.4 Hz, 1H), 5.22 (dd, J = 17.1, 1.4 Hz, 1H), 5.88−6.00 (m, 1H), 6.65 (d, J = 9.0 Hz, 1H), 7.54 (dd, J = 9.0, 2.4 Hz, 1H), 8.00 (d, J = 2.4 Hz, 1H), 9.65 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 23.6, 44.6, 109.6, 111.6, 115.5, 122.5, 126.9, 127.2, 135.5, 147.2, 167.5, 169.8; MS-EI m/z (%) 234 (M^+, 100); HRMS-EI m/z (M^+) calcd for $C_{12}H_{14}N_2O_3$ 234.1005, found 234.1007.

2-(Allylamino)-4-(trifluoromethyl)benzoic Acid 3e (Entry 4 in Table 2). Following the general procedure (method B), **3e** was obtained as a white solid. Mp 137−140 °C; IR (KBr) (cm^{-1}) 3383, 3300−2500, 1679; ^1H NMR (400 MHz, DMSO-d_6) δ 3.96 (d, J = 4.9 Hz, 2H), 5.17 (dd, J = 10.5, 1.5 Hz, 1H), 5.22 (dd, J = 17.1, 1.5 Hz, 1H), 5.88−6.00 (m, 1H), 6.85 (d, J = 8.3, 1.2 Hz, 1H), 6.92 (s, 1H), 7.97 (d, J = 8.3 Hz, 1H), 8.18 (brs, 1H), 13.2 (brs, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 44.3,108.0, 110.0, 113.2, 115.8, 122.5, 125.2, 132.9, 133.7, 134.0, 134.8, 150.5, 169.1; MS-EI m/z (%) 245 (M^+, 91), 200 (100); HRMS-EI m/z (M^+) calcd for $C_{11}H_{10}NO_2F_3$ 245.0664, found 245.0664.

2-(Allylamino)-5-chlorobenzoic Acid 3f[15] (Entry 5 in Table 2). Following the general procedure (method A), **3f** was obtained as an off-white solid. Mp 147−148 °C; IR (KBr) (cm^{-1}) 3375, 3300−2500, 1666; ^1H NMR (400 MHz, DMSO-d_6) δ 3.85−3.93 (m, 2H), 5.15 (dd, J = 10.2, 1.5 Hz, 1H), 5.21 (dd, J = 17.4, 1.5 Hz, 1H), 5.87−6.00 (m, 1H), 6.73 (d, J = 9.0 Hz, 1H), 7.37 (dd, J = 9.0, 2.7 Hz, 1H), 7.73 (d, J = 2.7 Hz, 1H), 7.93 (brs, 1H), 13.0 (brs, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 44.4, 111.1, 113.7, 115.7, 117.6, 130.4, 133.9, 135.0, 149.4, 168.9; MS-EI m/z (%) 211 (M^+, 100), 213 (M^+ + 2, 31).

2-(Allylamino)-4-chlorobenzoic Acid 3g (Entry 6 in Table 2). Following the general procedure (method B), **3g** was obtained as a white solid. Mp 148−149 °C; IR (KBr) (cm^{-1}) 3370, 3300−2500, 1670; ^1H NMR (400 MHz, DMSO-d_6) δ 3.90 (d, J = 4.6 Hz, 2H), 5.16 (dd, J = 10.2, 1.7 Hz, 1H), 5.22 (dd, J = 17.3, 1.7 Hz, 1H), 5.87−6.00 (m, 1H), 6.59 (dd,

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J = 8.6, 2.2 Hz, 1H), 6.70 (d, J = 2.2 Hz, 1H), 7.78 (d, J = 8.6 Hz, 1H), 8.12 (s, 1H), 12.9 (brs, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 44.3, 109.0, 110.9, 114.3, 115.7, 133.4, 134.8, 139.2, 151.5, 169.3; MS-EI m/z (%) 211 (M^+, 100), 213 (M^+ + 2, 33); HRMS-EI m/z (M^+) calcd for $C_{10}H_{10}NO_2Cl$ 211.0400, found 211.0398.

2-(Allylamino)-5-bromobenzoic Acid 3h[15] (Entry 7 in Table 2). Following the general procedure (method A), **3h** was obtained as a pale yellow solid. Mp 155−157 °C; IR (KBr) (cm^{-1}) 3372, 3300−2500, 1669; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87−3.89 (m, 2H), 5.21 (dd, J = 10.3, 1.7 Hz, 1H), 5.28 (dd, J = 17.3, 1.7 Hz, 1H), 5.87−6.00 (m, 1H), 6.57 (d, J = 9.0 Hz, 1H), 7.43 (dd, J = 9.0, 2.4 Hz, 1H), 7.76 (brs, 1H), 8.08 (d, J = 2.4 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 45.2, 106.1, 110.0, 113.7, 116.5, 133.8, 134.6, 138.2, 150.5, 172.5; MS-EI m/z (%) 255 (M^+, 98), 257 (M^+ + 2, 94), 210 (100).

2-(Allylamino)-4-bromobenzoic Acid 3i (Entry 8 in Table 2). Following the general procedure (method A), **3i** was obtained as a white solid. Mp 161−163 °C; IR (KBr) (cm^{-1}) 3367, 3300−2500, 1671; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (d, J = 4.6 Hz, 2H), 5.23 (dd, J = 10.2, 1.4 Hz, 1H), 5.30 (dd, J = 17.4, 1.4 Hz, 1H), 5.87−6.00 (m, 1H), 6.75 (dd, J = 8.6, 2.0 Hz, 1H), 6.83 (d, J = 2.0 Hz, 1H), 7.81 (d, J = 8.6 Hz, 1H), 7.70−7.90 (brs, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 45.2, 107.6, 114.6, 116.7, 118.3, 131.0, 133.6, 133.8, 152.1, 173.1; MS-EI m/z (%) 255 (M^+, 90), 257 (M^+ + 2, 87), 210 (100). Anal. Calcd for $C_{10}H_{10}BrNO_2$: C, 46.90; H, 3.94; N, 5.47. Found: C, 46.99; H, 3.95; N, 5.11.

3-(Allylamino)-2-naphthoic Acid 3j (Entry 9 in Table 2). Following the general procedure (method A), **3j** was obtained as a yellow solid. Mp 167−169 °C; IR (KBr) (cm^{-1}) 3398, 3300−2500, 1665; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.90−3.95 (m, 2H), 5.20 (dd, J = 10.5, 1.7 Hz, 1H), 5.32 (dd, J = 17.3, 1.7 Hz, 1H), 5.95−6.10 (m, 1H), 6.89 (s, 1H), 7.15 (dd, J = 7.8, 6.8 Hz, 1H), 7.41 (dd, J = 7.8, 6.8 Hz, 1H), 7.60 (d, J = 7..8 Hz, 1H), 7.79 (d, J = 7.8 Hz, 1H), 8.51 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 44.9, 104.3, 114.5, 115.7, 121.8, 124.4, 125.2, 128.7, 129.1, 133.5, 135.1, 137.2, 146.3, 169.7; MS-EI m/z (%) 227 (M^+, 100). Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.73; H, 5.77; N, 5.89.

4-Bromo-2-(3-methylbut-2-enylamino)benzoic Acid 3l (Scheme 2). Following the general procedure (method C), **3l** was obtained as a white solid. Mp 145−147 °C; IR (KBr) (cm^{-1}) 3375, 3300−2500, 1665; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.71 (s, 3H), 1.73 (s, 3H), 3.76 (d, J = 6.6 Hz, 2H), 5.25 (t, J = 6.6 Hz, 1H), 6.71 (dd, J = 8.6, 1.7 Hz, 1H), 6.85 (d, J = 1.7 Hz, 1H), 7.68 (d, J=8.6 Hz, 1H), 7.80 (brs, 1H), 12.8 (brs, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 17.8, 25.4, 109.2, 113.7, 116.9, 120.8, 128.5, 133.4, 135.3, 151.4, 169.4; MS-EI m/z (%) 283 (M^+, 55), 285 (M^+ + 2, 54), 252 (100); HRMS-EI m/z (M^+) calcd for $C_{12}H_{14}BrNO_2$ 283.0208, found 283.0212.

2-(3-Methylbut-2-enylamino)benzoic Acid 3m (Entry 1 in Table 3). Following the general procedure (method C), **3m** was obtained as a yellow solid. Mp 114−116 °C; IR (KBr) (cm^{-1}) 3384, 3300−2500, 1650; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.70 (s, 3H), 1.72 (s, 3H), 3.76 (d, J = 6.6 Hz, 2H), 5.28 (t, J = 6.6 Hz, 1H), 6.55 (dd, J = 8.0, 6.8 Hz, 1H), 6.69 (d, J = 8.8 Hz, 1H), 7.36 (ddd, J = 8.8, 6.8, 1.7 Hz, 1H), 7.78 (dd, J = 8.0, 1.7 Hz, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 17.8, 25.4, 109.9, 111.3, 114.1, 121.5, 131.6, 134.4, 134.8, 150.7, 169.9; MS-EI m/z (%) 205 (M^+, 73), 119 (100). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.23; H, 7.31; N, 6.62.

2-(2-Methylallylamino)benzoic Acid 3n (Entry 3 in Table 3). Following the general procedure (method C), **3n** was obtained as an off-white solid. Mp 91−93 °C; IR (KBr) (cm^{-1}) 3375, 3300−2500, 1659; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80 (s, 3H), 3.80 (s, 2H), 4.90 (s, 1H), 4.96 (s, 1H), 6.61 (dd, J = 8.0, 8.0 Hz, 1H), 6.63 (d, J = 8.8 Hz, 1H), 7.36 (dd, J = 8.8, 8.0 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 20.3, 48.7, 108.8, 111.0, 111.8, 114.8, 132.6, 135.4, 141.6, 151.9, 173.5; MS-EI m/z (%) 191 (M^+, 97), 132 (100).

2-(Cinnamylamino)benzoic Acid 3o[16] (Entry 4 in Table 3). Following the general procedure (method C), **3o** was obtained as an off-white solid. Mp 157−159 °C; IR (KBr) (cm^{-1}) 3377, 3300−2500, 1664; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07 (dd, J = 5.4, 1.5 Hz, 2H), 6.31 (dt, J = 15.9, 5.4 Hz, 1H), 6.55−6.70 (m, 2H), 6.74 (d, J = 8.6 Hz, 1H), 7.20−7.27 (m, 1H), 7.28−7.35 (m, 1H), 7.35−7.45 (m, 3H), 7.85 (brs, 1H), 8.00 (dd, J = 8.0, 1.7 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 44.9, 108.9, 111.8, 115.0, 126.1, 126.4, 127.6, 128.6, 131.4, 132.7, 135.6, 136.8, 151.6, 173.7; MS-EI m/z (%) 253 (M^+, 70), 117 (100).

2-(3,7-Dimethylocta-2,6-dienylamino)benzoic Acid 3p (Entry 5 in Table 3). Following the general procedure (method C), **3p** was obtained as a yellow oil. IR (neat) (cm^{-1}) 3378, 3300−2500, 1660; ^{1}H NMR (400 MHz, $CDCl_3$) for (*E*)-**3p** δ 1.61 (s, 3H), 1.68 (s, 3H), 1.72 (s, 3H), 2.00−2.17 (m, 4H), 3.82 (d, J = 6.4 Hz, 2H), 5.05−5.20 (m, 1H), 5.30−5.40 (m, 1H), 6.60 (dd, J = 8.5, 8.2 Hz, 1H), 6.66 (d, J = 8.5 Hz, 1H), 7.37 (ddd, J = 8.5, 8.5, 1.6 Hz, 1H), 7.98 (d, J = 8.2, 1.6 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) for (*E*)-**3p** δ 16.4, 17.7, 25.7, 26.5, 39.5, 41.0, 108.7, 111.6, 114.5, 121.1, 123.9, 132.7, 135.5, 139.1, 151.7, 173.9; MS-EI m/z (%) 273 (M^+, 84), 93 (100); HRMS-EI m/z (M^+) calcd for $C_{17}H_{23}NO_2$ 273.1729, found 273.1728.

Mixture of 2-(but-2-enylamino)benzoic Acid 3q and 2-(But-3-en-2-ylamino)benzoic Acid 3r (Entries 6 and 7 in Table 3). Following the general procedure (method C), mixture of **3q** and **3r** was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) for (*E*)- **3q** δ 1.72 (dd, J = 6.3, 1.4 Hz, 3H), 3.81 (dt, J = 5.6, 1.2 Hz, 2H), 5.50−5.65 (m, 1H), 5.65−5.80 (m, 1H), 6.55−6.65 (m, 1H), 6.68 (d, J = 8.6 Hz, 1H), 7.30−7.45 (m, 1H), 7.98 (dd, J = 8.1, 1.7 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) for (*E*)- **3q** δ 17.7, 44.7, 108.6, 111.7, 114.7, 127.1, 127.9, 132.6, 135.5, 151.7, 173.8; MS-EI m/z (%) 191 (M^+, 100).

2-(Cyclohex-2-enylamino)benzoic Acid 3s (Entry 8 in Table 3). Following the general procedure (method C), **3s** was obtained as an off-white solid. Mp 95−97 °C; IR (KBr) (cm^{-1}) 3362, 3300−2500, 1666; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50−1.90 (m, 3H), 1.90−2.20 (m, 3H), 4.11 (s, 1H), 4.05−4.15 (m, 1H), 5.76 (dd, J = 10.1, 2.6 Hz, 1H), 5.86−5.93 (m, 1H), 6.59 (dd, J = 8.0, 8.0 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 7.38 (ddd, J = 8.8, 8.0, 1.6 Hz, 1H), 7.98 (dd, J = 8.0, 1.6 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 19.8, 25.1, 28.9, 47.1, 108.8, 111.8, 114.5, 127.8, 130.6, 132.9, 135.5, 150.9, 173.8; MS-ESI m/z 218 (M^+ + H). Anal. Calcd for $C_{13}H_{15}NO_2 \cdot 0.1CH_3OH$: C, 71.37; H, 7.04; N, 6.35. Found: C, 71.77; H, 7.23; N, 5.95.

2-Amino-4-bromo-3-(3-methylbut-2-enyl)benzoic Acid 4a (Scheme 2). Following the general procedure (method C), **4a** was obtained as a white solid. Mp 181−183 °C; IR (KBr) (cm^{-1}) 3483, 3370, 3300−2500, 1658; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.66 (s, 3H), 1.77 (s, 3H), 3.43 (d, J = 6.4 Hz, 4H), 4.96 (t, J = 6.4 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 7.53 (d, J = 8.6 Hz, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 18.1, 25.4, 29.6, 109.4, 118.7, 119.9, 125.2, 130.0, 130.4, 132.5, 150.2, 169.6; MS-EI m/z (%) 283 (M^+, 45), 285 (M^+ + 2, 40), 252 (100); HRMS-EI m/z (M^+) calcd for $C_{12}H_{14}BrNO_2$ 283.0208, found 283.0211.

2-Amino-3-(3-methylbut-2-enyl)benzoic Acid 4b (Entry 1 in Table 3). Following the general procedure (method C), **4b** was obtained as a white solid. Mp 121−123 °C; IR (KBr) (cm^{-1}) 3436, 3340, 3300−2500, 1664; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (s, 3H), 1.77 (s, 3H), 3.23 (d, J = 6.8 Hz, 2H), 5.22 (dt, J = 6.8, 1.4 Hz, 1H), 6.63 (dd, J = 8.0, 7.4 Hz, 6H), 7.23 (dd, J = 7.4, 1.5 Hz, 1H), 7.86 (dd, J = 8.0, 1.5 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 17.9, 25.7, 30.7, 109.3, 115.9, 120.9, 126.5, 130.2, 134.6, 134.9, 149.8, 173.5; MS-EI m/z (%) 205 (M^+, 79), 252 (100). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.95; H, 7.34; N, 6.43.

(*E*)-2-Amino-4-(3-hydroxy-3-methylbut-1-enyl)benzoic Acid 5 (Scheme 2). A mixture of 4-bromoanthranilic acid **1i** (216 mg, 1 mmol), palladium(II) acetate (11 mg, 0.05 mmol), sodium

diphenylphosphinobenzene-3-sulfonate (TPPMS, 37 mg, 0.1 mmol), and 2-methyl-3-buten-2-ol **2b** (503 μL, 5 mmol) in 1 N aq NaOH (4 mL) was heated 100 °C for 48 h. After cooling, the reaction mixture was poured into 1 N aq HCl (4 mL) and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes−EtOAc) to give desired product **5** (217 mg, 0.98 mmol) as an off-white solid. Mp 149−151 °C; IR (KBr) (cm^{-1}) 3377, 3300−2500, 1659; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.26 (s, 6H), 4.75 (s, 1H), 6.35 (d, J = 16.1 Hz, 1H), 6.40 (d, J = 16.1 Hz, 1H), 6.60 (dd, J = 8.3, 1.5 Hz, 1H), 6.71 (d, J = 1.5 Hz, 1H), 7.63 (d, J = 8.3 Hz, 1H),; ^{13}C NMR (400 MHz, DMSO-d_6) δ 29.9, 69.3, 108.4, 112.5, 114.0, 124.6, 131.4, 141.3, 142.1, 151.7, 169.3; MS-EI m/z (%) 221 (M^+, 39), 252 (100); HRMS-EI m/z (M^+) calcd for $C_{12}H_{15}NO_3$ 221.1052, found 221.1051.

Ethyl 2-(allylamino)benzoate 7[10b] (Scheme 3). Following the general procedure (method A), **7** was obtained as a yellow oil. IR (neat) (cm^{-1}) 3364, 1681; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (t, J = 7.1 Hz, 3H), 3.86 (s, 2H), 4.31 (q, J = 7.1 Hz, 2H), 5.17 (dd, J = 10.4, 1.5 Hz, 1H), 5.30 (dd, J = 17.2, 1.5 Hz, 1H), 5.85−6.00 (m, 1H), 6.58 (dd, J = 7.9, 7.0 Hz, 1H), 6.65 (d, J = 8.5 Hz, 1H), 7.32 (ddd, J = 8.5, 7.0, 1.6 Hz, 1H), 7.90 (brs, 1H), 7.93 (dd, J = 7.9, 1.6 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.4, 45.2, 60.2, 110.4, 111.5, 114.6, 116.0, 131.6, 134.4, 134.6, 151.0, 168.7; MS-EI m/z (%) 205 (M^+, 100).

4-(Allylamino)-3-bromobenzoic Acid 9b (Entry 2 in Table 4). Following the general procedure (method A), **9b** was obtained as a white solid. Mp 170−173 °C; IR (KBr) (cm^{-1}) 3412, 3300−2500, 1675, 1599; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 2H), 5.05 (brs, 1H), 5.24 (dt, J = 10.5, 1.2 Hz, 1H), 5.29 (dd, J = 17.4, 1.2 Hz, 1H), 5.85−6.05 (m, 1H), 6.60 (d, J = 8.8 Hz, 1H), 7.92 (d, J = 8.8 Hz, 1H), 8.19 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 45.8, 108.5, 110.0, 117.1, 118.1, 131.3, 133.4, 134.7, 148.8, 170.9; MS-EI m/z (%) 255 (M^+, 100), 257 (M^+ + 2, 98). Anal. Calcd for $C_{10}H_{10}BrNO_2$: C, 46.90; H, 3.94; N, 5.47. Found: C, 47.13; H, 4.00; N, 5.13.

3-(Diallylamino)benzoic Acid 10a (Entry 1 in Table 4). Following the general procedure (method A), **10a** was obtained as an off-white solid. Mp 86−88 °C (Lit. 91 °C);[17] IR (KBr) (cm^{-1}) 3300−2500, 1683; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (d, J = 4.6 Hz, 4H), 5.10−5.25 (m, 4H), 5.80−5.95 (m, 2H), 6.87−6.95 (m, 1H), 7.27 (dd, J = 7.8, 7.8 Hz, 1H), 7.42 (d, J = 7.1 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 52.8, 113.6, 116.3, 117.4, 118.1, 129.1, 130.0, 133.4, 148.6, 172.9; MS-EI m/z (%) 217 (M^+, 100).

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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