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A Radical Pathway for Direct Substitution of Benzyl Alcohols with Water-Soluble Copper Catalyst in Water

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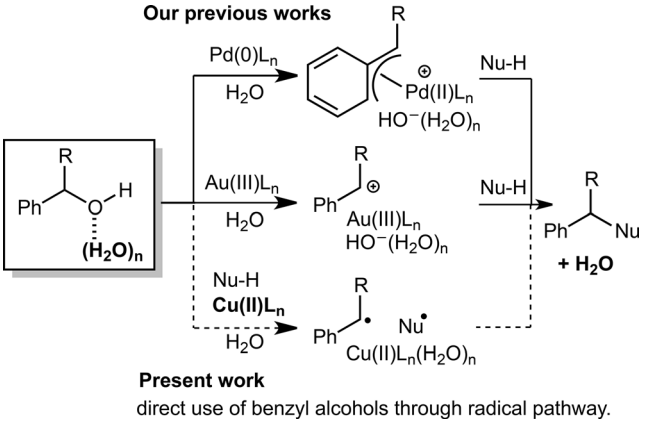
Abstract: We have developed a novel strategy for the direct substitution of benzyl alcohols with anthranilic acids using water-soluble copper catalysts through a radical pathway in water, which offers efficient and environmentally friendly *N*-, *S*-, and *C*-benzylations under neutral conditions. Radical scavengers strongly inhibited the benzylation. Radical clock experiments using α-cyclopropylbenzyl alcohol were conducted to observe the rapid isomerization of the cyclopropylmethyl radical to the allylmethyl radical. Hammett plots could be fitted to a two-parameter Hammett relationship containing both radical and polar contributions [log $(k_X/k_H) = -1.24\,\sigma^{\bullet} - 0.38\,\sigma$, $R^2 = 0.99$]. The relative parameter $\rho^{\bullet}/\rho$ of 3.3 suggested that these reactions involved a strong radical character with minor polar influence at the transition state.

Keywords: anthranilic acids; benzyl alcohols; benzylation; copper; radicals

Introduction

The direct substitution of hydroxy groups has become an atom-economical and environmentally benign methodology for the formation of C–C, C–S, and C–N bonds.[1] However, direct substitutions of alcohols are challenging because hydroxides are poor leaving groups compared to halides, thus requiring activating agents such as Lewis and Brønsted acids. Recently, *N*-monoalkylations using alcohols have been demonstrated under transition metal catalysis, which are usually achieved by the borrowing hydrogen method.[2,3]

We have been developing a unique strategy for the direct substitution of benzyl alcohols using water-soluble transition metal catalysts [M/TPPMS: M = Pd(0)[4] or Au(III)[5] and TPPMS = sodium diphenylphosphinobenzene-3-sulfonate] in water (Scheme 1). We believe that water activates the sp^3 C–O bond by a hydrogen bond between water and the hydroxy group of the alcohol, which enhances the formation of an active metal ion species by hydration. Theoretical calculations by Shinokubo and Oshima have elucidated the importance of hydration of the hydroxy group for the smooth generation of π-allylpalladium species.[6] Cozzi et al. proposed that the direct generation of carbocations in water from alcohols is driven by the formation of hydrogen bonds between water and the hydroxy group of the alcohol.[7] On the basis of our previous results, the hydrophobic effect also enhances the reaction in water, since water-insoluble substrates could be adapted to these strategies.[4a,5a] Therefore, no reaction or lower yield occurred when using co-solvents such as alcohols or polar organic solvents in water. Since water molecules have unusual chemical and physical properties compared to organic solvents, water should play an important role in the development of new and efficient reactions.



Scheme 1. Water-soluble transition metal-catalyzed direct substitution of hydroxyl groups.

It is well known that alkyl radicals are generated from the radical deoxygenation of alcohols (Barton–McCombie reaction[8] and Marko–Lam reaction[9]). Other concepts for the metal-catalyzed radical reaction of benzyl halides based on a single electron transfer (SET)[10] or atom transfer[11]-mediated pathway have been developed. Watson and co-workers reported that Cu(I) catalysts initiate radical reactions of nitroalkanes with benzyl bromides.[10b] However, to the best of our knowledge, there are no examples of the direct substitution of benzyl alcohols instead of benzyl halides *via* benzyl radicals.[12]

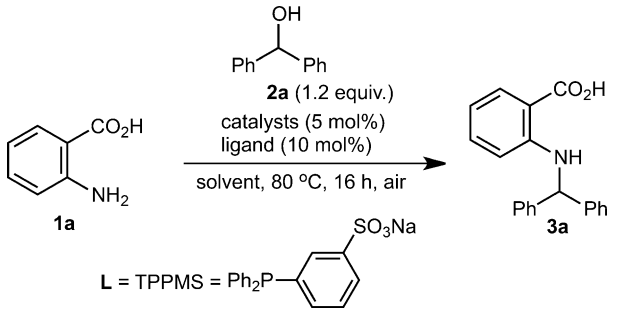
On the basis of our previous results and literature reports, we hypothesize that the activation of the sp^3 C–O bond of alcohols by hydration in the presence of a radical initiator could directly generate benzyl radicals, which have the potential to be powerful tools in direct transformations in water. Consequently, we herein report a radical pathway for direct substitution of benzyl alcohols initiated by a water-soluble copper catalyst (Scheme 1).[13,14] This new strategy should provide a mechanistic alternative to traditional nucleophilic substitution reactions or borrowing hydrogen methodology.

Results and Discussion

Effects of Catalysts and Solvents

We began by examining the reaction of anthranilic acid (**1a**) and benzhydrol (**2a**, 1.2 equiv.) in the presence of CuBr (5 mol%) and TPPMS (10 mol%) in water. Unfortunately, *N*-monobenzylated product **3a** was obtained in only 28% yield (Table 1, entry 1). The use of Cu_2O resulted in no reaction (entry 2). In contrast, the use of $CuBr_2$ instead of a Cu(I) catalyst afforded **3a** in good yield (entry 3). When the reaction was performed at 100 °C, the yield of **3a** was increased to 80% despite the possibility of forming the *N,N*-dibenzylated product, benzyl ester or decarboxylated product. With regard to the Cu(II) catalyst, $CuBr_2$ gave the best result (entries 3–9). Use of Lewis and Brønsted acids was ineffective (entries 10). Since the benzylation did not proceed in the presence of only Cu(II) catalyst (entry 11) or using organic solvents (entry 12), water must play an important role in our catalytic system. In a biphasic system such as DMF/H_2O (1:1), the reaction also did not proceed (entry 13).

Table 1. Effects of catalysts and solvents.[a]

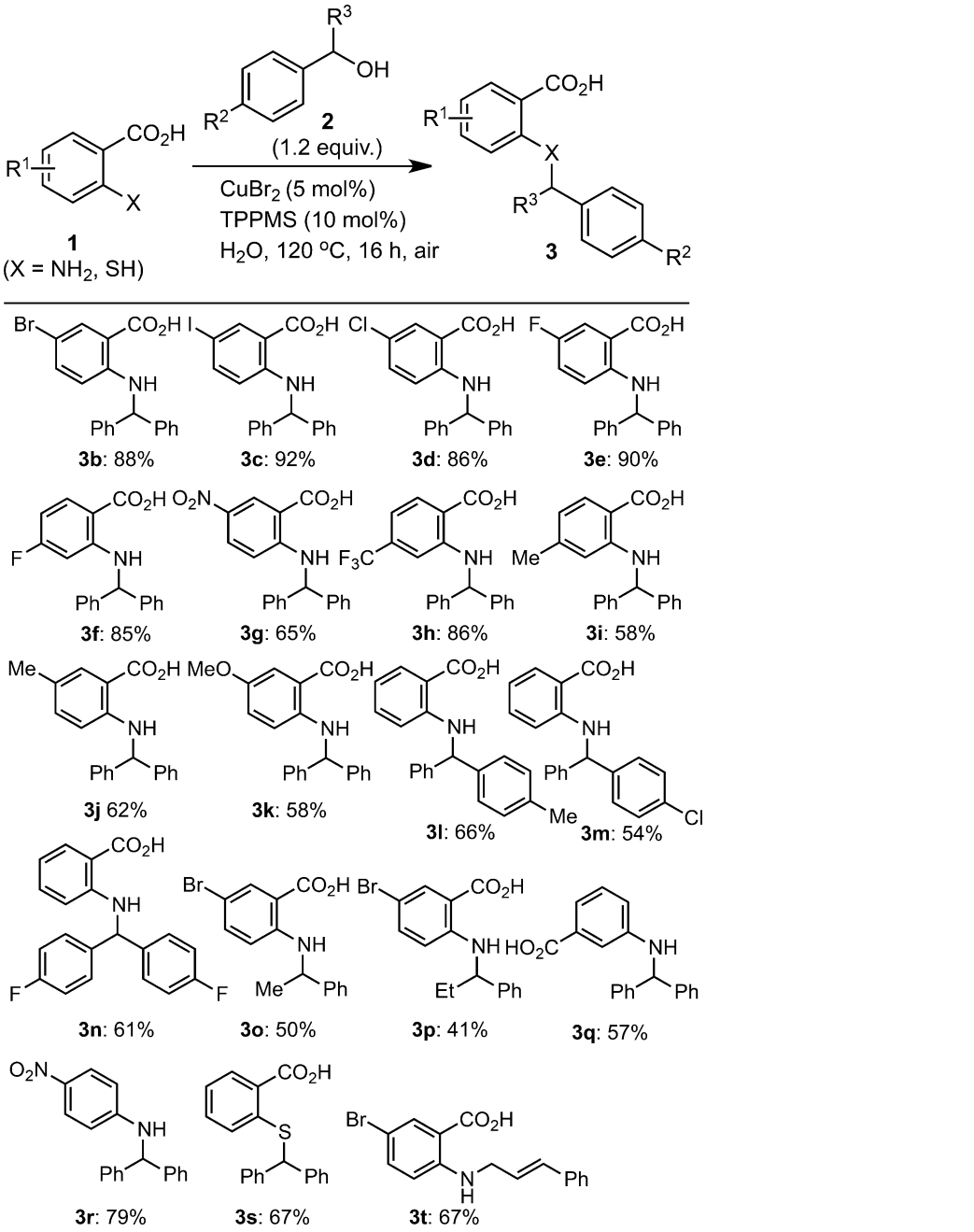


Entry	Catalyst	Solvent	Conv. [%][b]
1	CuBr/TPPMS	H_2O	28
2	Cu_2O/TPPMS	H_2O	trace
3	$CuBr_2$/TPPMS	H_2O	69 (80)[c]
4	$CuCl_2$/TPPMS	H_2O	53
5	$CuSO_4$/TPPMS	H_2O	50
6	$Cu(OAc)_2$/TPPMS	H_2O	12
7	CuO/TPPMS	H_2O	35
8	$Cu(OTf)_2$/TPPMS	H_2O	43
9	$Cu(acac)_2$/TPPMS	H_2O	12
10	$Sc(OTf)_3$ or HCl	H_2O	trace
11	$CuBr_2$	H_2O	8
12	$CuBr_2$/TPPMS	toluene, DMF, EtOH or dioxane	trace
13	$CuBr_2$/TPPMS	DMF/H_2O (1:1)	trace

[a] *Reaction conditions:* anthranilic acid (**1a**) (1 mmol), catalysts (5 mol%), TPPMS (10 mol%), benzhydrol (**2a**) (1.2 mmol), 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] At 100 °C.

Reaction Scope

Results for the reactions of several anthranilic acids **1** with benzyl alcohols **2** using $CuBr_2$ and TPPMS in H_2O are summarized in Scheme 2. The reaction of anthranilic acids with bromo, iodo, and chloro groups produced *N*-benzylated products **3b–d** in excellent yields with the carbon-halogen moiety left intact, which could be employed for further manipulation. *N*-Benzylation of 5-bromoanthranilic acid (**1b**) with benzhydrol (**2a**) could be performed up to a 10-mmol scale, with product **3b** purified only by recrystallization in 88% isolated yield. Anthranilic acids with fluoro groups also resulted in excellent yields (**3e**, 90%; **3f**, 85%). Strong electron-withdrawing nitro and trifluoromethyl groups were tolerated in the *N*-benzylation through the radical pathway (**3g**, 65%; **3h**, 86%). The anthranilic acids with electron-donating methyl and methoxy groups resulted in moderate to good yields (**3i**, 58%; **3j**, 62%; **3k**, 58%). The use of benzhydrol with methyl, chloro and fluoro groups resulted in moderate to good yields (**3l**, 66%; **3m**, 54%; **3n**, 61%). The reaction of α-alkylbenzyl alcohols afforded *N*-monobenzylated products (**3o**, 50%; **3p**, 41%). The reaction of 3-aminobenzoic acid or 4-nitroaniline also gave the desired products (**3q**, 57%; **3r**,

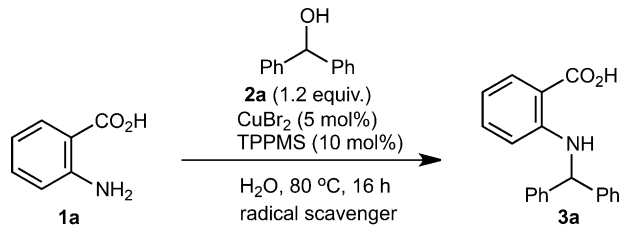


Scheme 2. Scope of anilines **1** and benzyl alcohols **2**. *Reaction conditions:* **1** (1 mmol), $CuBr_2$ (5 mol%), TPPMS (10 mol%), **2** (1.2 or 5 mmol), H_2O (4 mL), 120 °C, 16 h under air in a sealed tube. Yield of isolated product.

79%). Mercaptobenzoic acid could be used for the *S*-benzylation despite sulfur poisoning of the copper catalysts (**3s**, 67%). The reaction of cinnamyl alcohol afforded *N*-monoallylated product **3t** in 67% yield.

Control Experiments

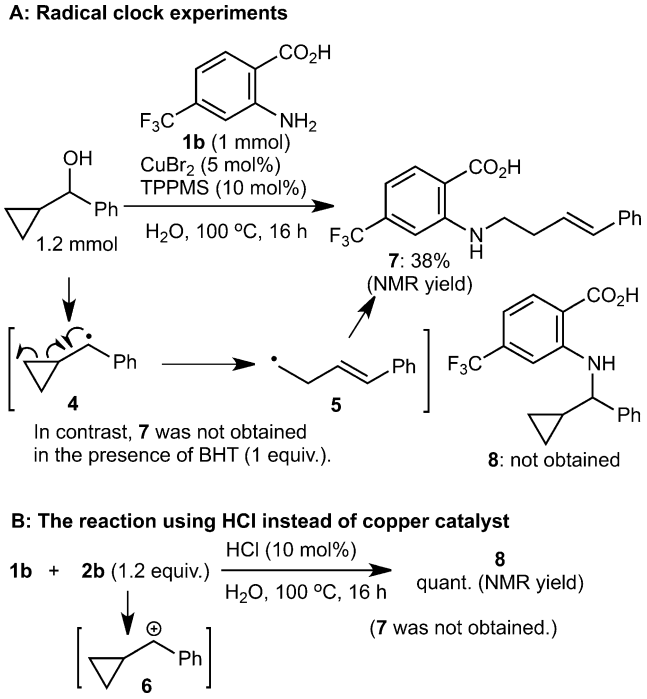
To gain insight into the radical reaction mechanism, we carried out the following control experiments. As expected, radical scavengers such as BHT, galvinoxyl and TEMPO strongly inhibited the radical reaction (Scheme 3), while the reaction using an Au(III) catalyst with BHT proceeded through a benzyl cation pathway (Scheme 3). Next, radical clock experiments using α-cyclopropylbenzyl alcohol were conducted to observe the rapid isomerization of the cyclopropylmethyl radical to the allylmethyl radical, which is well known in free-radical chemistry (Scheme 4).[15] If the cyclopropylmethyl radical **4** is generated, ring opening of cyclopropane **5** must be observed. The corresponding cyclopropyl ring fragmentation product **7** was only



Radical scavenger (equiv.)	NMR yield
BHT (1)	13% (56%)[a]
galvinoxyl (0.5)	27%
TEMPO (0.5)	trace
none	69%

[a] $AuCl_4Na \cdot 2\,H_2O$ (5 mol%) was used instead of $CuBr_2$.

Scheme 3. Experiments with radical scavengers.



Scheme 4. A: Radical clock experiments and B: reaction using HCl as catalyst.

obtained, while the reaction using HCl instead of copper catalyst afforded not the ring-opened product **7** but **8** *via* cyclopropylmethyl cation **6**, which could be stabilized by the cyclopropyl group.[16]

Hammett Studies

To demonstrate the effect of substituents on the rates of the C–O bond cleavage and C–N bond formation reactions, a Hammett study was conducted on the reaction of **1a** with 5-substituted anthranilic acids **1** (F, Me, OMe, Cl, and Br groups) followed by ^{1}H NMR spectroscopy to obtain the ratio of rate constants (Figure 1A). The Hammett plot shows no correlation of the typical polar substituent constant parameter ($R^2 = 0.1$ for σ). The fit was improved by employing the Creary scale of σ• parameter ($R^2 = 0.63$).[17] The experimental data could be fitted to a two-parameter Hammett relationship containing both radical and polar contributions [$\log (k_X/k_H) = -1.24\,\sigma^{\bullet} - 0.38\,\sigma$, $R^2 = 0.99$].[18] The relative parameter ρ•/ρ of 3.3 suggested that these reactions involved a strong radical character with minor polar influence at the transition state. Wallentin and co-workers reported that various σ scales could be combined with σ• to account for polar influences in radical reactions of iron-catalyzed cross-coupling.[18a] Next, a Hammett study based on *para*-substituted benzhydryl alcohols **2** (Me, F, and Cl

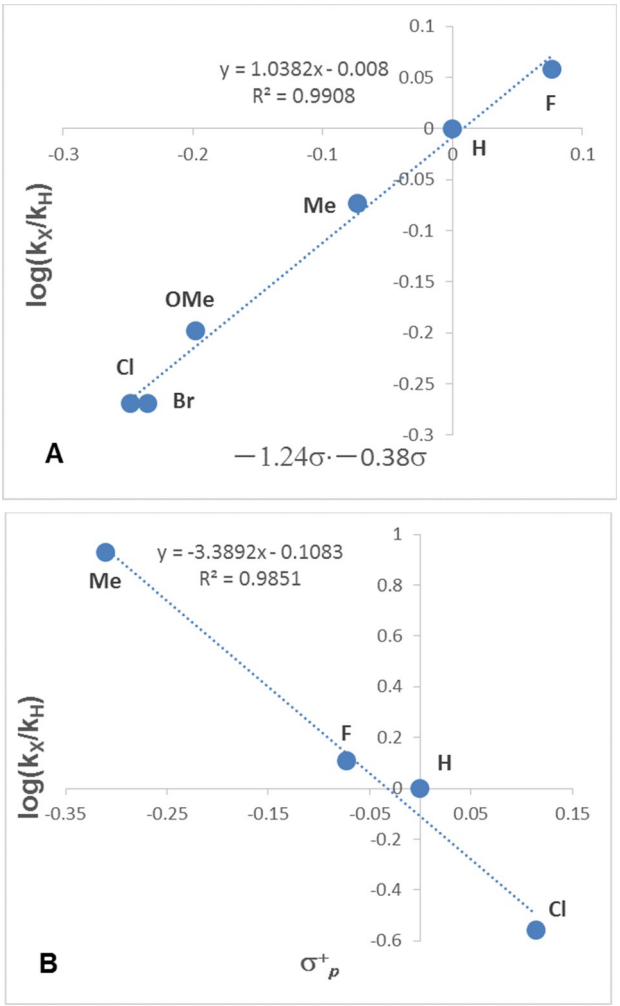
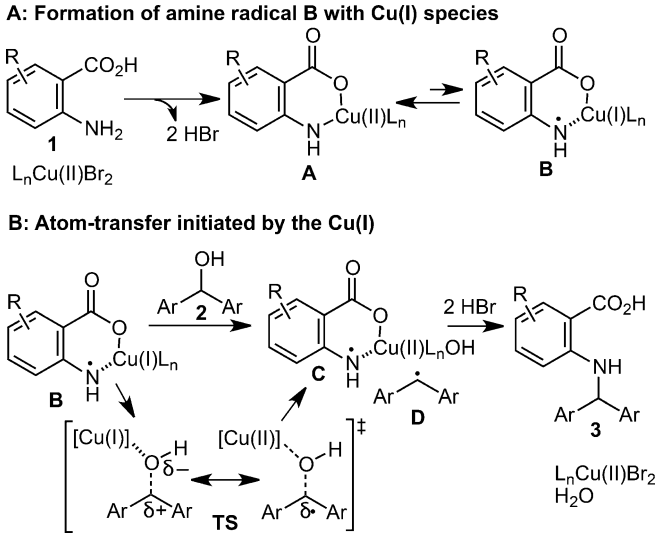


Figure 1. Hammett plot of experimental log (k_X/k_H) *vs.* calculated ρσ+ρσ• in the benzylation of 5-substituted anthranilic acids **1** (A), and the rate constants of benzylation by various substituted benzhydrols **2** (B).

groups) resulted in a good correlation ($R^2 = 0.99$ in Figure 1B) between the $\log(k_X/k_H)$ and the σ^+ value of the respective substituents that resulted in a negative ρ value of 3.39, suggesting that the C–O bond cleavage process involved a polar transition state.

Mechanistic Considerations

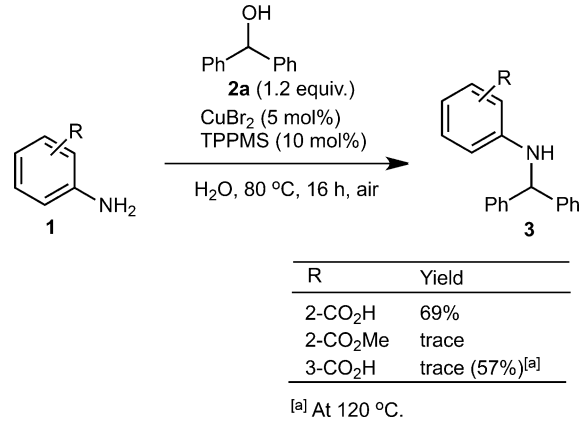
On the basis of our results and literature reports, the following mechanism can be suggested. First, anthranilic acid **1** coordinates to the Cu(II)/TPPMS catalyst to form Cu(II) intermediate **A**,[19] which is in equilibrium with amine radical **B** (Scheme 5A).[20] The Hammett study suggests that there is build-up of the amine radical in the transition state (see Figure 1A). The carboxyl group of **B** would enhance the benzylation by chelation to the copper catalyst, and allow for spin-delocalization. Indeed, *N*-benzylations of anthranilic acid methyl ester or 3-aminobenzoic acid resulted in no reaction (Scheme 6). Next, an atom-transfer event initiated by the Cu(I) complex **B** generates amine radical **C** along with benzyl radical **D**, followed by subsequent radical coupling to afford desired product **3** (Scheme 5B). The Hammett study also suggests that there is a build-up of positive charge in the transition state **TS** (see Figure 1B).



Scheme 5. Proposed mechanism.

Borrowing Hydrogen Pathway

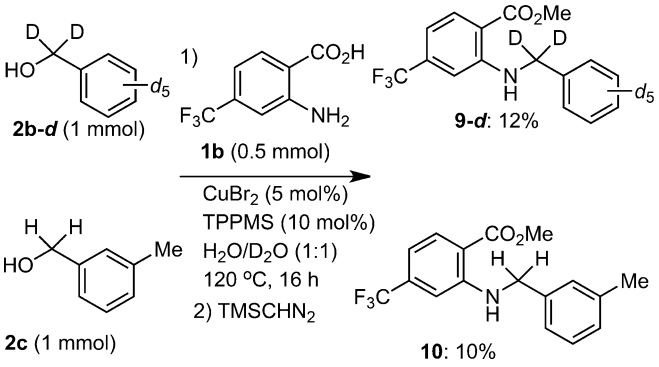
To exclude the possibility of the borrowing hydrogen pathway, we carried out a cross-over experiment using different benzyl alcohols (Scheme 7).[21] Deuterated benzyl alcohol-d_7 **2b-*d*** was converted into deuterated **9-*d***, and 3-methylbenzyl alcohol (**2c**) afforded the corresponding **10**, which was not labelled with deuterium. This result excluded the borrowing hydrogen mechanism in our catalytic system, since H/D scrambling products were not formed.



R	Yield
2-CO_2H	69%
2-CO_2Me	trace
3-CO_2H	trace (57%)[a]

[a] At 120 °C.

Scheme 6. Effect of carboxyl group.



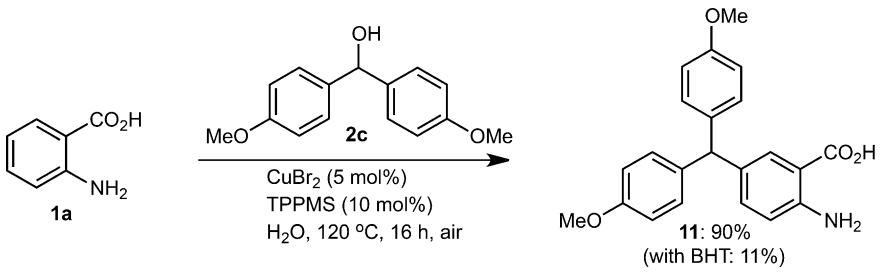
Scheme 7. Cross-over experiment using different benzyl alcohols.

C-Benzylation

4,4′-Dimethoxybenzhydrol (**2c**) afforded only *C*-benzylated product **11** in 90% yield with the amino group left intact (Scheme 8), while the addition of BHT (1 equiv.) inhibited this reaction significantly. Anthranilic acids **1** have been used as building blocks for medicinal purposes, e.g., mefenamic acid, which has non-steroidal anti-inflammatory and analgesic properties. Furthermore, anthranilic acids are important for the synthesis of benzo-fused heterocycles or the biosynthesis of tryptophan and several types of alkaloids.

Conclusions

In summary, we have developed an atom-transfer initiated radical pathway for copper-catalyzed direct



Scheme 8. Chemoselective *C*-benzylation of anthranilic acid **1a**.

substitution of benzyl alcohols, which is an environmentally benign method. This reaction could be applied to various anthranilic acids in moderate to excellent yields. Water plays an important role in the activation of the benzyl alcohols to form the corresponding benzyl radicals. Mechanistic studies on radical reactions supported this hypothesis. The strategy presented here should provide greater insights for the design of several new direct uses of benzyl alcohols.

Experimental Section

General Procedure

A mixture of anthranilic acid **1** (1 mmol), $CuBr_2$ (11 mg, 0.05 mmol), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 38 mg, 0.1 mmol) and benzhydryl alcohol **2** (1.2 mmol) in H_2O (4 mL) was heated at 120 °C for 16 h in a sealed tube under air. 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 under vacuum. The residue was washed with hexanes, then purified by flash column chromatography (silica gel, hexanes/EtOAc) to give the desired product **4**.

2-(Benzhydrylamino)benzoic acid (3a):[5a] Following the general procedure, **3a** was obtained as a white solid; yield: 222 mg (73%); mp 202–204 °C; IR (KBr): $\nu = 3362$, 3027, 1661 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta = 5.84$ (d, $J = 6.4$ Hz, 1H), 6.57 (t, $J = 7.2$ Hz, 1H), 6.59 (d, $J = 8.4$ Hz, 1H), 7.25 (tt, $J = 6.8$, 1.2 Hz, 3H), 7.33–7.41 (m, 9H), 7.82 (dd, $J = 8.4$, 2.0 Hz, 1H), 8.67 (d, $J = 6.0$ Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6): $\delta = 62.88$, 112.0, 114.4, 116.6, 128.7, 128.9, 130.4, 133.5, 136.0, 144.7, 152.0, 171.5; FAB-MS: $m/z = 304$ $[M+H]^+$.

2-(Benzhydrylamino)-5-bromobenzoic acid (3b);[5a] **Scale-up experiment:** A mixture of 2-amino-5-bromobenzoic acid (1.08 g, 5 mmol), $CuBr_2$ (56 mg, 0.25 mmol), TPPMS (182 mg, 0.5 mmol), and benzhydrol **2a** (1.1 g, 6 mmol) in H_2O (20 mL) was heated at 90 °C for 16 h under air. 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 under vacuum. The residue was recrystallized from hexane/AcOEt to give desired product **3b** as a pale yellow solid; yield: 1.64 g (4.4 mmol, 88%); mp 215–216 °C; IR (KBr): $\nu = 3380$, 3033, 1670 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta = 5.86$ (d, $J = 6.0$ Hz, 1H), 6.58 (d, $J = 8.8$ Hz, 1H), 7.24–7.28 (m, 2H), 7.34–7.42 (m, 10H), 7.89 (d, $J = 2.8$ Hz, 1H), 8.66 (d, $J = 6.4$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 60.72$, 106.1, 113.0, 115.6, 127.3, 127.9, 129.4, 133.9, 137.1, 143.0, 149.2, 169.5; FAB-MS: $m/z = 382$ $[M+H]^+$, 384 $[M+H+2]^+$.

2-(Benzhydrylamino)-5-iodobenzoic acid (3c):[5a] Following the general procedure, **3c** was obtained as a pale yellow solid; yield: 395 mg (92%); mp 223–225 °C; IR (KBr): $\nu = 3356$, 3029, 1671 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta = 5.85$ (d, $J = 6.4$ Hz, 1H), 6.45 (d, $J = 9.2$ Hz, 1H), 7.22–7.42 (m, 11H), 7.52 (dd, $J = 9.2$, 6.8 Hz, 1H), 8.05 (d, $J = 2.4$ Hz, 1H), 8.68 (d, $J = 6.0$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 60.7$, 75.8, 113.9, 116.0, 127.3, 127.9, 129.4, 139.9, 142.5, 143.0, 149.5, 169.4; FAB-MS: $m/z = 430$ $[M+H]^+$.

2-(Benzhydrylamino)-5-chlorobenzoic acid (3d): Following the general procedure, **3d** was obtained as a pale yellow solid; yield: 289 mg (86%); mp 210–212 °C; IR (KBr): $\nu = 3379$, 3029, 1671 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta = 5.85$ (d, $J = 6.0$ Hz, 1H), 6.63 (d, $J = 9.2$ Hz, 1H), 7.23–7.40 (m, 12H), 7.76 (d, $J = 2.8$ Hz, 1H), 8.64 (d, $J = 6.4$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 60.72$, 112.4, 115.2, 118.9, 127.3, 127.9, 129.4, 131.0, 134.5, 143.0, 148.9, 169.6; FAB-MS: $m/z = 338$ $[M+H]^+$, 340 $[M+H+2]^+$; anal. calcd. for $C_{20}H_{16}ClNO_2$: C 71.11, H 4.77, N 4.15; found: C 71.08, H 4.83, N 4.15.

2-(Benzhydrylamino)-5-fluorobenzoic acid (3e):[5a] Following the general procedure, **3e** was obtained as a white solid; yield: 289 mg (90%); mp 194–195 °C; IR (KBr): $\nu = 3369$, 3029, 1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.60$ (s, 1H), 6.50 (dd, $J = 9.2$, 4.4 Hz, 1H), 7.00–7.05 (m, 1H), 7.22–7.41 (m, 11H), 7.66 (dd, $J = 9.6$, 3.2 Hz, 1H), 8.12 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 61.12$, 111.5 (d, $J = 5.7$ Hz), 114.7 (d, $J = 6.6$ Hz), 117.1 (d, $J = 21.9$ Hz), 122.3 (d, $J = 22.9$ Hz), 127.3, 127.8, 129.3, 143.3, 147.2, 153.0 (d, $J = 231.7$ Hz), 169.7, (d, $J = 2.8$ Hz); FAB-MS: $m/z = 322$ $[M+H]^+$.

2-(Benzhydrylamino)-4-fluorobenzoic acid (3f):[5a] Following the general procedure, **3f** was obtained as a white solid; yield: 273 mg (85%); mp 200–201 °C; IR (KBr): $\nu = 3355$, 3029, 1665 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): $\delta = 5.87$ (d, $J = 6.8$ Hz, 1H), 6.35–6.41 (m, 2H), 7.26 (tt, $J = 6.0$, 1.2 Hz, 2H), 7.34–7.41 (m, 9H), 7.88 (t, $J = 7.6$ Hz, 1H), 8.88 (d, $J = 5.6$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 60.7$, 99.3 (d, $J = 25.8$ Hz), 102.9 (d, $J = 22.8$ Hz), 108.3 (d, $J = 1.9$ Hz), 127.3, 127.9, 129.4, 135.0 (d, $J = 11.5$ Hz), 142.9, 152.4 (d, $J = 12.4$ Hz), 166.6 (d, $J = 247.0$), 169.9; FAB-MS: $m/z = 322$ $[M+H]^+$.

2-(Benzhydrylamino)-5-nitrobenzoic acid (3g): Following the general procedure, **3g** was obtained as a white solid; yield: 226 mg (65%); mp 198–199 °C; IR (KBr): $\nu = 3334$, 3019, 1672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.74$ (d,

$J=5.6$ Hz, 1H), 6.60 (d, $J=10.0$ Hz, 1H), 7.21–7.37 (m, 10H), 8.12 (dd, $J=9.2$, 2.0 Hz, 1H), 8.95 (d, $J=2.8$ Hz, 1H), 9.06 (d, $J=5.6$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta=60.73$, 110.7, 113.3, 127.3, 128.2, 128.9, 129.5, 129.8, 136.1, 142.1, 154.1, 169.4; FAB-MS: $m/z=349$ $[M+H]^+$; anal. calcd. for $C_{20}H_{16}N_2O_4$: C 68.96, H 4.63, N 8.04; found: C 68.44, H 4.76, N 7.93.

2-(Benzhydrylamino)-4-(trifluoromethyl)benzoic acid (3h):[5a] Following the general procedure, **3h** was obtained as a white solid; yield: 320 mg (86%); mp 184–186 °C; IR (KBr): $\nu=3358$, 3030, 1673 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta=5.97$ (d, $J=6.0$ Hz, 1H), 6.86 (s, 1H), 6.87 (d, $J=8.0$ Hz, 1H), 7.26 (t, $J=7.2$ Hz, 2H), 7.34–7.43 (m, 9H), 8.01 (d, $J=8.4$ Hz, 1H), 8.85 (d, $J=6.0$ Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6): $\delta=62.75$, 111.0 (q, $J=4.7$ Hz), 112.4 (q, $J=3.8$ Hz), 114.9, 125.5 (q, $J=270.8$ Hz), 128.7, 129.1, 130.5, 134.6, 136.5 (q, $J=31.5$ Hz), 144.1, 151.8, 170.7; FAB-MS: $m/z=372$ $[M+H]^+$.

2-(Benzhydrylamino)-4-methylbenzoic acid (3i):[5a] Following the general procedure, **3i** was obtained as a white solid; yield: 184 mg (58%); mp 190–193 °C; IR (KBr): $\nu=3370$, 3029, 1654 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta=2.11$ (s, 3H), 5.84 (d, $J=6.8$ Hz, 1H), 6.40 (d, $J=8$ Hz, 1H), 6.46 (s, 1H), 7.19–7.39 (m, 11H), 7.70 (d, $J=8$ Hz, 1H), 8.64 (d, $J=6.4$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta=22.2$, 60.7, 108.9, 113.2, 116.8, 127.3, 127.7, 129.3, 132.2, 143.6, 144.9, 150.3, 170.6; FAB-MS: $m/z=318$ $[M+H]^+$.

2-(Benzhydrylamino)-5-methylbenzoic acid (3j):[5a] Following the general procedure, **3j** was obtained as a white solid; yield: 197 mg (62%); mp 224–227 °C; IR (KBr): $\nu=3383$, 3025, 1669 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta=2.13$ (s, 3H), 5.79 (d, $J=5.2$ Hz, 1H), 6.52 (d, $J=8.4$ Hz, 1H), 7.06 (dd, $J=8.8$, 2 Hz, 1H), 7.23 (tt, $J=6.4$, 1.6 Hz, 2H), 7.31–7.38 (m, 8H), 7.62 (d, $J=1.6$ Hz, 1H), 8.46 (d, $J=5.2$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta=20.3$, 60.8, 111.3, 113.4, 124.0, 127.3, 127.7, 129.3, 132.0, 135.6, 143.6, 148.3, 170.6; FAB-MS: $m/z=318$ $[M+H]^+$.

2-(Benzhydrylamino)-5-methoxybenzoic acid (3k): Following the general procedure, **3k** was obtained as a yellow solid; yield: 193 mg (58%); mp 231–233 °C; IR (KBr): $\nu=3381$, 3029, 1672 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta=3.65$ (s, 3H), 5.78 (s, 1H), 6.58 (d, $J=9.2$ Hz, 1H), 6.95 (dd, $J=8.8$, 3.2 Hz, 1H), 7.23 (tt, $J=6.4$, 1.6 Hz, 2H), 7.31–7.39 (m, 10H), 8.26 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta=56.0$, 61.3, 111.6, 114.7, 115.3, 112.8, 127.3, 127.7, 129.3, 143.7, 145.2, 149.7, 170.3; FAB-MS: $m/z=334$ $[M+H]^+$; anal. calcd. for $C_{21}H_{19}NO_3\cdot0.1\,H_2O$: C 75.25, H 5.77, N 4.18; found: C 75.15, H 5.78, N 4.10.

2-[Phenyl(*p*-tolyl)methylamino]benzoic acid (3l):[5a] Following the general procedure, **3l** was obtained as a white solid; yield: 224 mg (66%); mp 192–193 °C; IR (KBr): $\nu=3358$, 3025, 1662 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.32$ (s, 3H), 5.61 (s, 1H), 6.56 (d, $J=8.8$ Hz, 1H), 6.58–6.62 (m, 1H), 7.14 (d, $J=8.0$ Hz, 2H), 7.23–7.37 (m, 9H), 7.98 (dd, $J=8.0$, 1.6 Hz, 1H), 8.30 (brs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta=21.11$, 60.60, 111.3, 113.2, 115.4, 127.3, 127.6, 129.3, 129.9, 132.1, 134.7, 136.9, 140.5, 143.6, 150.2, 170.6; FAB-MS: $m/z=318$ $[M+H]^+$.

2-[(4-Chlorophenyl)(phenyl)methylamino]benzoic acid (3m):[5a] Following the general procedure, **3j** was obtained as a white solid; yield: 184 mg (54%); mp 205–207 °C; IR (KBr): $\nu=3357$, 3027, 1669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.62$ (d, $J=4.8$ Hz, 1H), 6.51 (d, $J=8.4$ Hz, 1H), 6.62–6.66 (m, 1H), 7.25–7.37 (m, 11H), 7.99 (dd, $J=8.0$, 1.2 Hz, 1H), 8.27 (d, $J=5.2$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta=60.10$, 111.5, 113.2, 115.7, 127.4, 127.9, 129.2, 129.3, 129.4, 132.2, 132.3, 134.8, 142.4, 143.0, 150.0, 170.6; FAB-MS: $m/z=338$ $[M+H]^+$, 340 $[M+H+2]^+$.

2-[Bis(4-fluorophenyl)methylamino]benzoic acid (3n):[5a] Following the general procedure, **3k** was obtained as a white solid; yield: 207 mg (61%); mp 198–199 °C; IR (KBr): $\nu=3362$, 3029, 1663 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.62$ (d, $J=5.2$ Hz, 1H), 6.50 (d, $J=8.4$ Hz, 1H), 6.65 (t, $J=8.0$ Hz, 1H), 7.03 (dt, $J=8.8$, 2.4 Hz, 5H), 7.22–7.35 (m, 5H), 7.99 (dd, $J=8.0$, 1.6 Hz, 1H), 8.23 (d, $J=5.6$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta=59.3$, 111.5, 113.2, 115.8, 116.0 (d, $J=20$ Hz), 129.3, 129.4, 132.2, 134.8, 139.4 (d, $J=3.8$ Hz), 150.0, 161.8 (d, $J=240$ Hz), 170.6; FAB-MS: $m/z=340$ $[M+H]^+$.

5-Bromo-2-(1-phenylethylamino)benzoic acid (3o): Following the general procedure, **3o** was obtained as a white solid; yield: 159 mg (50%); mp 174–175 °C; IR (KBr): $\nu=3373$, 3029, 1669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.60$ (d, $J=6.8$ Hz, 3H), 4.57 (q, $J=9.2$ Hz, 1H), 6.35 (d, $J=9.2$ Hz, 1H), 7.22–7.36 (m, 7H), 8.06–8.09 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta=25.0$, 52.1, 105.5, 112.7, 115.4, 126.2, 127.4, 129.2, 133.9, 137.0, 145.0, 149.4, 169.4; FAB-MS: $m/z=320$ $[M+H]^+$, 322 $[M+H+2]^+$; anal. calcd. for $C_{15}H_{15}BrNO_2$: C 56.27, H 4.41, N 4.37; found: C 56.57, H 4.48, N 4.39.

5-Bromo-2-[(1-phenylpropyl)amino]benzoic acid (3p): Following the general procedure, **3p** was obtained as a yellow solid; yield: 137 mg (41%); mp 152–154 °C; IR (KBr): $\nu=3357$, 3029, 1670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.02$ (t, $J=7.6$ Hz, 3H), 1.91 (quin, $J=7.2$ Hz, 2H), 4.33 (t, $J=6.4$ Hz, 1H), 6.35 (d, $J=9.2$ Hz, 1H), 7.22–7.35 (m, 7H), 8.08 (d, $J=2.4$ Hz, 1H), 8.17 (brs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta=10.9$, 31.4, 58.1, 105.4, 112.6, 115.3, 126.8, 127.5, 129.0, 133.9, 137.0, 143.6, 149.8, 169.5; FAB-MS: $m/z=334$ $[M+H]^+$, 336 $[M+H+2]^+$; anal. calcd. for $C_{16}H_{16}BrNO_2$: C 57.50, H 4.83, N 4.19; found: C 57.62, H 4.86, N 4.17.

3-(Benzhydrylamino)benzoic acid (3q):[22] Following the general procedure, **3q** was obtained as a white solid; yield: 173 mg (57%); mp 175–176 °C; IR (KBr): $\nu=3394$, 3027, 1671 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.56$ (s, 1H), 6.74 (ddd, $J=8.0$, 2.4, 0.8 Hz, 1H), 7.19 (t, $J=8.0$ Hz, 1H), 7.24–7.46 (m, 12H), 7.41 (dt, $J=7.6$, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta=61.4$, 114.5, 117.7, 117.8, 127.4, 127.8, 128.9, 129.2, 131.8, 143.7, 148.5, 168.3; FAB-MS: $m/z=304$ $[M+H]^+$.

***N*-Benzhydryl-4-nitroaniline (3r):**[23] Following the general procedure, **3r** was obtained as a yellow solid; yield: 241 mg (79%); mp 182–183 °C; IR (KBr): $\nu=3405$, 1508 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=4.98$ (d, $J=4.4$ Hz, 1H), 5.63 (d, $J=4.8$ Hz, 1H), 6.51 (d, $J=7.2$ Hz, 2H), 7.22–7.40 (m, 10H), 8.03 (d, $J=7.2$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta=60.8$, 112.5, 126.4, 127.8, 127.9, 129.1, 137.0, 142.5, 154.1; FAB-MS: $m/z=305$ $[M+H]^+$.

2-(Benzhydrylthio)benzoic acid (3s):[24] Following the general procedure, **3s** was obtained as a white solid; yield: 216 mg (67%); mp 202–204 °C; IR (KBr): $\nu=3014$, 1682 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.65$ (s, 1H), 7.12–7.49 (m, 14H), 8.07 (dd, $J=7.6$, 1.2 Hz, 1H); ^{13}C NMR

(100 MHz, DMSO-d_6): δ = 53.7, 124.8, 127.7, 127.7, 128,8, 129.2, 131.2, 132.4, 140.4, 141.4, 168.0; FAB-MS: m/z = 321 $[M+H]^+$.

5-Bromo-2-(cinnamylamino)benzoic acid (3t): Following the general procedure, **3t** was obtained as a white solid; yield: 222 mg (67%); mp 188–190 °C; IR (KBr): ν = 3377, 3021, 1666 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 4.05 (d, J = 6.0 Hz, 2H), 6.38 (dt, J = 16.0, 5.6 Hz, 1H), 5.58 (d, J = 16.0 Hz, 1H), 6.76 (d, J = 9.2 Hz, 1H), 7.23 (tt, J = 7.2, 1.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 2H), 7.42 (d, J = 7.2 Hz, 2H), 7.49 (dd, J = 9.2, 2.4 Hz, 1H), 7.86 (d, J = 2.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 44.1, 104.7, 111.8, 114.2, 126.2, 126.7, 127.5, 128.6, 130.6, 133.4, 136.4,136.7, 149.7, 168.8; EI-MS: m/z (%) = 333 (M^++2, 16.4), 331 (M^+, 17.0), 59 (100); anal. calcd. for $C_{16}H_{14}BrNO_2$: C 57.85, H 4.25, N 4.22; found: C 58.12, H 4.48, N 4.18.

(*E*)-2-[(4-Phenylbut-3-en-1-yl)amino]-4-(trifluoromethyl)-benzoic acid (7): Following the general procedure, **7** was obtained as a white solid; yield 83 mg (25%); mp 150–151 °C; IR (KBr): ν = 3347, 3029, 1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.63 (ddd, J = 13.7, 6.7, 1.3 Hz, 2H), 3.39 (t, J = 6.8 Hz, 2H), 6.23 (td, J = 15.6, 6.8 Hz, 1H), 6.57 (d, J = 16.4 Hz, 1H), 6.83 (dd, J = 8.0, 1.6 Hz, 1H), 6.93 (s, 1H), 7.22 (tt, J = 6.0, 1.2 Hz, 1H), 7.26 (m, 1H), 7.30 (dt, J = 7.6, 1.2 Hz, 2H), 7.38 (d, J = 7.2 Hz, 2H), 7.83 (s, 1H), 8.00 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 32.6, 42.2, 108.1 (d, J = 4.8 Hz), 110.4 (d, J = 3.8 Hz), 113.6, 124.4 (q, J = 271.8 Hz), 126.5, 127.7, 128.0, 129.0, 132.3, 133.4, 134.7 (q, J = 31.4 Hz), 137.6, 151.1, 169.6; EI-MS: m/z (%) = 335 (M^+, 13.4), 200 (100); HR-MS (EI): m/z = 335.12, calcd. for $C_{18}H_{16}F_3NO_2$ [M^+]: 335.11; anal. calcd. for $C_{18}H_{16}F_3NO_2$: C 64.47, H 4.81, N 4.18; found: C 64.24, H 4.81, N 4.23.

2-[(Cyclopropylphenylmethyl)amino]-4-(trifluoromethyl)-benzoic acid (8): Following the general procedure, **8** was obtained as a white solid; yield: 118 mg (70%); mp 170–172 °C; IR (KBr): ν = 3366, 3009, 1671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.39–0.75 (m, 4H), 1.24–1.36 (m, 1H), 3.91 (d, J = 7.2 Hz, 1H), 6.63 (s, 1H), 6.76 (dd, J = 8.8, 1.6 Hz, 1H), 7.22–7.37 (m, 6H), 8.09 (d, J = 8 Hz, 1H), 8.45 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 3.4, 4.7, 19.3, 60.8, 109.4 (d, J = 3.3 Hz), 110.7 (d, J = 3.8 Hz), 114.0, 124.2 (q, J = 271.8 Hz), 126.8, 127.6, 129.1, 133.3, 134.1 (q, J = 31.4 Hz), 143.1, 150.2, 169.7; FAB-MS: m/z = 336 $[M+H]^+$; anal. calcd. for $C_{18}H_{16}F_3NO_2$: C 64.47, H 4.81, N 4.18; found: C 64.54, H 4.77, N 4.26.

2-Amino-5-[bis(4-methoxyphenyl)methyl]benzoic acid (11):[5b] Following the general procedure, **11** was obtained as a white solid; yield: 327 mg (90%); mp 190–191 °C; IR (KBr): ν = 3475, 3364, 3015, 1656 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 3.71 (s, 6H), 5.30 (s, 1H), 6.67 (d, J = 8.8 Hz, 1H), 6.84 (td, J = 9.6, 3.2 Hz, 4H), 6.95–7.00 (m, 5H), 7.41 (d, J = 2.0 Hz, 1H), 8.46 (brs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 53.8, 55.5, 109.8, 114.2, 117.0, 130.3, 131.1, 131.4, 135.1, 137.1, 150.4, 158.0, 170.0; FAB-MS: m/z = 364 $[M+H]^+$.

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