JOC The Journal of Organic Chemistry

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Chemoselective Benzylation of Unprotected Anthranilic Acids with Benzhydryl Alcohols by Water-Soluble Au(III)/TPPMS in Water

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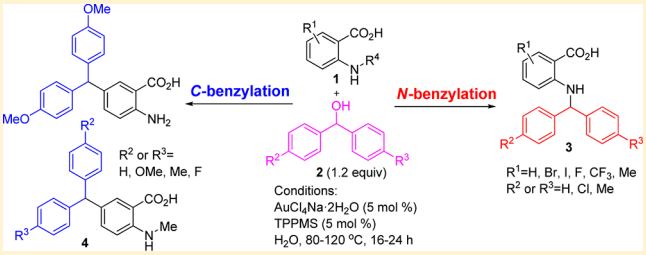
Supporting Information

ABSTRACT: A novel and efficient method for the benzylation of unprotected anthranilic acids with benzhydryl alcohols using water-soluble Au(III)/TPPMS in water is developed. Water plays an important role in our catalytic system. This new protocol could be used for not only *N*-benzylation, but also chemoselective *C*-benzylation by the Friedel–Crafts reaction.



INTRODUCTION

The gold-catalyzed direct substitution reaction of alcohols with various nucleophiles has become one of the most efficient and environmentally friendly synthetic strategies for alkylation.[1] Such efficiency is primarily due to the Lewis acid character of the gold catalyst that allows the activation of several sp^3 C–O bonds, thus promoting unique chemical transformations.

Benzyl halides are chemically unstable, and their synthesis from benzyl alcohols is achieved by halogenation, which is undesirable from an environmental point of view. Therefore, the application of alcohols as benzylating agents has the benefit of high atom efficiency and the formation of water as the only byproduct. However, the application of alcohols in nucleophilic substitution reactions is limited due to the poor leaving group ability of the hydroxyl groups. Thus, the direct catalytic substitution of underivatized benzyl alcohols is a promising strategy in organic chemistry.

Recently, Campagne and Prim reported the gold(III)-catalyzed direct amination of benzhydryl alcohols.[11] Ohshima and Mashima also reported the direct amination of the hydroxyl group with highly functionalized nitrogen nucleophiles such as acid-sensitive Boc protected amines by Au(III).[1b] In these cases, however, nucleophiles were limited to nitrogen compounds such as 4-nitroaniline, amides, and carbamates. Furthermore, most of these reactions are usually conducted in organic solvents, and extrusion of moisture is essential.[2] Water has unique reactivity and selectivity that cannot be attained with organic solvents. Therefore, in recent years, water has emerged as an attractive tool for new transition metal-catalyzed reactions.

We have been studying the development of syntheses without protecting groups and selective reactions toward various functional groups in water.[3] Thus, we became interested in further expanding the nucleophile scope in the gold-catalyzed direct substitution reaction to water-soluble unprotected substrates. In general, synthesis without protecting groups represents a distinct challenge and has been fraught with a number of difficulties, not the least of which is chemoselectivity.[4] One of the most effective ways for achieving synthesis without protecting groups is the development of selective reactions toward various functional groups in water. We recently reported a unique strategy for benzylation and C–H activation by the (η^3-benzyl)palladium system from a palladium catalyst and benzyl alcohol in water.[5] Water first activates the sp^3 C–O bond, followed by stabilization of OH^- by hydration, for the smooth generation of the activated Pd(II) cation species, which can then undergo innovative direct transformation reactions.

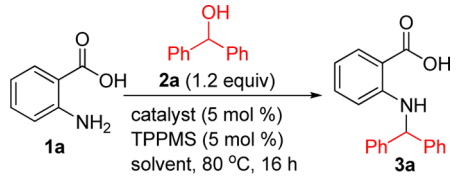
In light of our ongoing efforts to develop new methods for direct substitution reaction of benzyl alcohols, we herein report the water-soluble gold(III)-catalyzed benzylation of unprotected anthranilic acids with benzhydryl alcohols in water. Notably, the reaction proceeds chemoselectively to give *N*-benzylated **3** and *C*-benzylated **4** with the amino group left intact. To the best of our knowledge, there are no examples of the direct substitution of benzhydryl alcohols with unprotected water-soluble anthranilic acids as nucleophiles by Au(III)/TPPMS in water. Additionally, when using protocols based on previous methods such as $NaAuCl_4{\cdot}2H_2O$ in CH_2Cl_2 or Pd(0)/TPPMS in water, the substrate scope generally does not extend to unprotected water-soluble anthranilic acids.

Anthranilic acid **1a** is a versatile and low-cost starting material for synthesis of benzofused heterocycles. It also plays a vital part in the biosynthesis of tryptophan and several types of alkaloids. Derivatives of **1a** have been used for medicinal purposes, e.g., mefenamic acid, which has nonsteroidal antiflammatory and analgesic properties. Therefore, the chemistry of anthranilic acids **1** is of importance in medicinal and biological chemistry.

Received: May 15, 2013
Published: June 8, 2013

dx.doi.org/10.1021/jo401064f | J. Org. Chem. 2013, 78, 6714–6720

Table 1. Effect of Catalysts and Solvents[a]



entry	catalyst	ligand	solvent	conversion (%)[b]
1	$AuCl_4Na{\cdot}2H_2O$	TPPMS	H_2O	78 (77% yield)
2	none	none	H_2O	NR[d]
3	$AuCl_4Na{\cdot}2H_2O$	none	H_2O	14
4	none	TPPMS	H_2O	29
5	$HAuCl_4{\cdot}3H_2O$	TPPMS	H_2O	75
6	$AuCl_3$	TPPMS	H_2O	39
7	AuCl	TPPMS	H_2O	57
8	$TsOH{\cdot}H_2O$, MsOH or HCl	none	H_2O	Trace[c]
9	$Sc(OTf)_3$, $Yb(OTf)_3$, $Y(OTf)_3$ or $La(OTf)_3$	none	H_2O	Trace[c]
10	$AuCl_4Na{\cdot}2H_2O$	none	CH_2Cl_2[d]	Trace[c]
11	$Pd(OAc)_2$	TPPMS[e]	H_2O[f]	Trace[c]
12	$AuCl_4Na{\cdot}2H_2O$	TPPMS	1,4-dioxane	30
13	$AuCl_4Na{\cdot}2H_2O$	TPPMS	DMF, EtOH or Toluene	Trace[c]
14	$AuCl_4Na{\cdot}2H_2O$	none	DMF, EtOH or Toluene	Trace[c]
15	$AuCl_4Na{\cdot}2H_2O$	TPPMS	K_2CO_3 aq.[g]	Trace[c]

[a]Reaction conditions: **1a** (1 mmol), catalyst (5 mol %), ligand (5 mol %), benzhydrol **2a** (1.2 equiv), solvent (4 mL), 80 °C, 16 h under air. [b]The conversion was determined by ^{1}H NMR analysis of the crude product using *p*-nitroanisole as an internal standard. [c]By TLC analysis. [d]At 40 °C (bp). [e]10 mol %. [f]At 120 °C in a sealed tube. [g]2 equiv.

RESULTS AND DISCUSSION

First, we heated a mixture of anthranilic acid **1a** and benzhydryl alcohol **2a** (1.2 equiv) in the presence of $AuCl_4Na{\cdot}2H_2O$ (5 mol %) and sodium diphenylphosphinobenzene-3-sulfonate[6] (TPPMS, 5 mol %) in water at 80 °C for 16 h under air.[7] *N*-Benzylated **3a** was obtained in 78% yield and 77% isolated yield (Table 1, entry 1). The reaction did not proceed in the absence of the gold catalyst and phosphine ligand, and recovery of SM **1a** was detected by TLC analysis (entry 2). Using only $AuCl_4Na{\cdot}2H_2O$ or only TPPMS resulted in low yield (entry 3, 14%; entry 4, 29%). Komiya and co-workers reported that a gold(III) complex having a water-soluble phosphine ligand, $AuMe_2I$(TPPTS), was prepared, and reductive elimination involving C−C bond formation at Au(III) in water was faster than in organic solvents.[7f] Kunz and co-workers reported that gold(I) complexes with imidazolyl and thiazolyl-based water-soluble diphos-type ligands were prepared, and their potential as chemotherapeutics was investigated.[7d] Thus, in our catalytic system, $AuCl_3$(TPPMS) or a cationic aqueous complex $[AuCl_2(TPPMS)(H_2O)]^+Cl^-$ might be formed, which plays an important role in activation of the sp^3 C−O bond. With regard to the gold catalyst, the use of $HAuCl_4{\cdot}3H_2O$ also gave the product **3a** in good yield (entry 5, 75%). In contrast, When the $AuCl_3$ or AuCl were used, the reaction proceeded slowly (entry 6, 39%; entry 7, 57%). Thus, we decided to use more stable and easier to handle $AuCl_4Na{\cdot}2H_2O$ as the catalyst for further studies. To compare $AuCl_4Na{\cdot}2H_2O$ with other efficient catalysts, we tested the reaction using Brønsted acids such as $TsOH{\cdot}H_2O$, MsOH or HCl, and Lewis acids such as $Sc(OTf)_3$ $Yb(OTf)_3$, $Y(OTf)_3$ or $La(OTf)_3$. However, the reaction did not proceed (entries 8 and 9). Furthermore, using $AuCl_4Na{\cdot}2H_2O$ in CH_2Cl_2[1] (entry 10) or Pd(0)/TPPMS in water[5] (entry 11) also resulted in no reaction, clearly showing the superiority of Au(III)/TPPMS for the *N*-benzylation of unprotected anthranilic acid **1a** in water. Since the reaction resulted in low yields or no reaction when using 1,4-dioxane, DMF, EtOH or toluene as solvents (entries 12, 13 and 14), water is clearly essential for the *N*-benzylation in our catalytic system. Under basic conditions in the presence of K_2CO_3 (2 equiv), the reaction did not proceed (entry 15). Therefore, Au(III)/TPPMS functions as a Lewis acid for activation of benzhydryl alcohol **2a**, followed by formation of a benzylic cation species.

Results for the *N*-benzylation of a number of anthranilic acids **1** with benzhydryl alcohol **2a**, or conversely, anthranilic acid **1a** with several benzhydryl alcohols **2**, using $AuCl_4Na{\cdot}2H_2O$ and TPPMS in water, are summarized in Figure 1. The anthranilic acids with 5-bromo and 5-iodo groups resulted in moderate to good yields with the carbon−halogen moieties left intact (**3b**, 84%; **3c**, 51%), which could be employed for further manipulation. The reaction of anthranilic acids with electron-withdrawing fluoro and trifluoromethyl groups also proceeded to give *N*-benzylated products in good yields (**3d**, 89%; **3e**, 90%; **3f**, 90%). In contrast, anthranilic acids with electron-donating methyl groups proceeded slowly (**3g**, 79%; **3h**, 22%). The scope of the reaction with respect to alcohols **2** was further examined, and the reactions of anthranilic acid **1a** with benzhydryl alcohols **2** with methyl, chloro and fluoro groups resulted in good yields (**3i**, 91%; **3j**, 90%; **3k**, 88%). Furthermore, *N*-benzylation of 2-amino-4-(trifluoromethyl)-benzoic acid **1b** with 1-phenylethylalcohol **2b** or 1-phenyl-1-propanol **2c** also afforded desired *N*-benzylated product in good yield (**3l**, 75%; **3m**, 73% in Scheme 1). In contrast, 1-hydroxyindan **2d** resulted in no reaction.

Surprisingly, benzhydryl alcohol with electron-donating methoxy groups **2e** afforded only *C*-benzylated **4a** by Friedel−Crafts reaction in 86% yield with the amino group left intact (Scheme 2).[8] Furthermore, when using *N*-methylanthranilic acid **1b** as a substrate, *C*-benzylation occurred to give *C*-benzylated **4** in good yield (**4b**, 74%; **4c**, 84%; **4d**,

dx.doi.org/10.1021/jo401064f | J. Org. Chem. 2013, 78, 6714−6720

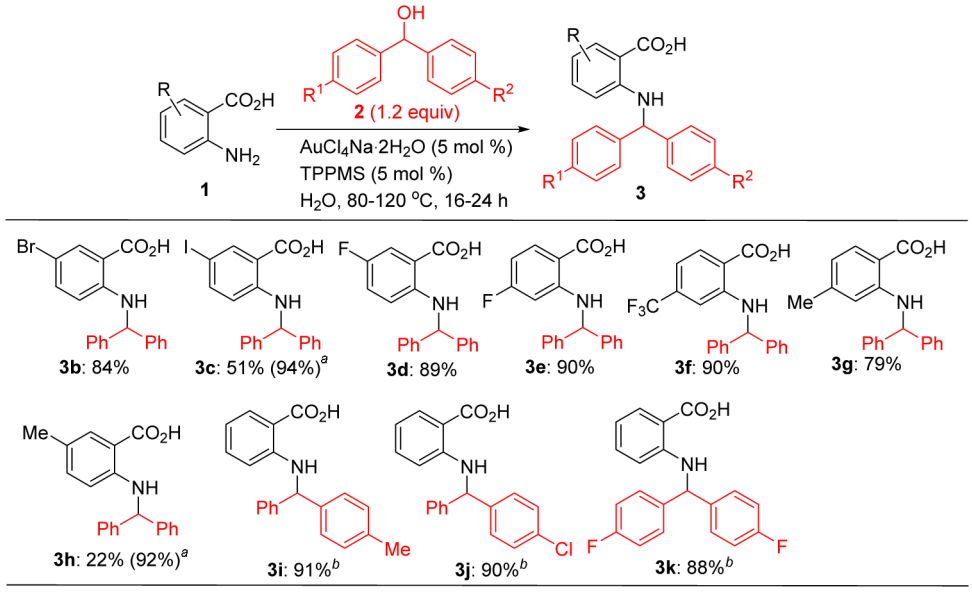
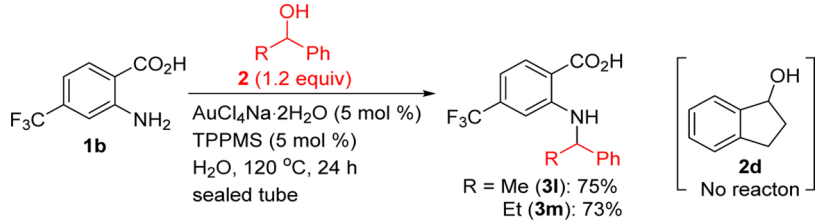
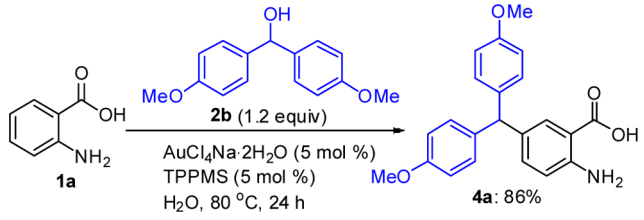


Figure 1. Scope of anthranilic acids **1** and benzhydryl alcohols **2**. Reaction conditions: anthranilic acids **1** (1 mmol), $AuCl_4Na·2H_2O$ (5 mol %), TPPMS (5 mol %), alcohols **2** (1.2 equiv), H_2O (4 mL), 80 °C, 16 h in a sealed tube, except when (*a*) at 120 °C, 24 h in a sealed tube, or (*b*) at 100 °C, 24 h.

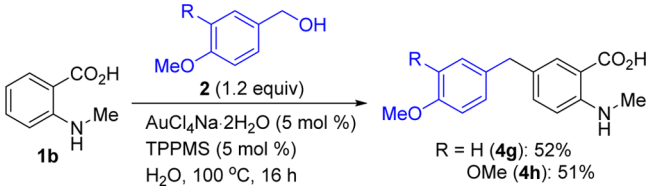
Scheme 1. Scope of Alcohols 2



Scheme 2. Chemoselective *C*-Benzylation of Anthranilic Acid 1a



Scheme 3. Chemoselective *C*-Benzylation with Benzyl Alcohols 2



86%; **4e**, 85%; **4f**, 75% in Figure 2). Interestingly, *C*-benzylation with simple benzyl alcohols such as 4-methoxybenzylalcohol **2f** or veratry alcohol **2g** resulted in good yield (**4g**, 52%; **4h**, 51% in Scheme 3). The sterically demanding *N*-methyl substituent would influence the selectivity of the direct substitution. These results show that our Au(III)/TPPMS system might possibly be used for *C*-benzylation with other substrates by Friedel–Crafts reaction in water.[9]

On the basis of our results and literature reports, the following mechanism can be suggested (Scheme 4). First, water-soluble gold(III) intermediate **5** might form from anthranilic acid **1a** and benzhydryl alcohols **2** in the presence of $AuCl_4Na·2H_2O$ and TPPMS, since Au(III)-picolinate complex **I** is reported as the active catalyst for direct amination of alcohols.[1b] Water must play an important role for the smooth generation of the intermediate **5**, which is stabilized by hydration, since the reaction did not occur without water and water-soluble phosphine ligand, TPPMS. Additionally, anthranilic acid **1a** has been used to form coordination complexes with many metals such as gallium, aluminum, and lithium, and their structures were determined using X-ray crystallography.[10] Next, benzyl cation species **7** forms, followed by nucleophilic attack of the nitrogen of anthranilic acid **6**, to give *N*-benzylated **3** (path A). In contrast, a benzyl cation with electron-donating methoxy groups **8** directs the Friedel–Crafts reaction to afford *C*-benzylated **4a** (path B). According to the HSAB principle, soft acids prefer to bind to soft bases. Therefore, the carbon atom at the C5 position of anthranilic acid **6**, being a soft nucleophile center, will prefer to bind to soft acid **8** because of the +R effect of the *p*-methoxy groups on the benzene ring.[11] While benzyl cation **7** could form an ion pair with the water-soluble Au(III) complex **6** in the aqueous hydrophilic arena, the intermediate **8**, which is a long-lived cation, might interact with

dx.doi.org/10.1021/jo401064f | J. Org. Chem. 2013, 78, 6714–6720

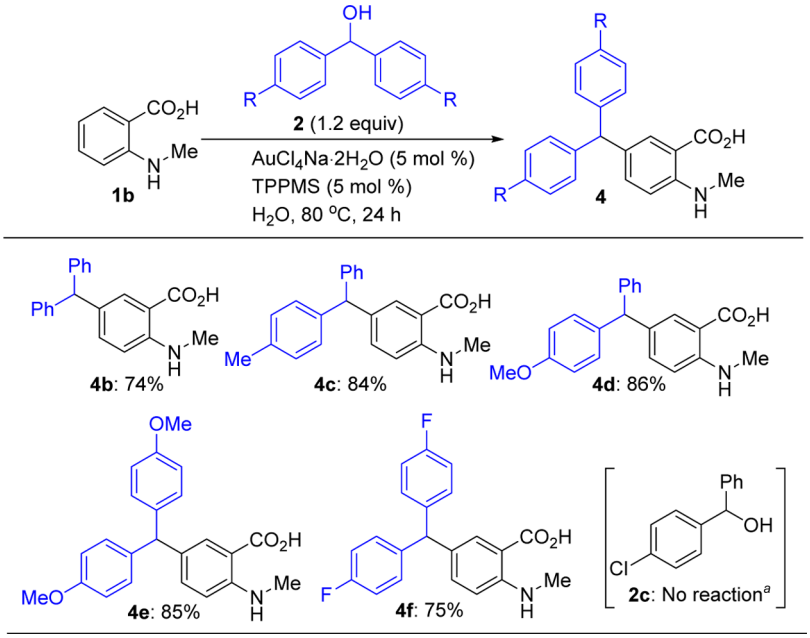
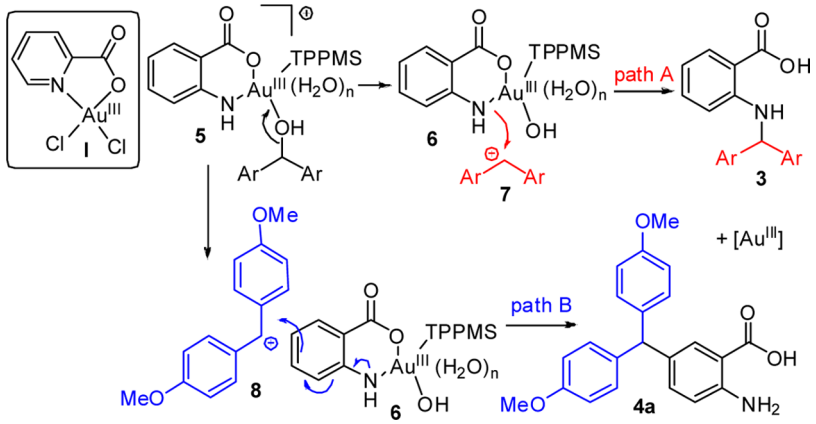


Figure 2. Chemoselective *C*-benzylation of *N*-methylanthranilic acid **1b** with benzhydryl alcohols **2**. Reaction conditions: *N*-methylanthranilic acid 1b (1 mmol), $AuCl_4Na{\cdot}2H_2O$ (5 mol %), TPPMS (5 mol %), alcohol 2 (1.2 equiv), H_2O (4 mL), 80 °C, 24 h in a sealed tube, except when (*a*) at 100 °C in a sealed tube.

Scheme 4. Possible Mechanism

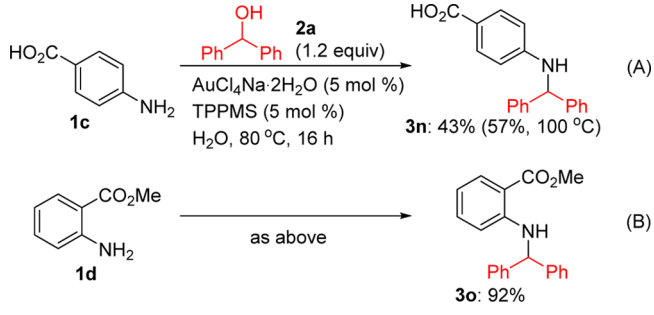


the benzene ring of anthranilic acid **6** by the hydrophobic effect. Indeed the *C*-benzylation using benzhydryl alcohol with electron-withdrawing chloro group **2** did not proceed (see Figures 1 and 2). Additionally, the carboxyl group of anthranilic acid would enhance the reaction, since the reaction of 4-aminobenzoic acid **1c** proceeded slowly (Scheme 5A vs entry 1 in Table 1). Anthranilic acid methyl ester **1d** afforded *N*-benzylated **3n** in 92% yield (Scheme 5B). Ester **1d** also might form a coordination active complex with Au(III)/TPPMS in water.

CONCLUSIONS

In summary, we developed the first benzylation of unprotected anthranilic acids with benzhydryl alcohols using a water-soluble gold(III)/TPPMS catalyst system in water, one of the most efficient and environmentally friendly synthetic strategies for benzylation. Notably, water plays an important role in our catalytic system. This new protocol could be used for *N*-benzylation and chemoselective *C*-benzylation by Friedel–Crafts reaction. We are currently investigating the scope of various water-soluble nucleophiles, such as highly functionalized bioactive compounds,[12] and are developing new reactions using the water-soluble Au(III)/TPPMS system in aqueous media.

Scheme 5. *N*-Benzylation of 4-Aminobenzoic Acid 1c or Ester 1d



dx.doi.org/10.1021/jo401064f | J. Org. Chem. 2013, 78, 6714–6720

EXPERIMENTAL SECTION

The mass analyzer type is double-focusing magnetic sector mass spectrometer for the HRMS measurements.

General Procedure. A mixture of anthranilic acids **1** (1 mmol), $AuCl_4Na{\cdot}2H_2O$ (20 mg, 0.05 mmol), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 18 mg, 0.05 mmol) and benzhydryl alcohols **2** (1.2 mmol) in H_2O (4 mL) was heated at 80−120 °C for 16−24 h in a sealed tube. 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 the desired product **3** or **4**.

2-(Benzhydrylamino)benzoic acid 3a (Table 1, Entry 1).[13] Following the general procedure, **3a** was obtained as a white solid: 234 mg (77%); mp 209−211 °C; IR (KBr) (cm^{-1}) 3362, 2876, 1661; ^1H NMR (400 MHz, DMSO-d_6) δ 5.84 (d, J = 6.4 Hz, 1H), 6.57 (dd, J = 6.8, 6.8 Hz, 1H), 6.59 (d, J = 8.4 Hz, 1H), 7.25 (t, J = 7.2 Hz, 2H), 7.30−7.45 (m, 9H), 7.83 (dd, J = 8.0, 1.6 Hz, 1H), 8.68 (d, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 60.2, 110.7, 112.6, 115.0, 126.8, 127.2, 128.8, 131.6, 134.3, 142.9, 149.6, 170.1; MS (ESI) m/z 302 $[M - H]^-$.

2-(Benzhydrylamino)-5-bromobenzoic acid 3b (Figure 1).[13] Following the general procedure, **3b** was obtained as an off-white solid: 321 mg (84%); mp 230−232 °C; IR (KBr) (cm^{-1}) 3379, 3025, 1669; ^1H NMR (400 MHz, DMSO-d_6) δ 5.86 (dd, J = 6.4 Hz, 1H), 6.56 (d, J = 9.2 Hz, 1H), 7.23−7.29 (m, 2H), 7.32−7.43 (m, 9H), 7.89 (d, J = 2.4 Hz, 1H), 8.68 (d, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 60.1, 105.5, 112.4, 115.0, 126.8, 127.3, 128.9, 133.4, 136.6, 142.5, 148.6, 168.9; MS (EI) m/z (%) 383 (M^++2, 17.3), 381 (M^+, 17.4), 167 (100).

2-(Benzhydrylamino)-5-iodobenzoic acid 3c (Figure 1). Following the general procedure, **3c** was obtained as a pale yellow solid: 403 mg (94%); mp 233−234 °C; IR (KBr) (cm^{-1}) 3355, 3036, 1672; ^1H NMR (400 MHz, DMSO-d_6) δ 5.85 (d, J = 6.4 Hz, 1H), 6.45 (d, J = 9.2 Hz, 1H), 7.22−7.29 (m, 2H), 7.32−7.40 (m, 8H), 7.52 (dd, J = 8.8, 2.4 Hz, 1H), 8.05 (d, J = 2.0 Hz, 1H), 8.68 (d, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 60.0, 75.4, 113.1, 115.5, 126.8, 127.3, 128.9, 139.3, 142.0, 142.5, 148.9, 168.9; MS (ESI) m/z 428 $[M - H]^-$. Anal. Calcd for $C_{20}H_{16}INO_2$: C, 55.96; H, 3.76; N, 3.26. Found: C, 55.65; H, 3.84; N, 3.04.

2-(Benzhydrylamino)-5-fluorobenzoic acid 3d (Figure 1). Following the general procedure, **3d** was obtained as a white solid: 285 mg (89%); mp 215−216 °C; IR (KBr) (cm^{-1}) 3369, 3030, 1669; ^1H NMR (400 MHz, DMSO-d_6) δ 5.84 (d, J = 6.0 Hz, 1H), 6.60 (dd, J = 9.2, 4.4 Hz, 1H), 7.16−7.30 (m, 3H), 7.32−7.42 (m, 8H), 7.54 (dd, J = 10.0, 3.2 Hz, 1H), 8.49 (d, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 60.5, 110.8 (d, J = 5.8 Hz), 114.1 (d, J = 7.6 Hz), 116.5 (d, J = 22.9 Hz), 121.8 (d, J = 22.9 Hz), 126.8, 127.3, 128.8, 142.8, 146.6, 152.4 (d, J = 231 Hz), 169.2; MS (ESI) m/z (%) 320 $[M - H]^-$. Anal. Calcd for $C_{20}H_{16}FNO_2$: C, 74.75; H, 5.02; N, 4.36. Found: C, 75.18; H, 4.99; N, 4.25.

2-(Benzhydrylamino)-4-fluorobenzoic acid 3e (Figure 1). Following the general procedure, **3e** was obtained as a white solid: 289 mg (90%); mp 200−201 °C; IR (KBr) (cm^{-1}) 3357, 3024, 1672; ^1H NMR (400 MHz, DMSO-d_6) δ 5.89 (d, J = 6.4 Hz, 1H), 6.35−6.45 (m, 2H), 7.27 (tt, J = 6.8, 1.6 Hz, 2H), 7.36 (t, J = 7.6 Hz, 4H), 7.40 (dd, J = 8.4, 1.6 Hz, 4H), 7.89 (dd, J = 8.4, 6.8 Hz, 1H), 8.91 (d, J = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 60.0, 98.7 (d, J = 25.7 Hz), 102.4 (d, J = 21.9 Hz), 107.7, 126.8, 127.4, 128.9, 134.5 (d, J = 11.4 Hz), 142.4, 151.8 (d, J = 12.4 Hz), 166.0 (d, J = 247 Hz), 169.4; MS (EI) m/z (%) 321 (M^+, 23.3), 167 (100); HRMS (EI) m/z calcd for $C_{20}H_{16}FNO_2$ $[M^+]$, 321.1165, found 321.1165.

2-(Benzhydrylamino)-4-(trifluoromethyl)benzoic acid 3f (Figure 1). Following the general procedure, **3f** was obtained as a white solid: 334 mg (90%); mp 193−195 °C; IR (KBr) (cm^{-1}) 3364, 3029, 1671; ^1H NMR (400 MHz, DMSO-d_6) δ 5.99 (d, J = 6.4 Hz, 1H), 6.86 (s, 1H), 6.87 (d, J = 8.0 Hz, 1H), 7.27 (tt, J = 7.6, 1.4 Hz, 2H), 7.37 (t, J = 8.0 Hz, 4H), 7.37 (d, J = 8.0 Hz, 4H), 8.01 (d, J = 8.0 Hz, 1H), 8.89 (d, J = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 60.0, 109.0 (d, J = 3.8 Hz), 110.7 (d, J = 3.8 Hz), 113.8, 123.6 (d, J = 273 Hz), 126.7, 127.4, 128.9, 132.9, 133.7 (q, J = 29.6 Hz), 142.3, 149.4, 169.3; MS (EI) m/z (%) 335 (M^+, 1.5), 226 (100); HRMS (EI) m/z calcd for $C_{21}H_{16}F_3NO_2$ $[M^+]$, 371.1133, found 371.1131.

2-(Benzhydrylamino)-4-methylbenzoic acid 3g (Figure 1). Following the general procedure, **3g** was obtained as a white solid: 250 mg (79%); mp 206−207 °C; IR (KBr) (cm^{-1}) 3368, 3030, 1658; ^1H NMR (400 MHz, DMSO-d_6) δ 2.11 (s, 3H), 5.85 (d, J = 6.8 Hz, 1H), 6.40 (d, J = 8.0 Hz, 1H), 6.45 (s, 1H), 7.25 (tt, J = 7.2, 1.6 Hz, 2H), 7.35 (t, J = 8.0 Hz, 4H), 7.39 (dd, J = 8.0, 2.0 Hz, 4H), 7.71 (d, J = 8.4 Hz, 1H), 8.68 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.7, 60.0, 108.2, 112.7, 116.3, 126.8, 127.2, 128.8, 131.6, 143.0, 144.4, 149.8, 170.1; MS (ESI) m/z 316 $[M - H]^-$. Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.51; H, 5.91; N, 4.19.

2-(Benzhydrylamino)-5-methylbenzoic acid 3h (Figure 1). Following the general procedure, **3h** was obtained as an off-white solid: 292 mg (92%); mp 257−260 °C; IR (KBr) (cm^{-1}) 3381, 3028, 1667; ^1H NMR (400 MHz, DMSO-d_6) δ 2.14 (s, 3H), 5.81 (d, J = 6.4 Hz, 1H), 6.52 (d, J = 8.8 Hz, 1H), 7.07 (dd, J = 8.8, 2.4 Hz, 1H), 7.24 (tt, J = 7.2, 1.6 Hz, 2H), 7.34 (t, J = 8.0 Hz, 4H), 7.38 (d, J = 8.0 Hz, 4H), 7.63 (d, J = 1.6 Hz, 1H), 8.49 (d, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 19.7, 60.3, 110.5, 112.8, 123.4, 126.8, 127.1, 128.8, 131.4, 135.1, 143.1, 147.7, 170.1; MS (ESI) m/z 316 $[M - H]^-$. Anal. Calcd for $C_{21}H_{19}NO_2{\cdot}0.7H_2O$: C, 76.43; H, 6.23; N, 4.24. Found: C, 76.19; H, 5.82; N, 4.13.

2-[Phenyl(*p*-tolyl)methylamino]benzoic acid 3i (Figure 1).[14] Following the general procedure, **3i** was obtained as a white solid: 289 mg (91%); mp 191−192 °C; IR (KBr) (cm^{-1}) 3357, 3024, 1665; ^1H NMR (400 MHz, DMSO-d_6) δ 2.25 (s, 3H), 5.78 (d, J = 6.4 Hz, 1H), 6.50−6.60 (m, 2H), 7.15 (d, J = 7.6 Hz, 2H), 7.20−7.30 (m, 4H), 7.34 (t, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 7.6, 1.2 Hz, 1H), 8.63 (d, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.6, 60.0, 110.6, 112.6, 114.9, 126.7, 126.7, 127.1, 128.7, 129.3, 131.6, 134.2, 136.3, 139.9, 143.0, 149.7, 170.1; MS (EI) m/z (%) 317 (M^+, 27.7), 181 (100).

2-[(4-Chlorophenyl)(phenyl)methylamino]benzoic acid 3j (Figure 1).[14] Following the general procedure, **3j** was obtained as a white solid: 304 mg (90%); mp 201−203 °C; IR (KBr) (cm^{-1}) 3357, 3023, 1667; ^1H NMR (400 MHz, DMSO-d_6) δ 5.89 (d, J = 6.4 Hz, 1H), 6.55−6.65 (m, 2H), 7.20−7.30 (m, 2H), 7.30−7.45 (m, 8H), 7.83 (dd, J = 8.4, 1.4 Hz, 1H), 8.65 (d, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 59.4, 110.8, 112.6, 115.2, 126.8, 127.4, 128.6, 128.8, 128.9, 131.6, 131.7, 134.3, 141.9, 142.4, 149.5, 170.1; MS (ESI) m/z 338 $[M - H+2]^-$, 336 $[M - H]^-$.

2-[Bis(4-fluorophenyl)methylamino]benzoic acid 3k (Figure 1). Following the general procedure, **3k** was obtained as a white solid: 299 mg (88%); mp 199−200 °C; IR (KBr) (cm^{-1}) 3362, 2887, 1664; ^1H NMR (400 MHz, DMSO-d_6) δ 5.91 (d, J = 6.0 Hz, 1H), 6.55−6.65 (m, 2H), 7.19 (dd, J = 8.8, 2.0 Hz, 4H), 7.27 (t, J = 8.0 Hz, 1H), 7.41 (dd, J = 6.4, 6.4 Hz, 4H), 7.83 (d, J = 8.0 Hz, 1H), 8.60 (d, J = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 58.6, 110.8, 112.6, 115.2, 115.6 (J = 21 Hz), 128.8 (J = 7.6 Hz), 131.7, 134.3, 138.8 (J = 2.8 Hz), 149.4, 161.26 (J = 242 Hz), 170.1; MS (EI) m/z (%) 339 (M^+, 21.8), 203 (100); HRMS (EI) m/z calcd for $C_{20}H_{15}F_2NO_2$ $[M^+]$, 339.1071, found 339.1073.

2-(1-Phenylethylamino)-4-(trifluoromethyl)benzoic acid 3l (Scheme 1). Following the general procedure, **3l** was obtained as a white solid: 232 mg (75%); mp 156−158 °C; IR (KBr) (cm^{-1}) 3370, 2986, 1668; ^1H NMR (400 MHz, DMSO-d_6) δ 1.50 (d, J = 6.4 Hz, 3H), 4.74−4.84 (m, 1H), 6.76 (s, 1H), 6.80 (d, J = 8.4 Hz, 1H), 7.23 (t, J = 6.8 Hz, 1H), 7.30−7.40 (m, 4H), 7.98 (d, J = 8.4 Hz, 1H), 8.50 (d, J = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 24.4, 51.5, 108.7, 110.2 (d, J = 3.9 Hz), 113.4, 123.6 (d, J = 272 Hz), 125.7, 127.0, 128.7, 132.8, 133.6 (q, J = 31.4 Hz), 144.2, 149.6, 169.3; MS (EI) m/z (%) 309 (M^+, 31.1), 105 (100); HRMS (EI) m/z calcd for $C_{16}H_{14}F_3NO_2$ $[M^+]$, 309.0977, found 309.0976.

2-(1-Phenylpropylamino)-4-(trifluoromethyl)benzoic acid 3m (Scheme 1). Following the general procedure, **3m** was obtained as a white solid: 236 mg (73%); mp 167−169 °C; IR (KBr) (cm^{-1})

3363, 2973, 1671; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.92 (t, J = 7.3 Hz, 3H), 1.75−1.90 (m, 2H), 4.57 (dd, J = 13.3, 6.6 Hz, 1H), 6.75 (s, 1H), 6.79 (dd, J = 8.3, 1.4 Hz, 1H), 7.20−7.28 (m, 1H), 7.30−7.40 (m, 4H), 7.97 (dd, J = 8.2, 0.5 Hz, 1H), 8.61 (d, J = 6.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.4, 30.7, 57.3, 108.6, 110.0, 113.2, 123.5 (d, J = 272 Hz), 126.1, 127.0, 128.5, 132.8, 133.5 (q, J = 31.5 Hz), 142.8, 149.9, 169.3; MS (EI) m/z (%) 323 (M^+, 12.5), 117 (100); HRMS (EI) m/z calcd for $C_{17}H_{16}F_3NO_2$ [M^+], 323.1133, found 323.1133.

4-(Benzhydrylamino)benzoic acid 3n (Scheme 5A).[14] Following the general procedure, **3n** was obtained as a white solid: 181 mg (57%); mp 203−205 °C; IR (KBr) (cm^{-1}) 3420, 2867, 1668; ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.77 (d, J = 7.2 Hz, 1H), 6.69 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 7.2 Hz, 1H), 7.24 (tt, J = 7.2, 1.2 Hz, 2H), 7.33 (dd, J = 7.2, 7.2 Hz, 4H), 7.39 (d, J = 7.2 Hz, 4H), 7.62 (d, J = 8.8 Hz, 2H), 12.0 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 60.2, 112.0, 117.6, 127.0, 127.3, 128.5, 130.8, 142.7, 151.6, 167.4; MS (EI) m/z (%) 303 (M^+, 26.4), 167 (100).

Methyl 2-(benzhydrylamino)benzoate 3o (Scheme 5B).[13] Following the general procedure, **3o** was obtained as a white solid: 293 mg (92%); mp 108−110 °C; IR (KBr) (cm^{-1}) 3356, 1683; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 5.63 (d, J = 4.8 Hz, 1H), 6.54 (d, J = 8.4 Hz, 1H), 6.59 (t, J = 8.0 Hz, 1H), 7.20−7.40 (m, 11H), 7.93 (d, J = 8.0 Hz, 1H), 8.46 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.6, 61.9, 110.4, 112.7, 115.1, 127.2, 127.3, 128.8, 131.5, 134.5, 142.5, 150.0, 169.1; MS (EI) m/z (%) 317 (M^+, 42.6), 167 (100).

2-Amino-5-[bis(4-methoxyphenyl)methyl]benzoic acid 4a (Scheme 2). Following the general procedure, **4a** was obtained as a white solid: 313 mg (86%); mp 185−187 °C; IR (KBr) (cm^{-1}) 3475, 3365, 2961, 1661; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.71 (s, 6H), 5.31 (s, 1H), 6.68 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.8 Hz, 4H), 6.94−6.98 (m, 1H), 6.98 (d, J = 8.8 Hz, 4H), 7.40 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 53.2, 55.0, 109.2, 113.6, 116.5, 129.8, 130.5, 130.9, 134.6, 136.6, 149.9, 157.4, 169.5; MS (EI) m/z (%) 363 (M^+, 100). Anal. Calcd for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.61; H, 5.91; N, 3.54.

5-Benzhydryl-2-(methylamino)benzoic acid 4b (Figure 2). Following the general procedure, **4b** was obtained as a white solid: 235 mg (74%); mp 202−203 °C; IR (KBr) (cm^{-1}) 3373, 3024, 1664; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.81 (s, 3H), 5.49 (s, 1H), 6.66 (d, J = 8.8 Hz, 1H), 7.10 (d, J = 7.2 Hz, 4H), 7.14 (dd, J = 8.8, 2.4 Hz, 1H), 7.20 (tt, J = 7.2, 1.2 Hz, 2H), 7.30 (dd, J = 7.2, 7.2 Hz, 4H), 7.54 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 29.3, 54.7, 109.6, 111.0, 126.1, 128.3, 128.9, 129.1, 131.7, 135.3, 144.2, 150.2, 169.8; MS (EI) m/z (%) 317 (M^+, 100). Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.41; H, 5.77; N, 4.27.

2-(Methylamino)-5-[phenyl(*p*-tolyl)methyl]benzoic acid 4c (Figure 2). Following the general procedure, **4c** was obtained as a white solid: 278 mg (84%); mp 217−219 °C; IR (KBr) (cm^{-1}) 3389, 2887, 1674; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.26 (s, 3H), 2.81 (s, 3H), 5.43 (s, 1H), 6.64 (d, J = 8.8 Hz, 1H), 6.98 (d, J = 8.0 Hz, 2H), 7.05−7.15 (m, 5H), 7.19 (dd, J = 7.2, 7.2 Hz, 1H), 7.29 (dd, J = 7.2, 7.2 Hz, 2H), 7.52 (d, J = 2.0 Hz, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.6, 29.2, 54.3, 109.4, 110.9, 126.0, 128.3, 128.8, 128.9, 129.3, 131.6, 135.1, 135.3, 141.2, 144.4, 150.2, 169.8; MS (EI) m/z (%) 331 (M^+, 100); HRMS (EI) m/z calcd for $C_{22}H_{21}NO_2$ [M^+], 331.1572, found 331.1573. Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.63; H, 6.67; N, 4.23.

5-[(4-Methoxyphenyl)(phenyl)methyl]-2-(methylamino)-benzoic acid 4d (Figure 2). Following the general procedure, **4d** was obtained as a white solid: 299 mg (86%); mp 165−167 °C; IR (KBr) (cm^{-1}) 33384, 2911, 1668; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.81 (s, 3H), 3.71 (s, 3H), 5.42 (s, 1H), 6.65 (d, J = 8.8 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 7.2 Hz, 2H), 7.13 (dd, J = 8.8, 2.0 Hz, 1H), 7.19 (dd, J = 7.2, 7.2 Hz, 1H), 7.29 (dd, J = 7.6, 7.6 Hz, 2H), 7.53 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 29.3, 53.9, 55.0, 109.5, 110.9, 113.7, 126.0, 128.3, 128.8, 129.5, 129.9, 131.6, 135.3, 136.2, 144.6, 150.2, 157.5, 169.8; MS (EI) m/z (%) 347 (M^+, 100); HRMS (EI) m/z calcd for $C_{22}H_{21}NO_3$ [M^+], 347.1521, found 347.1520. Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.23; H, 5.97; N, 3.88.

5-[Bis(4-methoxyphenyl)methyl]-2-(methylamino)benzoic acid 4e (Figure 2). Following the general procedure, **4e** was obtained as a white solid: 321 mg (85%); mp 177−179 °C; IR (KBr) (cm^{-1}) 3396, 2940, 1665; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.81 (s, 3H), 3.71 (s, 6H), 5.35 (s, 1H), 6.64 (d, J = 8.8 Hz, 1H), 6.85 (d, J = 8.8 Hz, 4H), 6.99 (d, J = 8.8 Hz, 4H), 7.11 (dd, J = 8.4, 2.0 Hz, 1H), 7.51 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 29.3, 53.1, 55.0, 109.4, 110.9, 113.6, 129.8, 129.9, 131.5, 135.2, 136.6, 150.1, 157.4, 169.8; MS (EI) m/z (%) 377 (M^+, 100); HRMS (EI) m/z calcd for $C_{23}H_{23}NO_4$ [M^+], 377.1627, found 377.1628. Anal. Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.20; H, 6.24; N, 3.67.

5-[Bis(4-fluorophenyl)methyl]-2-(methylamino)benzoic acid 4f (Figure 2). Following the general procedure, **4f** was obtained as a white solid: 265 mg (75%); mp 184−186 °C; IR (KBr) (cm^{-1}) 3380, 2908, 1670; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.82 (s, 3H), 5.54 (s, 1H), 6.66 (d, J = 8.8 Hz, 1H), 7.05−7.20 (m, 9H), 7.50 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 29.2, 52.9, 109.5, 111.1, 115.1 (d, J = 21 Hz), 128.9, 130.6, 130.7, 135.1, 140.3 (d, J = 2.8 Hz), 150.3, 160.7 (d, J = 241 Hz), 169.7; MS (EI) m/z (%) 353 (M^+, 100); HRMS (EI) m/z calcd for $C_{21}H_{17}F_2NO_2$ [M^+], 353.1227, found 353.1225.

5-(4-Methoxybenzyl)-2-(methylamino)benzoic acid 4g (Scheme 3). Following the general procedure, **4g** was obtained as a pale yellow solid: 141 mg (52%); mp 155−157 °C; IR (KBr) (cm^{-1}) 3390, 2905, 1665; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.80 (s, 3H), 3.70 (s, 3H), 3.74 (s, 2H), 6.57 (d, J = 8.7 Hz, 1H), 6.79 (dt, J = 8.7, 3.0 Hz, 2H), 7.05 (dt, J = 8.7, 3.0 Hz, 2H), 7.19 (dd, J = 8.7, 2.3 Hz, 1H), 7.55 (d, J = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 29.8, 55.5, 110.2, 111.5, 114.3, 127.6, 130.0, 131.7, 134.3, 135.6, 150.7, 158.0, 170.4; MS (EI) m/z (%) 271 (M^+, 100); HRMS (EI) m/z calcd for $C_{16}H_{17}NO_3$ [M^+], 271.1208, found 271.1209.

5-(3,4-Dimethoxybenzyl)-2-(methylamino)benzoic acid 4h (Scheme 3). Following the general procedure, **4h** was obtained as a pale yellow solid: 153 mg (51%); mp 165−167 °C; IR (KBr) (cm^{-1}) 3380, 2908, 1651; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.80 (s, 3H), 3.71 (s, 6H), 3.73 (s, 2H), 6.63 (d, J = 8.7 Hz, 1H), 6.67 (dd, J = 8.3, 1.8 Hz, 1H), 6.79 (d, J = 1.8 Hz, 1H), 6.84 (d, J = 8.3 Hz, 1H), 7.25 (dd, J = 8.5, 2.1 Hz, 1H), 6.61 (d, J = 2.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 29.8, 55.9, 56.0, 110.2, 111.5, 112.4, 113.0, 120.9, 127.4, 131.7, 134.8, 135.6, 147.5, 149.2, 150.7, 170.4; MS (EI) m/z (%) 301 (M^+, 100); HRMS (EI) m/z calcd for $C_{17}H_{19}NO_4$ [M^+], 301.1314, found 301.1312.

Table 1, Entry 1. (The yield was determined by ^{1}H NMR analysis of the crude product using *p*-nitroanisole as an internal standard.)

A mixture of anthranilic acid **1a** (138 mg, 1 mmol), $AuCl_4Na{\cdot}2H_2O$ (20 mg, 0.05 mmol), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 18 mg, 0.05 mmol) and benzhydryl alcohol **2a** (221 mg, 1.2 mmol) in H_2O (4 mL) was heated at 80 °C for 16 h in a sealed tube. After the reaction mixture was cooled, *p*-nitroanisole (153 mg, 1 mmol, internal standard) was added to the reaction mixture, which was extracted with AcOEt. The organic layer was washed with brine, and concentrated in vacuo. The residue was analyzed by ^{1}H NMR spectroscopy.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

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Notes

The authors declare no competing financial interest.

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