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Synthesis of Aminobenzoic Acid Derivatives via Chemoselective Carbene Insertion into the −NH Bond Catalyzed by Cu(I) Complex

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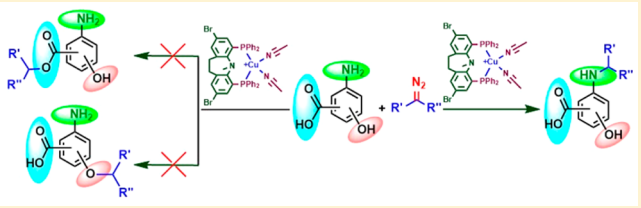
Supporting Information

ABSTRACT: Phosphine ligand stabilized air-stable Cu(I) complexes have been successfully used to functionalize the aromatic aminobenzoic acids in a chemoselective manner without implementing protection and deprotection strategy under mild reaction conditions. This chemoselective carbene insertion into −NH bond over −COOH and −OH bonds leads to the wide range of carboxy and hydroxy functionalized α-amino esters (27 examples). All of the isolated new products have been fully characterized using standard analytical methods.



INTRODUCTION

Aromatic aminobenzoic acid derivatives are important building blocks for many natural as well as synthetic molecules.[1] These derivatives have been used to alter biochemical and structural properties of peptides.[2a] Derivatives of anthranilic acid are synthons for acridine synthesis, which shows potential activity against cancer and malaria.[2b,c] In this regard, direct synthesis of aminobenzoic acid derivatives without a protection and deprotection strategy is a long-standing challenging task for synthetic chemists. It can be noted from the literature that only a few methods are known to perform this chemistry effectively. Widely used methods are (i) selective nucleophilic substitution using the corresponding halide derivative in the presence of base[3] (Scheme 1a), (ii) imine formation using the corresponding aldehyde followed by reduction[1b,4] (Scheme 1b), and (iii) transition metal complex promoted coupling reactions such as Buchwald−Hartwig,[5] Ullmann,[6] and Chan−Lam cross-coupling[7] reactions (Scheme 1c,d). Along with these conventional methods, a few additional methods have appeared in the literature.[8]

Owing to the low solubility of aminobenzoic acids in an aprotic solvent, one has to use a protic or a more polar solvent as protic solvents or solvents which can act as a nucleophile produce solvent-substituted side products. In the case of imine formation followed by reduction methods, one has to use a reducing agent, which is cost inefficient. Among all of the cross-coupling reactions, the Ullmann coupling reaction shows wide scope compared to other methods. It can be noted from the literature that the Buchwald−Hartwig cross-coupling reaction proceeds via protection and deprotection of an acid functional group whenever an acid functional group is present in the substrate.[5a,c] In the case of the Chan−Lam coupling, to the best of our knowledge there is no report on aminobenzoic acids; however, it is an important method for making a C−N bond. These cross-coupling reactions proceed under harsh reaction conditions, which causes unwanted side products and functional group intolerance. Mostly, the above-mentioned methods work for simple aromatic amines and show less tolerance for acid- and alcohol-substituted amines. Although a considerable amount of progress has been made in recent years, known methods suffer from poor selectivity and low yield and leave much room for further development of cheap, atom-efficient, and viable methods to improve the product selectivity and yield.

On the other hand, transition metal complex mediated (isolated complexes or in situ generated) carbene insertion into the X−H (X = NH, O, R_3Si, S, R_3C, or R_2B) bond is also one of the fastest developing synthetic strategies.[9] Thus far, most successfully employed transition-metal catalysts for carbene insertion into X−H bonds are Rh,[10] Fe,[11] and Cu[12] along with N-, O-, C-, and P-based ligands. One of the promising and challenging tasks in this strategy is selectively inserting the carbene into the desired X−H bond in the presence of other functional groups (which are equally capable of undergoing insertion) without using any functional group protecting agent.[13] It is also worthwhile to mention here that the phosphine-based ligands are less explored for carbene chemistry, particularly with the Cu(I) ion.[14]

In this regard, we recently reported a chemoselective carbene insertion into the −NH bond over the −OH bond.[13a] In order to gain a wider scope for our catalyst (**1**) and considering the importance of aromatic aminobenzoic acid derivatives, in this paper, we have developed a strategy to derivatize the aromatic amino acids by inserting the carbene selectively into the −NH bond over −COOH and −OH bonds (Scheme 2).

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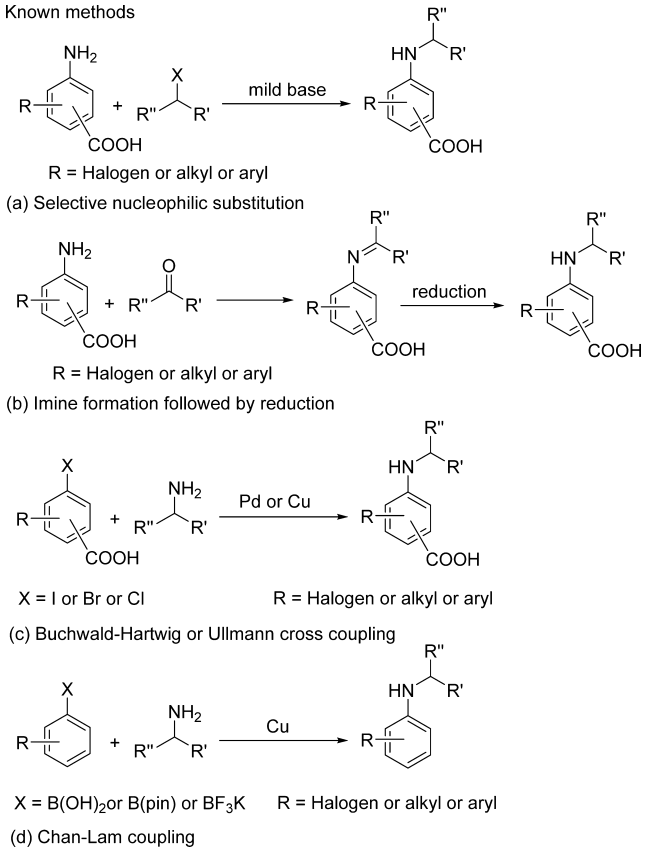
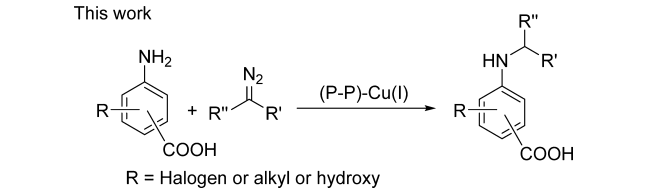
Scheme 1. Different Approaches To Access Aromatic Amino Acid Derivatives: Some Representative Examples



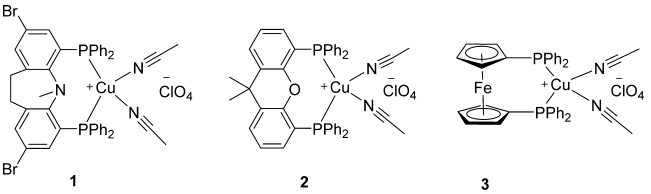
Scheme 2. Proposed Chemoselective Carbene insertion into −NH Bond over −COOH Bond



RESULTS AND DISCUSSION

We have synthesized catalysts **1**−**3** (Scheme 3) using the literature procedures[12h] and confirmed the reported analytical

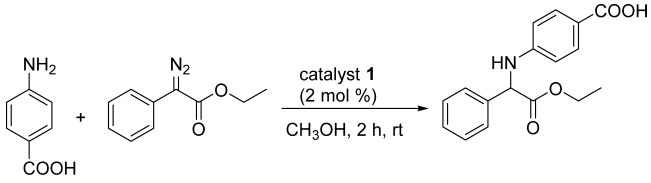
Scheme 3. Copper Complexes used as Catalysts in the Current Study



data. The compounds were used for carbene insertion into −NH bonds as follows. Catalysts **1**−**3** are stabilized by bis-phosphine ligands. Although the catalysts **1** and **2** contain pincer-type ligands, these bis-phosphine ligands are known to coordinate to the Cu(I) center in a η^2 fashion only.

We started our investigation with 4-aminobenzoic acid and α-phenyl diazoacetate in methanol using 2 mol % of catalyst **1** (Scheme 4). The reaction was completed in 2 h and furnished

Scheme 4. Reaction of α-Phenyl Diazoacetate with 4-Aminobenzoic Acid



−NH-inserted product in 81% yield. Evidence for selective carbene insertion into the −NH bond was obtained from ^{1}H NMR and IR spectroscopy. We observed a broad singlet at 12.18 ppm and a sharp band at 3388 cm^{-1}, respectively, for the presence of free acid in the product. In order to gain more evidence, we subjected a suitable single crystal to X-ray diffraction studies, and we found that the carbene is inserted only into the −NH bond and not into the −COOH bond (Figure S1, Supporting Information).

On the basis of our previous experience with catalyst **1**[13a] and the solubility issue of aminobenzoic acids, we were forced to choose methanol as a solvent for further optimization of reaction conditions. We anticipated that phosphine-coordinated Cu(I) complexes (**2** and **3**) with rigid structural and electronic features similar to those of catalyst **1** will also give similar selective carbene insertion into the −NH bond over the −COOH bond. Therefore, we have tested two more copper complexes of 1,1′-bis(diphenylphosphino)ferrocene (dppf) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthen(xantphos) (complexes **2** and **3**) as catalysts for carbene insertion reaction. We have also screened various Cu(I) sources as catalysts for carbene insertion reaction (Table 1).

We have chosen *p*-aminobenzoic acid and α-phenyl diazoacetate to yield carbene-inserted product. For catalyst **1**, we observed 81% of −NH-inserted product in 2 h (Table 1, entry 1). Contrary to our expectations, catalysts **2** and **3** produced low yields, though these catalysts compete with catalyst **1** in the case of simple anilines.[12h] Catalyst **2** offered 54% of −NH-inserted product over 2 h (Table 1, entry 2), and catalyst **3** offered only 31% of −NH-inserted product over 6 h (Table 1, entry 3). We have also examined readily available copper salts such as Cu(OTf) and $[(CH_3CN)_4Cu]ClO_4$ for carbene insertion reaction and observed 47% and 46% yields of −NH-inserted product along with <10% of −COOH inserted product, respectively (Table 1, entries 4 and 6). In the case of CuCl, we observed 42% of −NH-inserted product in 2 h (Table 1, entry 5); however, −COOH-inserted product was not observed. When we used a nitrogen-based ligand such as 1,10-phenanthroline, the reaction was completed within 1 h and gave 51% of −NH-inserted product along with <10% of −COOH-inserted product (Table 1, entry 7). When we used $[(CH_3CN)_4Cu]ClO_4$ along with PPh_3, we observed only 25% −NH-inserted product (Table 1, entry 8). In the case of $[(CH_3CN)_4Cu]ClO_4$ along with, bis(diphenylphosphino)-methane(dppm) or 1,2-bis(diphenylphosphino)ethane(dppe), we observed only 34% and 37% −NH-inserted product, respectively (Table 1, entries 9 and 10). It is important to mention here that all of the Cu(I) salts used in this study dissolved in the presence of our choice of substrates and gave

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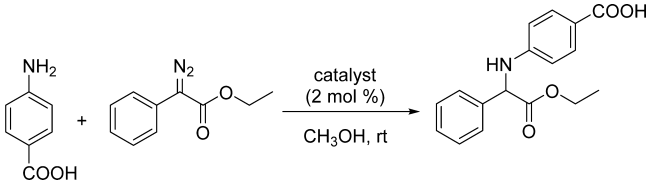
Table 1. Screening of Various Copper Sources as Catalysts for Chemoselective Carbene Insertion into the −NH Bond of 4-Aminobenzoic Acid



entry[a]	catalyst	time (h)	yield (%) (−NH/−COOH)
1	**1**	2	81/−
2	**2**	2	54/−
3	**3**	6	31/−
4	CuOTf	2	47/9
5	CuCl	2	42/−
6	$(CH_3CN)_4CuClO_4$	2	46/5
7[b]	$(CH_3CN)_4CuClO_4$ + 1,10-phenanthroline	1	51/8
8	$(CH_3CN)_4CuClO_4$ + $2PPh_3$	3	25/−
9	$(CH_3CN)_4CuClO_4$ + dppe	3	37/4
10	$(CH_3CN)_4CuClO_4$ + dppm	3	34/−
11[c]		12	10/8

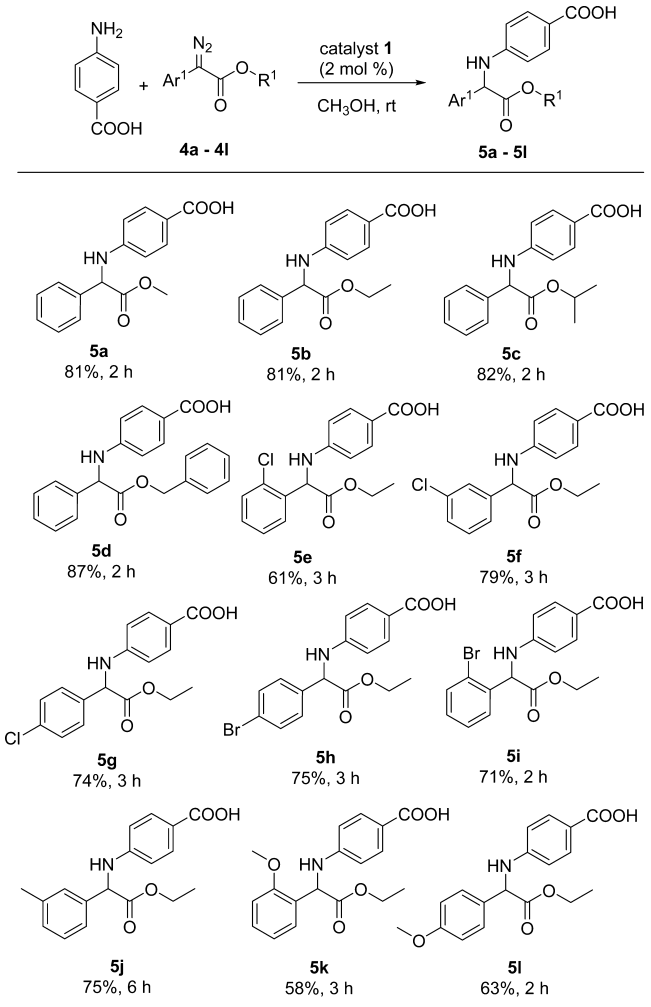
[a]All of the reactions were carried out with 0.5 mmol (with respect to 4-aminobenzoic acid) in 5 mL of methanol with 2 mol % of catalyst in a 25 mL Schlenk flask under dinitrogen atmosphere. [b]We observed 16% of a mixture of unidentified product. [c]When the reaction was carried out at 60 °C we observed many unidentified compounds on TLC.

different yields of carbene-inserted product depending upon the type of Cu(I) salt used in the reaction. This observation clearly reveals that the Cu(I) ion forms a complex with added substrates to yield carbene-inserted product; therefore, all of the Cu(I) ions serve as coordination catalysts in the present study. In the absence of the catalyst, the reaction was completed in 12 h at 60 °C and offered 10% −NH-inserted product (Table 1, entry 11). From the above results, it can be noted that the catalyst **1** is important to achieve highly selective carbene insertion into the −NH bond over the −COOH bond with relatively more yield. From the above study, it can also be noted that 2 mol % of catalyst **1** and methanol as a solvent are the best reaction conditions; therefore, for the following studies we used these experimental conditions to achieve our proposed goal.

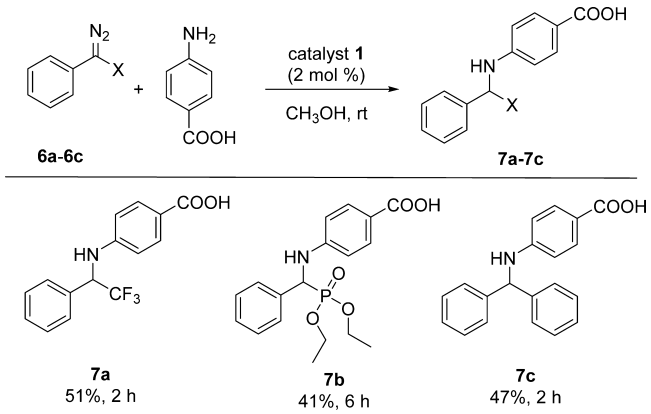
In order to show the substrate scope, we screened various α-aryl diazoacetate compounds (Scheme 5). All of the α-aryl diazoacetate compounds smoothly underwent the reaction and furnished very good yields. The α-aryl diazoacetate compounds with a simple phenyl ring on the aryl part produced very good yields in 2 h (**5a−d**); benzyl 2-diazo-2-phenylacetate produced 87% yield in 2 h (**5d**). Introduction of electron-donating or electron-withdrawing groups on the aryl part of the diazo compounds decreased the yields. The ethyl 2-(2-chlorophenyl)-2-diazoacetate offered 61% of −NH-inserted product in 3 h (**5e**), ethyl 2-diazo-2-(2-methoxyphenyl)acetate offered 58% of −NH-inserted product in 3 h (**5k**), and with ethyl 2-diazo-2-(4-methoxyphenyl)acetate, we observed 63% of −NH-inserted product in 2 h (**5l**).

We have also tested other diazo compounds for carbene insertion reactions. We have screened three more diazo compounds with various functional groups (Scheme 6). Out

Scheme 5. Scope of Different α-Aryl Diazoacetate Derivatives toward Chemoselective Carbene Insertion into the −NH Bond of 4-Aminobenzoic Acid



Scheme 6. Scope of Different α-Aryl Diazo Derivatives toward Chemoselective Carbene insertion into the −NH Bond of 4-Aminobenzoic Acid



of these three diazo compounds (1-diazo-2,2,2-trifluoroethyl)-benzene (**6a**) and diethyl (diazo(phenyl)methyl)phosphonate (**6b**) displayed selectivity and offered the corresponding −NH-inserted products in 51% (**7a**) and 41% (**7b**) yield, respectively. However, (diazomethylene)dibenzene (**6c**) did not selectively

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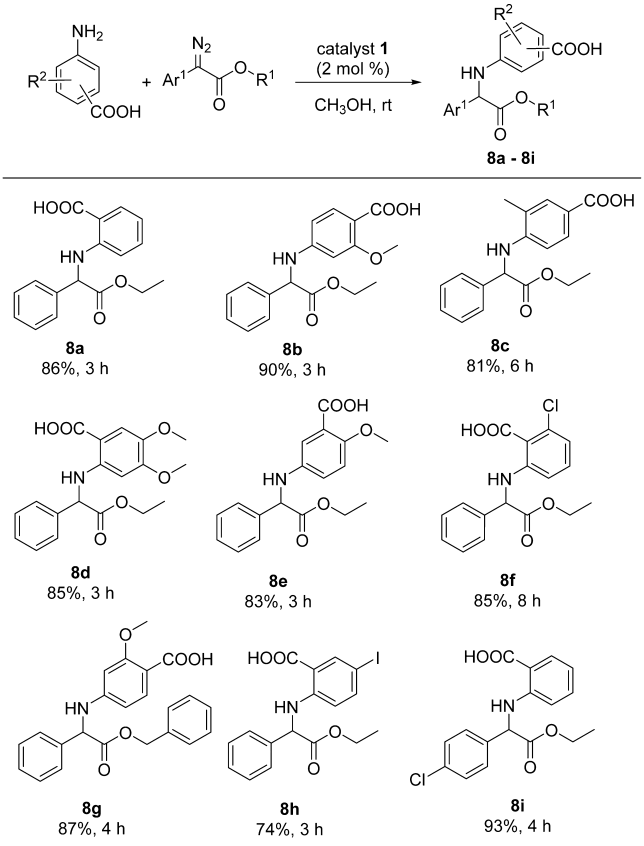
insert into the −NH bond (**6c** is known to insert into −COOH bond without catalyst also) and offered 47% of −NH-inserted product (**7c**) and 18% of −COOH-inserted product. This might be due to the highly reactive nature of these diazo compounds.

We have also screened variety of 2-, 3-, and 4-aminobenzoic acid derivatives in order to show the feasibility of carbene insertion reactions (Scheme 7). The anthranilic acid underwent

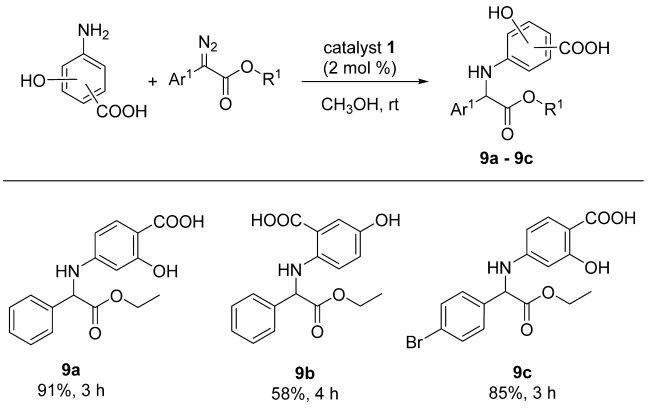
Scheme 7. Scope of Aminobenzoic Acid Derivatives toward Chemoselective Carbene Insertion of α-Aryl Diazoacetate into the −NH Bond



the reaction smoothly and offered good yields (86%) in 3 h (**8a**). Anthranilic acid with ethyl 2-(4-chlorophenyl)-2-diazoacetate offered the highest yield 93% in 4 h (**8i**). Similarly, 3-aminobenzoic acid derivative and 5-amino-2-methoxybenzoic acid underwent the reaction and gave 83% yield in 3 h (**8e**). Similarly, 2-, 3-, and 4-aminobenzoic acid derivatives also underwent the reaction smoothly and offered good to excellent yields. Among 4-aminobenzoic acid derivatives, 4-amino-2-methoxybenzoic acid produced the highest yield (90%) in 3 h (**8b**).

We have also attempted carbene insertion into the 4-amino-2-hydroxybenzoic acid, which has three different functional groups in a single substrate. Interestingly, the carbene was inserted only into the −NH bond over −COOH and −OH bonds (**9a**) (Scheme 8). In a similar manner, we have synthesized two more derivatives (**9b** and **9c**). The 2-amino-4-hydroxybenzoic acid produced 58% yield in 4 h with ethyl 2-diazo-2-phenylacetate, whereas 4-amino-2-hydroxybenzoic acid offered 85% yield in 3 h with ethyl 2-(4-bromophenyl)-2-diazoacetate.

Scheme 8. Chemoselective Carbene insertion of α-Aryl Diazoacetate into the −NH Bond over −COOH and −OH Bonds



Apart from the substrates given above, we have also attempted to use a few more aminobenzoic acid derivatives with three functional groups; however, owing to the poor solubility, we ended up with trace amounts of product, and in some cases, we recovered aminobenzoic acid derivatives and carbene dimer. It is noteworthy to mention here that we did not observe methanol (solvent)-inserted product when we studied all of the above-mentioned substrates. The standard nucleophilicity of $-NH_2$, −OH, and −COOH trend is well correlated with the observed selectivity.

In conclusion, we have successfully used a catalyst **1** to functionalize a large number of aromatic amino acids (N-functionalization) via carbene insertion into the −NH bond over −COOH and −OH bonds in a highly chemoselective manner. We have demonstrated that our methodology can be applied to a wide range of substrates for chemoselective carbene insertion into −NH bond over other functional groups. We synthesized a variety of novel aromatic amino acid derivatives and fully characterized using various standard spectroscopic techniques. We also found that, among all the catalysts used in this study, catalyst **1** has turned out to be the best catalyst for chemoselective carbene insertion reaction. More studies on the catalyst **1** and related mechanistic investigations are underway in our research laboratory.

EXPERIMENTAL SECTION

General Information. Unless otherwise specified, all of the reactions were carried out using oven-dried glassware and standard Schlenk techniques under dry nitrogen atmosphere. All of the solvents were distilled prior to use using standard procedures. Methanol was distilled from CaH_2 and used as obtained. Commercially available chemicals were used as received unless otherwise mentioned. Catalysts **1**−**3**[12h] and all diazo compounds[15] were prepared following the standard literature procedures (Cu(I) salts of organic ligands are explosive in nature therefore should be prepared in minimum quantity and used with adequate care). TLC was performed on precoated silica gel 60 F_{254} on aluminum plates and UV light (254 nm). Column chromatography was performed on silica gel 100−200 mesh size. ^1H and ^{13}C NMR spectra were recorded at 400 MHz (^1H) and 100 MHz (^{13}C), and chemical shifts (δ) are given in ppm. The residual solvent signals were used as references for ^1H NMR and ^{13}C NMR. HR-MS was recorded on a UHD Q-TOF mass spectrometer.

General Procedure for Cu(I)-Catalyzed Carbene Insertion into the −NH Bond over the −COOH Bond. An oven-dried 25 mL Schlenk flask was loaded with aminobenzoic acid (0.5 mmol) and catalyst (2 mol %), and then 4 mL of methanol was added to the reaction mixture. The diazo compound (0.55 mmol) was dissolved in

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1 mL of methanol and added to the reaction mixture at 0 °C, and then the reaction mixture was allowed to reach room temperature and stirred for the reported time. The progress of the reaction was monitored by TLC using an appropriate mixture of hexane and ethyl acetate (~1:1) as eluent. After completion of reaction, the solvent was evaporated under reduced pressure, and the crude residue was purified using column chromatography on silica gel using (3:1) hexane/ethyl acetate. The unreacted aminobenzoic acids were recovered from column chromatography.

*4-((2-Methoxy-2-oxo-1-phenylethyl)amino)benzoic acid (**5a**):* white solid (116 mg, 81% yield); mp 222−224 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (s, 1H), 7.65 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 7.1 Hz, 2H), 7.39 (t, J = 7.3 Hz, 2H), 7.34 (d, J = 7.2 Hz, 1H), 7.11 (d, J = 7.8 Hz, 1H), 6.71 (d, J = 8.7 Hz, 2H), 5.37 (d, J = 7.8 Hz, 1H), 3.65 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.8, 167.4, 150.9, 137.3, 131.1, 128.8, 128.3, 127.7, 118.6, 112.1, 59.3, 52.5; IR (film) 3418, 3061, 2958, 2550, 1740, 1664, 1606, 1526, 1478, 1423, 1320, 1296, 1173, 938, 773, 729, 696 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd (for $C_{16}H_{16}NO_4$) 286.1079, found 286.1071.

*4-((2-Ethoxy-2-oxo-1-phenylethyl)amino)benzoic acid (**5b**):* white solid (122 mg, 81% yield); mp 207−209 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.18 (s, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.56 (d, J = 7.2 Hz, 2H), 7.45 (t, J = 7.3 Hz, 2H), 7.42−7.36 (m, 1H), 7.16 (d, J = 7.8 Hz, 1H), 6.77 (d, J = 8.4 Hz, 2H), 5.39 (d, J = 7.7 Hz, 1H), 4.26−4.10 (m, 2H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.2, 167.3, 150.8, 137.2, 130.9, 128.6, 128.1, 127.5, 118.4, 112.0, 61.0, 59.2, 13.9; IR (film) 3388, 2925, 1734, 1665, 1603, 1531, 1490, 1415, 1321, 1288, 1172, 1024, 836, 774, 736, 699 cm^{-1}; HRMS-ESI (m/z) [M + Na]$^+$ calcd (for $C_{17}H_{17}NNaO_4$) 322.1055, found 322.1057.

*4-((2-Isopropoxy-2-oxo-1-phenylethyl)amino)benzoic acid (**5c**):* white solid (130 mg, 82% yield); mp 182−184 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (s, 1H), 7.66 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 7.4 Hz, 2H), 7.39 (t, J = 7.4 Hz, 2H), 7.33 (t, J = 7.2 Hz, 1H), 7.06 (d, J = 7.7 Hz, 1H), 6.72 (d, J = 8.6 Hz, 2H), 5.27 (d, J = 7.7 Hz, 1H), 4.93 (dt, J = 12.4, 6.2 Hz, 1H), 1.21 (d, J = 6.2 Hz, 3H), 1.02 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 170.8, 167.5, 151.0, 137.2, 131.0, 128.7, 128.2, 127.6, 118.5, 112.1, 68.8, 59.6, 21.5, 21.2; IR (film) 3379, 2986, 2541, 1727, 1665, 1602, 1533, 1488, 1414, 1351, 1319, 1285, 1175, 1141, 1103, 919, 832, 773, 697 cm-1; HRMS-ESI (m/z) [M + H]$^+$ calcd (for $C_{18}H_{20}NO_4$) 314.1392, found 314.1379.

*4-((2-(Benzyloxy)-2-oxo-1-phenylethyl)amino)benzoic acid (**5d**):* white solid (159 mg, 87% yield); mp 189−191 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.17 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 7.0 Hz, 2H), 7.45−7.33 (m, 3H), 7.30 (dd, J = 8.5, 4.7 Hz, 3H), 7.19 (dd, J = 6.4, 2.8 Hz, 2H), 7.15 (d, J = 7.8 Hz, 1H), 6.73 (d, J = 8.3 Hz, 2H), 5.45 (d, J = 7.8 Hz, 1H), 5.16 (q, J = 12.7 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.2, 167.5, 150.9, 137.1, 135.8, 131.1, 128.8, 128.4, 128.3, 128.1, 127.8, 127.7, 118.7, 112.2, 66.4, 59.4; IR (film) 3377, 2987, 2534, 1725, 1668, 1602, 1530, 1414, 1318, 1284, 1259, 1171, 723, 693 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd (for $C_{22}H_{20}NO_4$) 362.1392, found 362.1376.

*4-((1-(2-Chlorophenyl)-2-ethoxy-2-oxoethyl)amino)benzoic acid (**5e**):* white solid (102 mg, 61% yield); mp 196−198 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.14 (s, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.51 (td, J = 5.9, 2.4 Hz, 2H), 7.37 (dt, J = 4.5, 3.6 Hz, 2H), 7.21 (d, J = 7.9 Hz, 1H), 6.68 (d, J = 8.4 Hz, 2H), 5.59 (d, J = 7.8 Hz, 1H), 4.16 (m, 2H), 1.13 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 170.2, 150.6, 135.0, 133.2, 131.1, 130.0, 129.7, 128.9, 127.7, 118.8, 111.8, 61.4, 56.5, 13.9; IR (film) 3384, 2989, 2541, 1735, 1666, 1602, 1530, 1475, 1421, 1288, 1242, 1175, 1148, 1022, 838, 774, 752 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd (for $C_{17}H_{17}ClNO_4$) 334.0846, found 334.0831.

*4-((1-(3-Chlorophenyl)-2-ethoxy-2-oxoethyl)amino)benzoic acid (**5f**):* white solid (133 mg, 79% yield); mp 178−180 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.13 (s, 1H), 7.66 (d, J = 8.7 Hz, 2H), 7.58 (s, 1H), 7.50−7.37 (m, 3H), 7.17 (d, J = 8.2 Hz, 1H), 6.72 (d, J = 8.7 Hz, 2H), 5.44 (d, J = 8.1 Hz, 1H), 4.14 (m, 2H), 1.13 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.1, 168.0, 151.0, 140.2, 133.8, 131.5, 131.0, 128.7, 127.7, 126.8, 119.0, 112.6, 62.0, 59.1, 14.3; IR (film) 3390, 2988, 2539, 1737, 1669, 1605, 1532, 1490, 1423, 1321, 1290, 1174, 1020, 971, 839, 773, 731, 672 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd (for $C_{17}H_{17}ClNO_4$) 334.0846, found 334.0830.

*4-((1-(4-Chlorophenyl)-2-ethoxy-2-oxoethyl)amino)benzoic acid (**5g**):* white solid (125 mg, 74% yield); mp 177−179 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.17 (s, 1H), 7.65 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 7.16 (d, J = 7.9 Hz, 1H), 6.71 (d, J = 8.5 Hz, 2H), 5.40 (d, J = 7.9 Hz, 1H), 4.17−4.08 (m, 2H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 170.8, 150.6, 136.3, 132.8, 130.9, 129.4, 128.6, 112.1, 61.2, 58.4, 13.9; IR (film) 3380, 2996, 2539, 1733, 1670, 1605, 1529, 1491, 1422, 1316, 1291, 1245, 1172, 1143, 1092, 1016, 835, 769 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd (for $C_{17}H_{17}ClNO_4$) 334.0846, found 334.0832.

*4-((1-(4-Bromophenyl)-2-ethoxy-2-oxoethyl)amino)benzoic acid (**5h**):* off-white solid (142 mg, 75% yield); mp 180−182 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.15 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 7.9 Hz, 1H), 6.71 (d, J = 8.5 Hz, 2H), 5.38 (d, J = 7.9 Hz, 1H), 4.20−4.05 (m, 2H), 1.13 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 170.8, 167.4, 150.6, 136.8, 131.6, 131.0, 129.8, 121.4, 118.6, 112.2, 61.3, 58.6, 14.0; IR (film) 3408, 3380, 2925, 2545, 1734, 1670, 1604, 1526, 1485, 1417, 1318, 1288, 1173, 1140, 1016, 767 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd (for $C_{17}H_{17}BrNO_4$) 378.0341, found 378.0335.

*4-((1-(2-Bromophenyl)-2-ethoxy-2-oxoethyl)amino)benzoic acid (**5i**):* white solid (134 mg, 71% yield); mp 195−197 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.13 (s, 1H), 7.68 (t, J = 7.6 Hz, 3H), 7.47 (d, J = 6.6 Hz, 1H), 7.42 (t, J = 7.4 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.23 (d, J = 7.8 Hz, 1H), 6.65 (d, J = 8.4 Hz, 2H), 5.52 (d, J = 7.8 Hz, 1H), 4.16 (m, 2H), 1.14 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 170.1, 167.2, 150.5, 136.5, 132.9, 131.0, 130.2, 128.8, 128.2, 123.9, 118.7, 111.7, 61.4, 58.9, 13.8; IR (film) 3384, 2986, 2542, 1735, 1667, 1602, 1573, 1531, 1423, 1312, 1289, 1241, 1176, 1149, 1022, 839, 775 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd (for $C_{17}H_{17}BrNO_4$) 378.0341, found 378.0331.

*4-((2-Ethoxy-2-oxo-1-(m-tolyl)ethyl)amino)benzoic acid (**5j**):* white solid (117 mg, 75% yield); mp 192−194 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (s, 1H), 7.67 (d, J = 8.5 Hz, 2H), 7.28 (m, 3H), 7.14 (d, J = 6.6 Hz, 1H), 7.04 (d, J = 7.7 Hz, 1H), 6.71 (d, J = 8.6 Hz, 2H), 5.26 (d, J = 7.7 Hz, 1H), 4.20−4.05 (m, 2H), 2.30 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.3, 167.4, 150.9, 137.9, 137.1, 131.0, 128.9, 128.6, 128.0, 124.8, 118.4, 112.0, 61.1, 59.4, 21.0, 14.0; IR (film) 3389, 2983, 2537, 1733, 1666, 1600, 1573, 1530, 1487, 1413, 1286, 1251, 1176, 1160, 1021, 951, 837, 776, 742, 698 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd (for $C_{18}H_{20}NO_4$) 314.1392, found 314.1385.

*4-((2-Ethoxy-1-(2-methoxyphenyl)-2-oxoethyl)amino)benzoic acid (**5k**):* white solid (97 mg, 58% yield); mp 176−178 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (s, 1H), 7.66 (d, J = 8.6 Hz, 2H), 7.33 (dd, J = 14.2, 7.0 Hz, 2H), 7.06 (d, J = 8.1 Hz, 1H), 6.94 (dd, J = 17.0, 8.2 Hz, 2H), 6.68 (d, J = 8.7 Hz, 2H), 5.49 (d, J = 8.1 Hz, 1H), 4.18−4.06 (m, 2H), 3.83 (s, 3H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.2, 167.4, 156.8, 151.1, 131.0, 129.6, 128.1, 125.5, 120.6, 118.2, 111.6, 111.4, 60.9, 55.8, 53.5, 14.0; IR (film) 3382, 2985, 2542, 1732, 1667, 1602, 1531, 1491, 1418, 1321, 1289, 1247, 1173, 1139, 1025, 843, 763 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd (for $C_{18}H_{20}NO_5$) 330.1341, found 330.1353.

*4-((2-Ethoxy-1-(4-methoxyphenyl)-2-oxoethyl)amino)benzoic acid (**5l**):* white solid (104 mg, 63% yield); mp 156−158 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (s, 1H), 7.66 (d, J = 7.8 Hz, 2H), 7.42 (d, J = 7.8 Hz, 2H), 7.02 (d, J = 7.1 Hz, 1H), 6.94 (d, J = 7.8 Hz, 2H), 6.70 (d, J = 7.8 Hz, 2H), 5.24 (d, J = 7.1 Hz, 1H), 4.19−4.01 (m, 2H), 3.74 (s, 3H), 1.12 (t, J = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.5, 167.4, 159.1, 150.9, 130.9, 129.1, 128.8, 118.3, 114.1, 112.0, 61.0, 58.7, 55.1, 14.0; IR (film) 3413, 2915, 2542, 1733, 1668, 1517, 1479, 1418, 1293, 1259, 1173, 1024, 842, 768 cm^{-1}; HRMS-ESI (m/z) [M + Na]$^+$ calcd (for $C_{18}H_{19}NNaO_5$) 352.1161, found 352.1157.

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*4-((2,2,2-Trifluoro-1-phenylethyl)amino)benzoic acid (**7a**):* light brown semisolid (75 mg, 51% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.18 (s, 1H), 7.68 (d, J = 7.9 Hz, 2H), 7.63 (d, J = 7.1 Hz, 2H), 7.45−7.35 (m, 4H), 6.90 (d, J = 7.9 Hz, 2H), 5.76−5.62 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 150.5, 134.1, 131.2, 128.7, 128.4, 128.3, 126.7, 123.9, 112.4, 56.9 (q, J = 29.4 Hz); IR (film) 3426, 3031, 2925, 2507, 1691, 1606, 1533, 1422, 1322, 1256, 1177, 1123, 1025, 1001, 844, 775, 705, 642 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd (for $C_{15}H_{13}F_3NO_2$) 296.0898, found 296.0886.

*4-(((Diethoxyphosphoryl)(phenyl)methyl)amino)benzoic acid (**7b**):* off-white solid (74 mg, 41% yield); mp 202−204 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.08 (s, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 7.6 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.26 (dd, J = 8.0, 6.5 Hz, 1H), 7.14 (dd, J = 9.7, 6.4 Hz, 1H), 6.85 (d, J = 8.8 Hz, 2H), 5.15 (dd, J = 24.3, 9.7 Hz, 1H), 4.09−3.99 (m, 2H), 3.93−3.85 (m, 1H), 3.78−3.68 (m, 1H), 1.17 (t, J = 7.0 Hz, 3H), 1.05 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 167.4, 151.3 (d, J = 12.7 Hz), 136.4, 130.8, 128.3 (d, J = 5.5 Hz), 128.1 (d, J = 2.0 Hz), 127.6 (d, J = 2.7 Hz), 118.4, 112.4, 62.5 (dd, J = 18.1, 6.9 Hz), 54.2, 52.7, 16.3 (d, J = 5.2 Hz), 16.0 (d, J = 5.5 Hz); IR (film) 3300, 2985, 2912, 1683, 1604, 1529, 1422, 1261, 1218, 1171, 1114, 1053, 1023, 969, 846, 774, 699 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd (for $C_{18}H_{23}NO_5P$) 364.1314, found 364.1311.

*4-(Benzhydrylamino)benzoic acid (**7c**):* white solid (71 mg, 47% yield); mp 199−201 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 7.62 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 7.3 Hz, 4H), 7.33 (t, J = 7.5 Hz, 4H), 7.22 (dd, J = 13.7, 7.0 Hz, 3H), 6.69 (d, J = 8.2 Hz, 2H), 5.76 (d, J = 7.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 151.6, 142.7, 130.9, 128.4, 127.3, 127.0, 112.1, 60.3; IR (film) 3358, 2722, 2478, 1672, 1601, 1521, 1494, 1391, 1337, 1247, 1177, 1119, 1024, 994, 825, 773, 751, 702 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd (for $C_{20}H_{18}NO_2$) 304.1338, found 304.1329.

*2-((2-Ethoxy-2-oxo-1-phenylethyl)amino)benzoic acid (**8a**):* white solid (130 mg, 86% yield); mp 172−174 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (d, J = 6.8 Hz, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.46 (d, J = 7.3 Hz, 2H), 7.38 (t, J = 7.4 Hz, 2H), 7.31 (t, J = 7.2 Hz, 1H), 7.25 (t, J = 7.5 Hz, 1H), 6.63−6.52 (m, 2H), 5.44 (d, J = 6.8 Hz, 1H), 4.19−4.06 (m, 2H), 1.12 (t, J = 7.1 Hz, 3H) (−COOH proton does not shown up); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.0, 170.0, 148.7, 137.7, 134.4, 131.8, 128.9, 128.3, 127.1, 115.5, 112.5, 111.4, 61.5, 59.1, 13.9; IR (film) 3328, 3000, 2884, 2551, 1738, 1668, 1573, 1515, 1447, 1408, 1305, 1246, 1158, 1022, 914, 850, 745, 700, 660 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd (for $C_{17}H_{18}NO_4$) 300.1236, found 300.1229.

*4-((2-Ethoxy-2-oxo-1-phenylethyl)amino)-2-methoxybenzoic acid (**8b**):* off-white solid (149 mg, 90% yield); mp 154−156 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.57 (s, 1H), 7.55−7.48 (m, 3H), 7.39 (t, J = 7.2 Hz, 2H), 7.34 (d, J = 6.8 Hz, 1H), 7.05 (d, J = 7.5 Hz, 1H), 6.40 (s, 1H), 6.27 (d, J = 8.0 Hz, 1H), 5.37 (d, J = 7.5 Hz, 1H), 4.13 (m, 2H), 3.71 (s, 3H), 1.13 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.3, 166.4, 160.8, 152.2, 137.4, 133.5, 128.7, 128.3, 127.6, 107.6, 104.6, 96.5, 61.2, 59.3, 55.4, 14.0; IR (film) 3387, 3205, 2972, 1707, 1606, 1529, 1455, 1419, 1352, 1296, 1212, 1181, 1134, 1017, 846, 748, 694 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd (for $C_{18}H_{20}NO_5$) 330.1341, found 330.1334.

*4-((2-Ethoxy-2-oxo-1-phenylethyl)amino)-3-methylbenzoic acid (**8c**):* white solid (126 mg, 81% yield); mp 190−192 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62 (s, 1H), 7.52 (d, J = 7.1 Hz, 3H), 7.37 (t, J = 7.3 Hz, 2H), 7.34−7.26 (m, 1H), 6.44 (d, J = 8.2 Hz, 1H), 5.67 (d, J = 6.8 Hz, 1H), 5.40 (d, J = 6.8 Hz, 1H), 4.20−4.07 (m, 2H), 2.25 (s, 3H), 1.12 (t, J = 7.1 Hz, 3H) (−COOH proton does not shown up); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.2, 167.3, 148.0, 137.4, 131.5, 129.2, 128.7, 128.2, 127.5, 122.0, 119.1, 109.8, 61.5, 59.3, 17.3, 13.9; IR (film) 3419, 2971, 2534, 1730, 1667, 1603, 1527, 1442, 1292, 1250, 1191, 1149, 1016, 953, 822, 771, 735, 704 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd (for $C_{18}H_{20}NO_4$) 314.1392, found 314.1387.

*2-((2-Ethoxy-2-oxo-1-phenylethyl)amino)-4,5-dimethoxybenzoic acid (**8d**):* light brown solid (153 mg, 85% yield); mp 169−171 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (d, J = 7.2 Hz, 1H), 7.47 (d, J = 7.4 Hz, 2H), 7.37 (t, J = 7.4 Hz, 2H), 7.30 (t, J = 7.2 Hz, 1H), 7.26 (s, 1H), 6.17 (s, 1H), 5.54 (d, J = 7.2 Hz, 1H), 4.20−4.04 (m, 2H), 3.63 (s, 3H), 3.62 (s, 3H), 1.12 (t, J = 7.1 Hz, 3H) (−COOH proton does not shown up); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.2, 169.5, 154.6, 145.7, 139.3, 138.1, 128.9, 128.3, 127.2, 114.3, 102.3, 96.8, 61.4, 59.3, 56.1, 55.4, 14.0; IR (film) 3336, 2992, 2581, 1741, 1657, 1573, 1521, 1457, 1416, 1240, 1178, 1029, 866, 816, 751 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd (for $C_{19}H_{22}NO_6$) 360.1447, found 360.1444.

*5-((2-Ethoxy-2-oxo-1-phenylethyl)amino)-2-methoxybenzoic acid (**8e**):* off-white semi solid (137 mg, 83% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (d, J = 7.2 Hz, 2H), 7.37 (t, J = 7.3 Hz, 1H), 7.33−7.26 (m, 1H), 7.02 (d, J = 2.6 Hz, 1H), 6.85 (dt, J = 8.9, 5.8 Hz, 2H), 6.18 (d, J = 8.3 Hz, 1H), 5.16 (d, J = 7.9 Hz, 1H), 4.16−4.02 (m, 2H), 3.68 (s, 3H), 1.10 (t, J = 7.1 Hz, 3H) (−COOH proton does not shown up); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.9, 167.6, 150.3, 140.9, 137.7, 128.7, 128.2, 127.6, 121.8, 117.6, 115.4, 114.3, 61.0, 60.5, 56.5, 14.0; IR (film) 3398, 3233, 1730, 1616, 1503, 1449, 1413, 1373, 1327, 1214, 1182, 1127, 1014, 812, 742, 699 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd (for $C_{18}H_{20}NO_5$) 330.1341, found 330.1334.

*2-Chloro-6-((2-ethoxy-2-oxo-1-phenylethyl)amino)benzoic acid (**8f**):* light brown semi solid (144 mg, 85% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.84 (s, 1H), 7.44 (d, J = 7.1 Hz, 2H), 7.38 (t, J = 7.4 Hz, 2H), 7.31 (dd, J = 8.3, 6.1 Hz, 1H), 7.11 (t, J = 8.2 Hz, 1H), 6.94 (d, J = 6.5 Hz, 1H), 6.71 (d, J = 7.5 Hz, 1H), 6.49 (d, J = 8.3 Hz, 1H), 5.41 (d, J = 6.5 Hz, 1H), 4.19−4.06 (m, 2H), 1.11 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 170.8, 167.9, 146.1, 137.2, 132.1, 131.9, 128.9, 128.3, 127.0, 118.2, 117.0, 111.3, 61.6, 59.0, 13.8; IR (film) 3396, 2983, 2930, 2507, 1736, 1570, 1501, 1452, 1371, 1254, 1176, 1120, 1022, 793, 695 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd (for $C_{17}H_{17}ClNO_4$) 334.0846, found 334.0838.

*4-((2-(Benzyloxy)-2-oxo-1-phenylethyl)amino)-2-methoxybenzoic acid (**8g**):* white solid (172 mg, 87% yield); mp 171−173 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.58 (s, 1H), 7.52 (d, J = 7.1 Hz, 3H), 7.38 (dt, J = 13.5, 6.9 Hz, 3H), 7.30 (d, J = 2.2 Hz, 3H), 7.26−7.18 (m, 2H), 7.11 (d, J = 7.8 Hz, 1H), 6.41 (s, 1H), 6.30 (d, J = 8.4 Hz, 1H), 5.49 (d, J = 7.8 Hz, 1H), 5.23−5.11 (m, 2H), 3.68 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 171.2, 165.8, 160.8, 152.2, 137.2, 135.8, 133.6, 128.7, 128.4, 128.3, 128.1, 127.7, 107.7, 104.8, 96.5, 66.4, 59.3, 55.3; IR (film) 3370, 3266, 3058, 2945, 1713, 1607, 1529, 1452, 1418, 1346, 1245, 1174, 1140, 1019, 979, 854, 729, 695 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd (for $C_{23}H_{22}NO_5$) 392.1498, found 392.1496.

*2-((2-Ethoxy-2-oxo-1-phenylethyl)amino)-5-iodobenzoic acid (**8h**):* off-white solid (157 mg, 74% yield); mp 188−190 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.21 (s, 1H), 8.96 (d, J = 6.7 Hz, 1H), 8.05 (d, J = 1.7 Hz, 1H), 7.56−7.50 (m, 1H), 7.45 (d, J = 7.2 Hz, 2H), 7.39 (t, J = 7.3 Hz, 2H), 7.36−7.30 (m, 1H), 6.43 (d, J = 8.9 Hz, 1H), 5.48 (d, J = 6.7 Hz, 1H), 4.22−4.07 (m, 2H), 1.13 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 170.6, 168.6, 147.9, 141.9, 139.4, 137.2, 128.9, 128.3, 127.0, 115.3, 113.9, 76.0, 61.5, 58.7, 13.8; IR (film) 3326, 2982, 2539, 1736, 1663, 1562, 1501, 1441, 1404, 1327, 1233, 1188, 1019, 804, 734, 693 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd (for $C_{17}H_{17}INO_4$) 426.0202, found 426.0191.

*2-((1-(4-Chlorophenyl)-2-ethoxy-2-oxoethyl)amino)benzoic acid (**8i**):* white solid (156 mg, 93% yield); mp 172−174 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.84 (s, 1H), 8.93 (d, J = 6.7 Hz, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.46 (q, J = 8.6 Hz, 4H), 7.25 (t, J = 7.7 Hz, 1H), 6.60 (t, J = 7.5 Hz, 1H), 6.52 (d, J = 8.4 Hz, 1H), 5.50 (d, J = 6.7 Hz, 1H), 4.21−4.07 (m, 2H), 1.13 (t, J = 7.1 Hz, 3H).^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 170.5, 170.0, 148.4, 136.8, 134.2, 132.9, 131.8, 128.9, 128.9, 128.6, 115.7, 112.5, 111.7, 61.6, 58.3, 13.8; IR (film) 3329, 2990, 2875, 1736, 1664, 1571, 1514, 1411, 1243, 1208, 1185, 1161, 1017, 752 cm^{-1}; HRMS-ESI (m/z) [M + H]$^+$ calcd (for $C_{17}H_{17}ClNO_4$) 334.0846, found 334.0837.

*4-((2-Ethoxy-2-oxo-1-phenylethyl)amino)-2-hydroxybenzoic acid (**9a**):* white solid (145 mg, 91% yield); mp 194−196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.42 (s, 1H), 7.47 (dd, J = 11.3, 8.1 Hz, 3H), 7.39 (t, J = 7.3 Hz, 2H), 7.33 (t, J = 7.2 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 6.37−6.28 (m, 1H), 6.05 (s, 1H), 5.31 (d, J = 7.6 Hz, 1H),

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4.18−4.06 (m, 2H), 1.12 (t, J = 7.1 Hz, 3H)(−OH proton does not shown up); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 172.2, 171.1, 163.3, 153.4, 137.2, 131.1, 128.8, 128.3, 127.7, 106.1, 101.4, 98.0, 61.2, 59.3, 14.0; IR (film) 3382, 3064, 2554, 2738, 1528, 1450, 1396, 1293, 1256, 1201, 1165, 1098, 1019, 840, 782, 720, 694 cm^{-1}; HRMS-ESI (m/z) $[M + Na]^+$ calcd (for $C_{17}H_{17}NNaO_5$) 338.1004, found 338.1009.

*2-((2-Ethoxy-2-oxo-1-phenylethyl)amino)-5-hydroxybenzoic acid (**9b**):* pale yellow solid (91 mg, 58% yield); mp 193−195 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.35 (d, J = 7.3 Hz, 1H), 7.46−7.40 (m, 2H), 7.36 (t, J = 7.4 Hz, 2H), 7.33−7.27 (m, 1H), 7.24 (d, J = 2.9 Hz, 1H), 6.77 (dd, J = 8.9, 3.0 Hz, 1H), 6.45 (d, J = 9.0 Hz, 1H), 5.32 (d, J = 7.1 Hz, 1H), 4.16−4.04 (m, 2H), 1.10 (t, J = 7.1 Hz, 3H) (−COOH proton does not shown up); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 171.3, 169.7, 147.3, 142.4, 138.1, 128.9, 128.2, 127.1, 122.7, 116.7, 113.9, 112.0, 61.3, 59.7, 13.9; IR (film) 3359, 3225, 2929, 2611, 1743, 1673, 1626, 1581, 1516, 1447, 1413, 1372, 1265, 1209, 1179, 1159, 1024, 944, 834, 806, 732, 698 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calcd (for $C_{17}H_{18}NO_5$) 316.1185, found 316.1177.

*4-((1-(4-Bromophenyl)-2-ethoxy-2-oxoethyl)amino)-2-hydroxybenzoic acid (**9c**):* off-white solid (169 mg, 85% yield); mp 181−183 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.44 (s, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 3H), 7.22 (d, J = 7.6 Hz, 1H), 6.32 (d, J = 6.7 Hz, 1H), 6.06 (s, 1H), 5.37 (d, J = 7.7 Hz, 1H), 4.19−4.07 (m, 2H), 1.13 (t, J = 7.1 Hz, 3H) (−OH proton does not shown up); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 170.5, 163.5, 153.1, 136.6, 131.5, 129.7, 121.4, 106.1, 98.3, 61.3, 58.4, 13.9; IR (film) 3389, 2981, 2542, 1734, 1628, 1581, 1526, 1438, 1398, 1287, 1250, 1204, 1166, 1013, 780 cm^{-1}; HRMS-ESI (m/z) $[M + H]^+$ calcd (for $C_{17}H_{17}BrNO_5$) 394.0290, found 394.0286.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01249.

^1H and ^{13}C NMR spectra and X-ray crystallographic data (PDF)

X-ray crystallographic data for **5b** (CIF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. Ashoka G. Samuelson (IISc, Bangalore, India) on the occasion of his 60th birthday.

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