One-pot Process for Palladium Catalyzed Direct C-H Acylation of Anilines in Water using a Removable Ortho Directing Group

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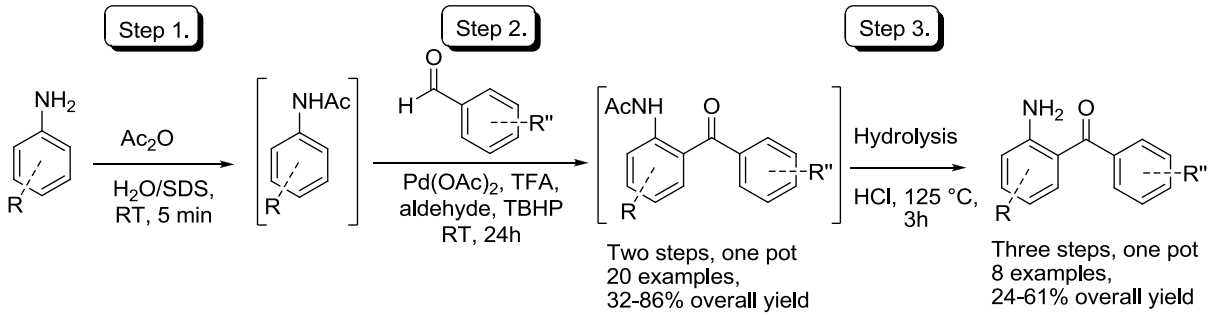


A new mild, practical method for the synthesis of aminobenzophenone derivatives through the palladium catalyzed cross-dehydrogenative coupling of anilines with aldehydes in water-SDS mixture is reported. The method involves the protection of aniline followed by its oxidative coupling with the aldehyde and finally the removal of the protecting group in one pot, under aqueous conditions. With these two or three-steps sequences in hand, several N-acetyl and unprotected aminobenzophenone derivatives were isolated in good to excellent yield.

Oxidative C – H bond activation is one of the most important topics in recent synthetic organic chemistry.[1] Compared to cross coupling reactions, the preactivation of the substrate is not needed for the introduction of new functional groups and the formation of by-products can be reduced. Using oxidative C-H couplings, a wide range of biaryl structures can be synthesized[2] that can potentially be the building blocks of biologically active natural products.[3] A key challenge in C-H activation chemistry is controlling the regioselectivity. The presence of a directing group in arenes ensures

selective activation of C-H bond through interaction with the transition metal catalyst during the reaction.[4]

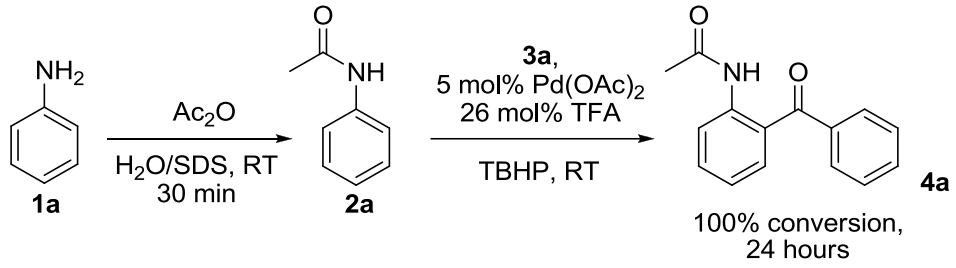
In the past few years, several synthetic methodologies were developed for the synthesis of benzophenone derivatives via palladium catalyzed ortho selective cross dehydrogenative C-H coupling. For these transformations O-phenylcarbamates, 2-arylpiridines, and mostly acetanilides are the substrates, which can be acylated with aldehydes[5], carboxylic acids[6], ketocarboxylic acids[7] or toluene[8] derivatives. In these homogenous organic reactions $Pd(TFA)_2$ or $Pd(OAc)_2$/TFA was the most effective catalyst, and TBHP as oxidant provided the best yields.

Recently, our group reported a mild implementation of this palladium-catalyzed coupling in aqueous media.[9] We performed the reaction in water at RT in the presence of catalytic amount of SDS. The surfactant additive highly accelerates the reaction.[10] Taking advantage of these conditions we synthesized several N-(2-benzoylphenyl) acetamide derivatives from N-phenylacetamides.

N-phenylacetamide substrates can be prepared from anilines with acetic anhydride in organic solvents.[11] However, Patel et al. showed that the protection of anilines took place straightforwardly under aqueous conditions with the support of SDS at room temperature. [12] Based on this aqueous N-acylation procedure and our previously developed palladium catalyzed coupling, we supposed that the aniline protection step and the C-H acylation step can be carried out successively in one pot using SDS/water as a solvent. This strategy would enable the one-pot ortho acylation of anilines via protection-coupling sequence under aqueous conditions, and also offers the possibility for the final deprotection of the anilides after the coupling to provide aminobenzophenones. In this three step synthesis, the acetyl group serves as a removable ortho directing group for C-H activation.

To demonstrate the compatibility of the procedures for aniline protection and the palladium-catalyzed ortho acylation, we treated aniline (**1a**) with 1.5 equivalents of acetic anhydride in SDS/water at room temperature. The acylation took place with full conversion after 0.5 hours providing the acetanilide as suitable substrate for C-H activation. Then we added 5 mol% $Pd(OAc)_2$ catalyst, 26 mol% TFA, 2 eq. benzaldehyde (**3a**) and 2 eq. TBHP (Scheme 1).

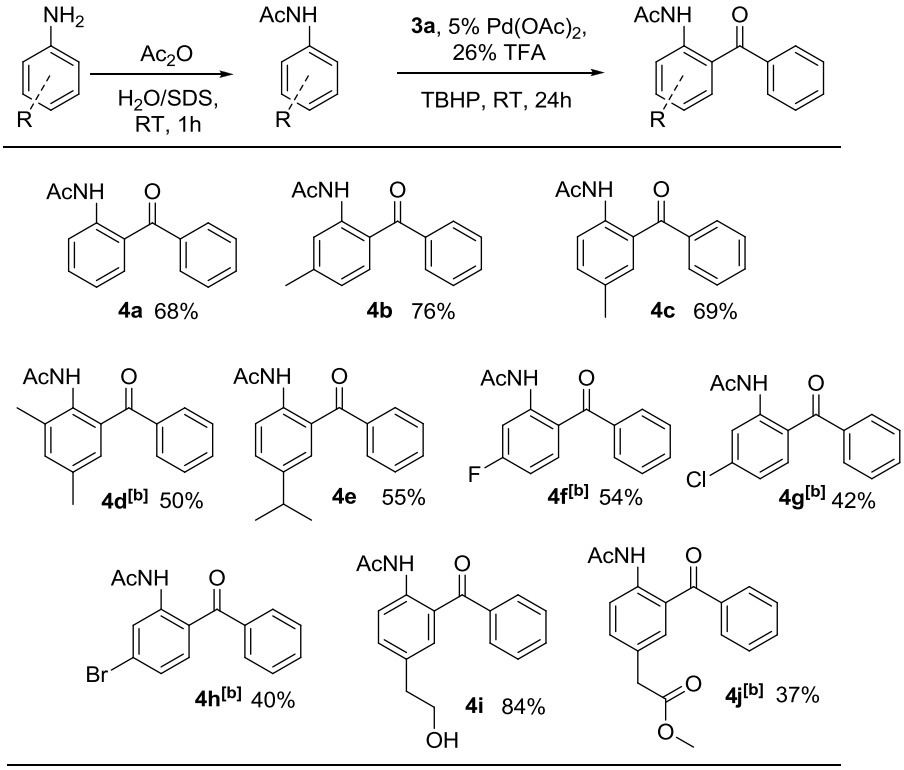
Scheme 1. One-pot ortho acylation of anilines via N protection and ortho C-H activation



To our delight, at room temperature we observed the transformation of acetanilide **(2a)** to N-(2-benzoylphenyl)acetamide (**4a**) with 77% conversion after 4 hours, and complete reaction after 24 hours. This reaction sequence demonstrated the compatibility of the N and C acylation, therefore we aimed to explore the substrate scope of this reaction sequence for the preparation of acetamido benzophenones.

2-Acetamido benzophenone was prepared from aniline using the two step one-pot procedure, and compound **4a** was obtained in 68% yield (Scheme 2). Methyl substituted acetanilides gave N-(2-benzoylphenyl)acetamides (**4b** and **4c**) in good yields (76% and 69% yield respectively), while the dimethyl product **4d** was obtained in 50% yield. The bulky isopropyl group in the para position did not affect the reaction significantly (55%) compared to methyl group. In the presence of halogens (F, Cl, Br) the sequential reaction also worked, and the appropriate products were isolated with 54%, 42%, and 40% yield respectively after two reaction steps. The reaction under the applied conditions readily tolerated the presence of a free hydroxyl group, and we obtained N-(2-benzoyl-4-(2-hydroxyethyl)-phenyl)acetamide (**4i**) in high yield (84%). The sequential reaction could be achieved in the presence of ester function on the aniline part and the appropriate benzophenone derivative (**4j**) was obtained.

Scheme 2. Substrate scope of anilines[a]

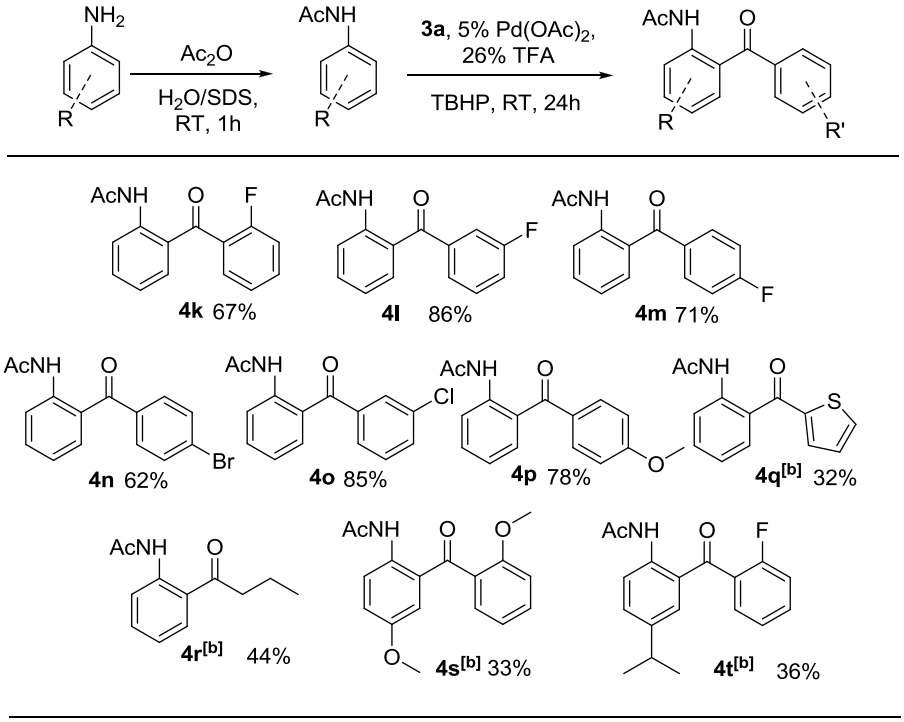


[a]*Reaction conditions* step1: acetanilide (1.0 mmol), SDS (0.05 mmol), water (4mL), acetic anhydride (1.5 mmol) at RT; step2: $Pd(OAc)_2$ (0.05 mmol), TFA (0.26 mmol), benzaldehyde (2.0 mmol), TBHP (2 mmol, 70 wt% in water), at RT, 24 h. Yields of isolated product.

[b]step2: $Pd(OAc)_2$ (0.075 mmol), TFA (0.39 mmol), benzaldehyde (2.0 mmol), TBHP (2 mmol, 70 wt% in water), at 40 °C, 24 h.

Substituents on the aromatic ring of the aldehyde substrate slightly influenced the isolated yields of the product (yield varied in the range of 62-86%, Scheme 3). Ortho, meta and para halogenated benzaldehydes, as well as methoxy benzaldehyde resulted in good yields (**4j**-**4o**). Aliphatic and heterocyclic aldehydes are also compatible with the reaction conditions, but their transformation required higher palladium catalyst loading (7.5 mol%) and 40°C (**4p**, **4q**). Electron rich anilines such as para anizidine and 4-isopropyl aniline were also acylated in position 2 with substituted aromatic aldehydes after the protection of free amino group, and the appropriate products (**4r** and **4s**) were obtained with 33% and 36% yield.

Scheme 3. Substrate scope of aldehydes[a]



[a]*Reaction conditions* step1: acetanilide (1.0 mmol), SDS (0.05 mmol), water (4mL), acetic anhydride (1.5 mmol) at RT; step2: $Pd(OAc)_2$ (0.05 mmol), TFA (0.26 mmol), benzaldehyde (2.0 mmol), TBHP (2 mmol, 70 wt% in water), at RT, 24 h. Yields of isolated product.

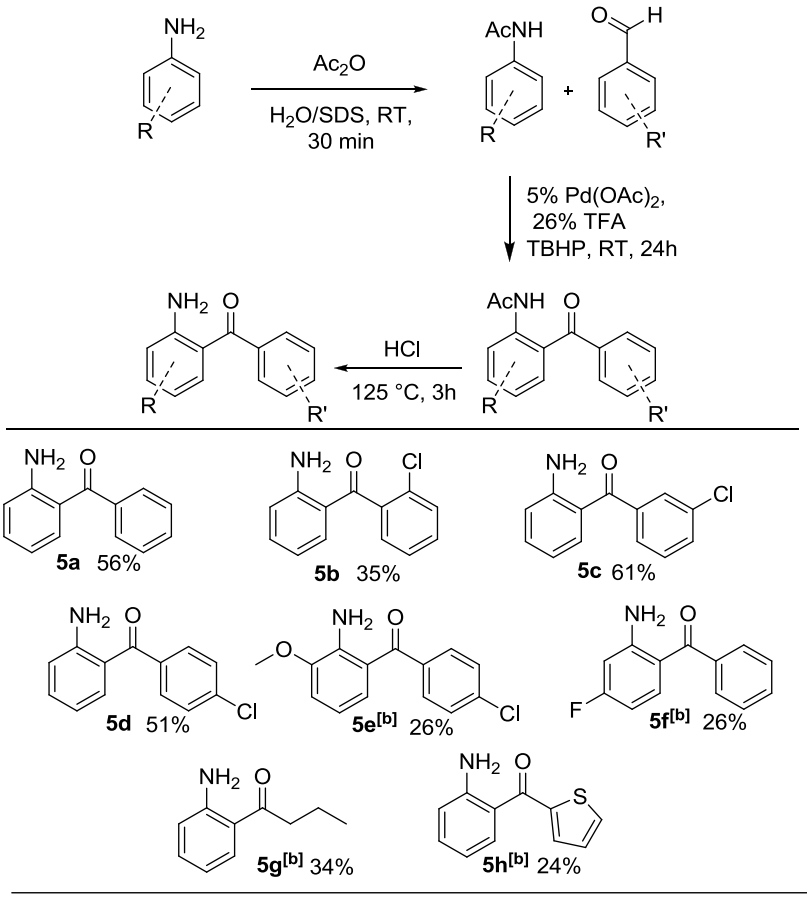
[b]step2: $Pd(OAc)_2$ (0.075 mmol), TFA (0.39 mmol), benzaldehyde (2.0 mmol), TBHP (2 mmol, 70 wt% in water), at 40 °C, 24 h.

We have demonstrated that anilines are reasonable starting materials for the palladium catalyzed C-H acetylation coupling under aqueous conditions in a two step one-pot process at room temperature. The conditions of N-acylation of the free amino group and the cross-dehydrogenative coupling are compatible. Moreover, during the synthesis of more complex structures, the protecting group is usually removed after several synthetic steps providing the desired functional group in target molecules.

In our case, removal of the acetyl group from the amino moiety would provide substituted anilines. This hydrolytic cleavage is usually performed under acidic conditions, which is also compatible with our sequence. Therefore we aimed to extend our procedure with a hydrolytic reaction step to obtain amino benzophenones in a three step, one-pot reaction from anilines using

acetyl group as a removable protecting and directing group for C-H activation. Accomplishing the protection, coupling and deprotection in a row without the isolation of the intermediate products shortens the reaction time and produces less waste. For this reason, after the acylation of aniline **(1a)**, and the palladium catalyzed cross dehydrogenative coupling of the formed

Scheme 4. Substrate scope of the three-step sequence[a]



[a]*Reaction conditions* step1: acetanilide (1.0 mmol), SDS (0.05 mmol), water (4mL), acetic anhydride (1.5 mmol) at RT; step2: $Pd(OAc)_2$ (0.05 mmol), TFA (0.26 mmol), benzaldehyde (2.0 mmol), TBHP (2 mmol, 70 wt% in water), at RT, 24 h; step3: 3.5 mL HCl (37 wt% in water), 125 °C. Yields of isolated product.

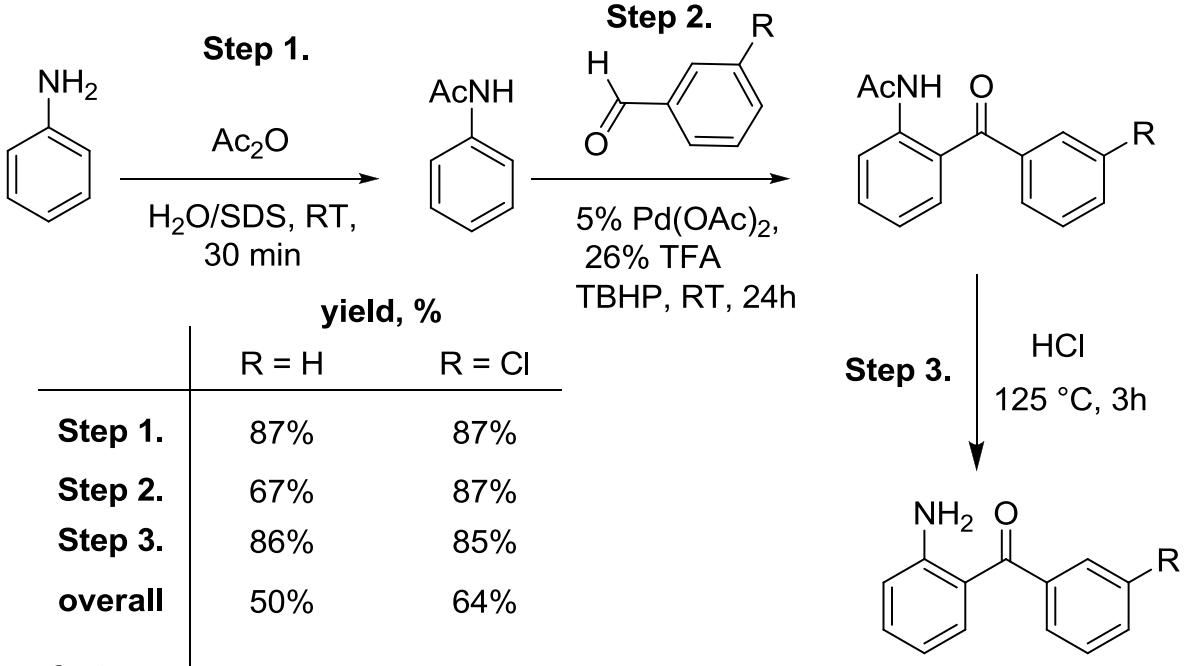
[b]step2: $Pd(OAc)_2$ (0.075 mmol), TFA (0.39 mmol), benzaldehyde (2.0 mmol), TBHP (2 mmol, 70 wt% in water), at 40 °C, 24 h.

acetanilide **(2a)** and benzaldehyde **(3a),** we treated the reaction mixture with 37% HCl at 125 °C. To our delight, complete hydrolysis took place in 3 hours providing the appropriate amino derivative of benzophenone **(5a)** and the desired compound was isolated with 56% yield. Next, we

examined the substrate scope of the extended three steps sequence. Following the protection and palladium catalyzed step the final hydrolysis completed in 3 hours in all cases (**5a-5h**, Scheme 4). Although, the yield varied in the range of 24-61% the three step one-pot process provide the desired product with the same efficiency compared to the step-by-step procedure.

In two cases, we compared the one-pot process to the reaction sequence with full isolation of the intermediate products (Scheme 5). Starting with aniline, we found that compound **5a** was obtained with 50% overall yield, while the one-pot process gave the product with similar efficiency (56%).

Scheme 5. Comparison of step-by-step and one-pot processes



	yield, %	
	R = H	R = Cl
Step 1.	87%	87%
Step 2.	67%	87%
Step 3.	86%	85%
overall	50%	64%
3 steps, one-pot	56%	61%

A similar outcome was observed in the preparation of aminobenzophenone **5c**.

In summary, we developed new sequential methods for the synthesis of 2- acetamido or 2-amino benzophenone derivatives. These methods both include the protection of aniline derivatives followed by palladium-catalyzed cross dehydrogenative coupling of aldehydes under aqueous conditions at room temperature. After the C-H activation step the appropriate acetamido derivatives

can be isolated or hydrolyzed in the same pot to obtain amino benzophenones,which provide simpler and faster synthetic routes to the desired target molecules. Three sequential chemical transformations without the isolation of each intermediate serve as a practical procedure, producing less waste, and requiring less energy and time for work up. All reactions were performed in water in the presence of SDS, which makes the method more attractive with regard to safety and economic aspects.

Experimental section

General procedure for the synthesis of N-(2-benzoylphenyl)acetamides 4. A round bottom flask was charged with 14.4 mg (0.05 mmol, 5 mol%, method A) or 21 mg (0.075 mmol, 7.5 mol%, method B) SDS, 4 mL water and 1 mmol (1 eq.) aniline. 141.7 μL acetic anhydride was added dropwise during stirring at RT. The reaction was monitored by TLC. After completition (0.5 – 1 hours), 11.2 mg (0.05 mmol, 5 mol%, method A) or 17 mg (0.075 mmol, 7.5 mol%, method B) $Pd(OAc)_2$, 20 μL (0.26 mmol, 26 mol%, method A) or 30 μL (0.39 mmol, 39 mol%, method B) TFA, 2 mmol (2 eq.) aldehyde and 250 μL (2 mmol, 2 eq., 70 wt% in water) TBHP was added during vigorous stirring. After 24 hours, the heterogeneous mixture was neutralized with $NaHCO_3$, extracted with EtOAc, and the combined organic layers were washed with water. The EtOAc solution was dried over $MgSO_4$, concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (hexane:EtOAc).

General procedure for the synthesis of (2-aminophenyl)(phenyl)methanones 5.

Following the general procedure for the synthesis of **4** described above 3.5 mL HCl (37 wt% in water) was added, and the reaction mixture was stirred at 125 °C for 3 hours. The reaction mixture was cooled to RT, and 4 mL EtOAc was added. The mixture was neutralized with $NaHCO_3$ during stirring. Than the layers were separated, the water phase was extracted with EtOAc, and the summarized organic phase was washed with water, and dryed over $MgSO_4$. The crude product was purified by silica gel column chromatography (hexane/EtOAc).

N-(2-benzoylphenyl)acetamide[8] (**4a)** Method A. White, solid; 147 mg (0.62 mmol, yield: 68%). m.p.: 73–82 °C. R_f : 0.68 (hexane:EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.80 (s, 1H), 8.61 (d, 1H, *J* = 8.37), 7.70-7.44 (m, 7H), 7.06 (t , 1H, *J* = 7.42 Hz), 2.21 (s, 3H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 199.6, 169.1, 140.4, 138.5, 134.1, 133.4, 132.4, 129.8, 128.2, 123.1, 121.9, 121.4, 25.2 ppm. IR (ATR): ν_{max} = 3212.6, 3163.4, 3027.3, 1673.9, 1600.6, 1477.0, 1287.1, 920.3, 750.4, 701.8, 634.5 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 239 (16 [M+]), 196 (100), 167 (15), 134 (13), 120 (24), 105 (10), 92 (12), 77 (24).

N-(2-benzoyl-5-methylphenyl)acetamide[8] **(4b)** Method A. White, solid; 193 mg (0.76 mmol, yield: 76%). m.p. 125-129°C Rf: 0.59 (in Hexane:EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 11.00 (s, 1H), 8.47 (s, 1H), 7.66-7.41 (m, 6H), 6.85 (d, 1H *J* = 8.69 Hz), 2.40 (s, 3H), 2.20 (s, 3H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 199.4, 169.1, 145.7, 140.6, 138.8, 133.8, 132.1, 129.6, 128.1, 122.7, 121.5, 120.3 25.2, 22.0 ppm. IR (ATR): ν_{max} = 3177, 2962, 1668, 1608, 1280, 1260, 1016, 794, 742, 698, 617 cm^{-1} MS (EI, 70 eV): *m/z* (%): 253 (41, [M$^+$]), 210 (100), 180 (16), 148 (20), 134 (30), 77 (28).

N-(2-benzoyl-4-methylphenyl)acetamide[8] **(4c)** Method A. White, solid; 174 mg (0.69 mmol, yield: 69%). m.p.: 158 – 163 °C. R_f: 0.51 (in Hexane:EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.62 (s, 1H), 8.47 (d, 1H, *J* = 8.37 Hz), 7.70 - 7.32 (m, 7H), 2.27 (s, 3H), 2.18 (s, 3H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 199.6, 168.9, 138.6, 137.8, 134.8, 133.4, 132.4, 131.6, 129.8, 128.2, 123.4, 121.5, 25.1, 20.6 ppm. IR (ATR) ν_{max} = 3207, 3162, 3026, 1669, 1487, 1291, 825, 742, 702 cm^{-1}; MS (EI, 70 eV) *m/z* (%): 253 (25, [M$^+$]), 210 (100), 180 (85), 134 (19), 106 (10), 77 (24).

N-(2-benzoyl-4,6-dimethylphenyl)acetamide[8] **(4d)** Method B. Yellow, solid; 133 mg (0.5 mmol, yield: 50 %). m.p.: 125–141°C. R_f : 0.25 (Hexane:EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.50 (s, 1H), 7.81 (d, 2H, *J* = 7.11 Hz), 7.58 (t, 1H, *J* = 7.27 Hz), 7.44 (t, 2H, *J* = 7.50 Hz), 7.18 (s, 1H), 7.03 (s, 1H), 2.29 (s, 3H), 2.23 (s, 3H), 1.98 (s, 3H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 197.9, 168.7, 137.3, 135.9, 135.2, 134.7, 133.7, 133.0, 132.0, 130.3, 128.4, 128.2, 23.3, 20.8, 18.6

ppm. IR ν = 3222, 3015, 2922, 1665, 1649, 1528, 1298, 1216.2, 710.2 cm^{-1}; MS (EI, 70 eV) *m/z* (%): 267 (17, [M+]), 224 (100), 208 (10), 180 (13), 162 (24), 148 (18), 120 (14), 105 (16), 91 (11), 77 (40).

N-(2-benzoyl-4-isopropylphenyl)acetamide[8] **(4e)** Method A. White, solid; 154 mg (0.55 mmol, yield: 55%). m.p. 83-88 °C. Rf: 0.43 (in Hexane:EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.62 (s, 1H), 8.49 (d, 1H *J* = 8.53 Hz), 7.72 – 7.37 (m, 7H), 2.85 (septet, 1H *J* = 6.79 Hz), 2.20 (s, 3H), 1.19 (d, 6H *J* = 6. 95 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 199.6, 169.0, 142.7, 138.6, 138.1, 132.5, 132.2, 131.2, 129.9, 128.3, 123.5, 121.7, 33.3, 25.1, 23.8 ppm. IR (ATR): ν_{max} = 3188, 3166, 2963, 1666, 1594, 1492, 1370, 1286, 1274, 827, 698 cm^{-1} MS (EI, 70 eV): *m/z* (%): 281 (42, $[M^+]$), 239 (40), 224 (100), 105 (31), 77 (28).

***N*-(2-benzoyl-5-fluoro-phenyl)acetamide**[8] **(4f)** Method B. Offwhite, oil. 138 mg (0.54 mmol, yield: 54%). R_f : 0.72 (hexane:EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 11.20 (s, 1H), 8.48 (dd, 1H, J_1=11.85, J_2=2.53), 7.64 - 7.43 (m, 6H), 6.77-6.69 (m, 1H), 2.20 (s, 3H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 198.7, 169.3, 165.6 (d, J_{CF} = 254.6 Hz), 143.3 (d, J_{CF} = 13.3 Hz), 138.6, 136.2, 136.1, 132.3, 129.4, 128.3, 118.8 (d, J_{CF} = 2.8 Hz), 109.0 (d, J_{CF} = 22.1 Hz), 108.2 (d, J_{CF} = 28.0 Hz), 25.2 ppm. IR (ATR): ν_{max} = 3270, 2926, 2854, 1591, 1521, 1425, 1255, 1235, 695 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 257 (18, [M+]), 214 (100), 198 (7), 185 (15), 152 (15), 138 (49), 110 (15), 105 (15), 83 (8), 77 (29).

N-(2-benzoyl-5-chlorophenyl)acetamide[8] **(4g)** Method B. Offwhite, solid; 115 mg (0.42 mmol, yield: 42%). m.p. 108-118°C (lit.: 70.5-75°C). Rf: 0.57 (in Hexane:EtOAc =1:2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.96 (s, 1H), 8.74 (s, 1H), 7.66-7.57 (m, 3H), 7.51-7.45 (m, 3H), 7.02 (dd, 1H, J_1 = 8.53 Hz J_2 = 2.05 Hz), 2.21 (s, 3H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 198.9, 169.2, 141.5, 140.6, 138.3, 134.6, 132.6, 129.6, 128.4, 122.1, 121.1, 120.9, 25.2 ppm. IR (ATR): ν_{max} = 3200, 2919, 1669, 1595, 1470, 1271, 926, 749, 697, 613 cm^{-1} MS (EI, 70 eV): *m/z* (%): 273 (16, [M+], 230 (100), 168 (30), 154 (35), 105 (32), 77 (60).

N-(2-benzoyl-5-bromophenyl)acetamide[8] **(4h)** Method B. Offwhite, solid; 127 mg (0.40 mmol, yield: 40%). m.p. 132-137 °C Rf: 0.51 (in Hexane:EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.90 (s, 1H), 8.88 (d, 1H, *J* = 1.74 Hz), 7.66-7.57 (m, 3H), 7.50-7.37 (m, 3H), 7.19 (dd, 1H, J_1 = 8.53 Hz J_2 = 1.90 Hz), 2.21 (s, 3H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 199.0, 169.1, 141.4, 138.2, 134.5, 132.6, 129.6, 129.3, 128.4, 125.1, 124.0, 121.3, 25.2 ppm. IR (ATR): ν_{max} = 3230, 1690, 1631, 1567, 1395, 1251, 915, 879, 753, 700, 654, 485 cm^{-1} MS (EI, 70 eV): *m/z* (%): 317 (25, [M+]), 276 (100), 200 (28), 167 (45), 105 (61), 77 (100), 51 (40).

N-(2-benzoyl-4-(2-hydroxyethyl)phenyl)-acetamide (4i) Method A. Off-white, solid; 238 mg (0.84 mmol, yield: 84%). m.p. 87-92 °C Rf: 0.5 (in Hexane:EtOAc = 2:1) ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.63 (s, 1H), 8.47 (d, 1H, *J* = 8.21 Hz), 7.69–7.39 (m, 7H), 3.79 (t, 2H, *J* = 6.48 Hz), 3.03 (br, 1H), 2.77 (t, 2H, *J* = 6.48 Hz), 2.17 (s, 3H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 199.3, 169.2, 138.3, 134.5, 133.6, 132.8, 132.5, 129.8, 128.2, 123.6, 121.7, 63.1, 38.1, 25.0 ppm. IR (ATR): ν_{max} = 3437, 2931, 1659, 1493, 1273, 705, 590 cm^{-1} MS (EI, 70 eV): *m/z* (%): 281 (8, [M^{+}]), 265 (60), 223 (100), 210 (28), 180 (10), 132 (13), 105 (15), 77 (30). HRMS: *m/z* [M + H]$^{+}$ calcd for $C_{17}H_{18}NO_3$: 284.1287; found: 284.1293.

Methyl 2-(4-acetamido-3-benzoylphenyl) acetate (4j)

Method B. Light yellow, oil; 58 mg (0.19 mmol, yield: 37%). Rf: 0.44 (in Hexane:EtOAc = 1:1) ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.64 (s, 1H), 8.50 (d, 1H *J* = 9.16 Hz), 7.65 – 7.39 (m, 7H), 3.59 (s, 3H), 3.49 (s, 2H), 2.14 (s, 3H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 199.3, 171.4, 169.2, 139.3, 138.3, 135.0, 134.1, 132.6, 130.0, 128.3, 127.7, 123.4, 121.7, 52.1, 40.2, 25.2 ppm. IR (ATR): ν_{max} = 3315, 2931, 1730, 1589, 1510, 1256, 705 cm^{-1} MS (EI, 70 eV): *m/z* (%): 311 (15, [M^{+}]), 269 (37), 210 (100), 180 (28), 132 (20), 77 (35). HRMS: *m/z* [M + H]$^{+}$ calcd for $C_{18}H_{19}FNO_2$: 312.1236; found: 312.1242.

N-(2-(2-fluorobenzoyl)phenyl)acetamide[8] **(4k)** Method A. White, solid; 171 mg (0.67 mmol, yield: 67%). m.p. 81-93°C. Rf: 0.41 (in Hexane:EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 11.26 (s, 1H), 8.66 (d, 1H, *J* = 8.53 Hz), 7.52 - 7.33 (m, 4H), 7.21-6.93 (m, 3H), 2.17 (s, 3H) ppm. ^{13}C NMR

(62.5 MHz, $CDCl_3$): δ = 197.0, 169.6, 162.3 (d, J_{CF} = 260.6 Hz), 141.2, 135.4, 134.0 (d, J_{CF} = 1.8 Hz), 133.0 (d, J_{FC} = 8.3 Hz), 130.1 (d, J_{CF} = 2.3 Hz), 127.4 (d, J_{CF} = 15.2 Hz), 124.2 (d, J_{CF} = 3.7 Hz), 122.3, 122.2, 120.7, 116.3 (d, J_{FC} = 21.6 Hz), 25.4 ppm. IR (ATR): ν_{max} = 3242, 1689, 1633, 1583, 1528, 1447, 1280, 1214, 1152, 925, 751, 632, 524 cm^{-1} MS (EI, 70 eV): *m/z* (%): 257 (40, $[M^+]$), 214 (100), 196 (36), 134 (35), 120 (45), 95 (30).

N-(2-(3-fluorobenzoyl)phenyl)acetamide[8] **(4l)** Method A. Pale-white, solid; 220 mg (0.86 mmol, yield: 86 %). m.p.: 63 – 65 °C. R_f : 0.47 (Hexane:EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.64 (s, 1H), 8.50 (d, 1H, *J* = 8.37 Hz), 7.49 – 7.26 (m, 5H), 7.21 – 7.13 (m, 1H), 6.97 (t, 1H *J* = 7.66 Hz), 2.11 (s, 3H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 198.0 (d, J_{CF} = 1.8 Hz), 169.2, 162.3 (d, J_{CF} = 248.6 Hz), 140.4, 134.6, 133.3, 129.9 (d, J_{CF} = 7.8 Hz), 125.6 (d, J_{CF} = 3.2 Hz), 122.7, 122.1, 121.6, 119.4 (d, J_{CF} = 21.1 Hz), 116.5 (d, J_{CF} = 22.5 Hz), 25.2 ppm. IR ν = 3221, 3077, 2962, 1667, 1479, 1292, 1254, 1010, 753, 719, 529 cm^{-1}; MS (EI, 70 eV) *m/z* (%): 257 (22, [M+]), 214 (100), 185 (17), 134 (23), 120 (53), 95 (33), 92 (24).

N-(2-(4-fluorobenzoyl)phenyl)-acetamide[8] **(4m)** Method A. Pale-white, solid; 182 mg (0.71 mmol, yield: 71 %). m.p.: 100 – 102 °C. R_f : 0.49 (Hexane:EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.63 (s, 1H), 8.58 (d, 1H, *J* = 8.37 Hz), 7.76 – 7.71 (m, 2H), 7.59 – 7.48 (m, 2H), 7.19 – 7.05 (m, 3H), 2.21 (s, 3H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 197.9, 169.1, 165.3 (d, J_{CF} = 254.6 Hz), 140.2, 134.6 (d, J_{CF} = 2.8 Hz), 134.2, 133.0, 132.5 (d, J_{CF} = 9.2 Hz), 123.3, 122.1, 121.7, 115.5 (d, J_{CF} = 22.1 Hz), 25.2 ppm. IR ν = 3221, 3070, 1662, 1595, 1479, 1289, 1225, 930.1, 847.9, 755.7, 599.8, 507.6 cm^{-1}; MS (EI, 70 eV) *m/z* (%): 257 (17, [M+]), 214 (100), 185 (15), 134 (19), 123 (25), 120 (30), 95 (34), 92 (16).

N-(2-(4-bromobenzoyl)phenyl)-acetamide[8] **(4n)** Method A. Offwhite, solid; 215 mg (0.68 mmol, yield: 62%). m.p.: 142 – 143 °C. R_f : 0.66 (hexane:EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.70 (s, 1H), 8.60 (d, 1H *J* = 8.37 Hz), 7.64-7.48 (m, 6H), 7.08 (t, 1H *J* = 7.19 Hz), 2.21 (s, 3H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 198.4, 169.1, 140.4, 137.3, 134.5, 133.1, 131.6, 131.3, 127.6, 122.9, 122.1, 121.6, 25.2 ppm. IR (ATR): ν_{max} = 3310, 3057, 1515, 1260, 757, 471 cm^{-}

[1]. MS (EI, 70 eV) *m/z* (%): 317 (26, [M+]), 276 (100), 196 (47), 167 (41), 157 (23), 134 (42), 120 (58), 92 (34).

N-(2-(3-chlorobenzoyl)phenyl)acetamide[8] **(4o)** Method A. Offwhite, solid; 233 mg (0.85 mmol, yield: 85%). m.p.: 76 – 82 °C. R_f : 0.76 (hexane:EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.75 (s, 1H), 8.60 (d, 1H, *J* = 8.37 Hz), 7.66-7.37 (m, 6H), 7.07 (t, 1H, *J* = 8.37 Hz), 2.20 (s, 3H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 198.0, 169.0, 140.5, 140.1, 134.6, 134.5, 133.2, 132.3, 129.5, 127.8, 122.6, 122.1, 121.5, 25.2 ppm. IR (ATR): ν_{max} = 3242, 3209, 3056, 1691, 1633, 1585, 1534, 1252, 752, 710 cm^{-1}. MS (EI, 70 eV) *m/z* (%): 273 (25 [M+]), 230 (100), 196 (50), 167 (16), 139 (18), 134 (25), 120 (50), 111 (27), 92 (26).

N-(2-(4-methoxybenzoyl)phenyl)acetamide[8] **(4p)** Method A. White, solid; 208 mg (0.78 mmol, yield: 78%). m.p. 115-121°C (lit.: 107-121°C). Rf: 0.25 (in Hexane:EtOAc = 1:1) ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.51 (s, 1H), 8.54 (d, 1H *J* = 8.37 Hz), 7.72 (d, 2H *J* = 8.85 Hz), 7.55 - 7.50 (m, 2H), 7.07 (t, 1H *J* = 7.58 Hz), 6.95 (d, 2H *J* = 8.85 Hz), 3.87 (s, 3H), 2.18 (s, 3H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 197.8, 169.0, 163.3, 139.7, 133.4, 132.7, 132.5, 130.8, 124.2, 122.0, 121.6, 113.6, 55.5, 25.1 ppm. IR (ATR): ν_{max} = 3307, 2927, 1671, 1646, 1497, 1253, 1020, 926, 758, 690, 598 cm^{-1} MS (EI, 70 eV): *m/z* (%): 269 (40, [M$^+$]), 226 (100), 219 (38), 135 (35), 92 (26).

***N*-(2-(thiophene-2-carbonyl)phenyl)-acetamide**[8] **(4q)** Method B. Yellow, oil; 78 mg (0.32 mmol, yield: 32%). Rf: 0.27 (in hexane:EtOAc = 3:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.25 (s, 1H), 8.52 (d, 1H *J* = 8.21 Hz), 7.80–7.74 (m, 2H), 7.57–7.51 (m, 2H), 7.17– 7.10 (m, 2H), 2.18 (s, 3H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 189.8, 168.9, 143.9, 139.1, 135.6, 134.9, 133.6, 131.6, 128.0, 124.2, 122., 121.8 ppm. IR (ATR): ν_{max} = 3320, 3091, 1692, 1614, 1507, 1406, 1261, 712, 645 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 245 (18, [M$^+$]), 202 (100), 170 (40), 134 (18), 119 (40), 111 (39).

N-(2-butyrylphenyl)acetamide[8] **(4r)** Method B. Offwhite, solid; 90 mg (0.44 mmol, yield:44%). m.p 43-46 °C (lit.: 46-47 °C). Rf: 0.75 (in hexane:EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ =

11.70 (s, 1H), 8.68 (d, 1H, *J* = 8.53 Hz), 7.86 (d, 1H, *J* = 7.90 Hz), 7.48 (t, 1H, *J* = 7.42 Hz), 7.05 (t, 1H, *J* = 7.42 Hz), 2.95 (t, 2H, *J* = 7.42 Hz), 2.18 (s, 3H), 1.71 (sextet, 2H, *J* = 7.42 Hz), 0.97 (t, 3H, *J* = 7.42 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 204.9, 169.3, 140.8, 134.6, 130.6, 122.1, 121.4, 120.6, 41.7, 25.4, 17.8, 13.6 ppm. IR (ATR): ν_{max} = 3214, 2961, 1691, 1646, 1586, 1521, 1467, 1362, 1199, 897, 750, 725, 515, 485 cm^{-1}. MS (EI, 70 eV): *m/z* (%): 205 (10, [M$^+$]), 162 (82), 120 (100), 92 (35), 65 (27).

N-(4-methoxy-2-(2-methoxybenzoyl)phenyl)-acetamide[8] **(4s)** Method B. Offwhite, solid; 98 mg (0.33 mmol, yield: 33%). m.p. 147-152 °C Rf: 0.57 (in Hexane:EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 12.06 (s, 1H), 8.42 (d, 1H, *J* = 2.53 Hz), 7.46 – 7.33 (m, 2H), 7.21 (dd, 1H, J_1 = 7.42 Hz J_2 = 1.74 Hz), 7.03 – 6.95 (m, 2H), 6.47 (dd, 1H, J_1 = 8.85 Hz J_2 = 2.53 Hz), 3.85 (s, 3H), 3.74 (s, 3H), 2.25 (s, 3H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 198.9, 169.8, 164.9, 156.2, 144.1, 136.8, 131.3, 129.4, 128.5, 120.3, 115.5, 111.2, 109.1, 103.7, 55.5, 25.6 ppm. IR (ATR): ν_{max} = 2921, 1694, 1580, 1510, 1431, 1239, 757, 625 cm^{-1} MS (EI, 70 eV): *m/z* (%): 299 (80), 256 (100), 242 (57), 226 (55), 164 (60), 150 (82), 135 (77), 123 (40), 92 (47), 77 (62).

N-(2-(2-fluorobenzoyl)-4-isopropylphenyl)-acetamide (4t) Method B. Brown, solid; 98 mg (0.36 mmol, yield: 36%). m.p. 88-90 °C (lit 162-163°C) Rf: 0.68 (in Hexane:EtOAc = 1:1) ^{1}H NMR (250 MHz, $CDCl_3$): δ = 11.12 (s, 1H), 8.55 (d, 1H, *J* = 8.69 Hz), 7.50-7.35 (m, 3H), 7.25 - 7.06 (m, 3H), 2.72 (sextet, *J* = 6.95 Hz), 2.16 (s, 3H), 1.07 (d, 6H, *J* = 6.95 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 196.9, 169.2, 161.5 (d, J_{CF} = 252.3 Hz), 142.7, 139.0, 133.5, 133.3 (d, J_{CF} = 8.3 Hz), 131.7 (d, J_{CF} = 2.3 Hz), 130.2 (d, J_{CF} = 2.8 Hz), 127.5 (d, J_{CF} = 14.3 Hz), 124.1 (d, JCF = 3.7 Hz), 122.3, 120.9, 116.2 (d, J_{CF} = 21.6 Hz), 33.2, 25.3, 23.6 ppm. IR (ATR): ν_{max} = 2962, 1664, 1609, 1491, 1271, 825, 760, 597 cm^{-1} MS (EI, 70 eV): 299 (30, [M$^+$]), 257 (27), 242 (100), 123 (34), 95 (20) *m/z* (%). HRMS: *m/z* [M + H]$^+$ calcd for $C_{18}H_{19}FNO_2$: 300.1400; found: 300.1408.

(2-aminophenyl)(phenyl)methanone[13] **(5a)** Method A. Brown, solid; 133 mg (0.56 mmol, yield: 56%). m.p.: 100 °C. R_f: 0.65 (Hexane:EtOAc = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.6 –7.43 (m, 6H), 7.26 (t, 1H, *J* = 7.27 Hz), 6.71 (d, 1H, *J* = 7.58 Hz), 6.57 (t, 1H, *J* = 7.11 Hz), 6.1 (s, 2H) ppm. ^{13}C NMR

(62.5 MHz, $CDCl_3$): δ = 199.0, 150.9, 140.0, 134.5, 134.2, 131.0, 129.1, 128.0, 118.1, 116.9, 115.4 ppm. IR ν = 3429, 3312, 1612, 1549, 1070, 935, 741, 700, 642, 428 cm^{-1}; MS (EI, 70 eV) *m/z* (%): 196 (100, [M+]), 120 (51), 105 (15), 92 (24), 77 (36), 65 (25), 51 (14).

(2-aminophenyl)(2-chlorophenyl)methanone (5b) Method A. Yellow, oil; 82 mg (0.35 mmol, yield: 35 %). R_f : 0.62 (Hexane:EtOAc = 1:1). ^1H NMR (250 MHz, $CDCl_3$): δ = 7.38–7.17 (m, 5H), 7.08 (dd, 1H, J_1 = 8.2 Hz J_2 = 1.3 Hz), 6.63 (d, 1H, *J* = 8.2 Hz), 6.49–6.42 (m, 1H), 6.20 (s, 2H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 197.2, 151.3, 139.8, 135.2, 134.6, 130.6, 130.3, 129.8, 128.3, 126.5, 117.4, 116.9, 115.7 ppm. IR ν = 3460, 3342, 2922, 1614, 1544, 1450, 1242, 930.1, 743.0, 636.6 cm^{-1}; MS (EI, 70 eV) *m/z* (%): 231 (32, [M+]), 196 (100), 167 (17), 139 (25), 120 (52), 111 (24), 92 (32), 65 (33).

(2-aminophenyl)(4-chlorophenyl)methanone[14] **(5c)** Method A. Yellow, solid; 107 mg (0.46 mmol, yield: 61%). m.p. 96-100 °C Rf: 0.63 (Hexane:EtOAc = 2:1) ^1H NMR (250 MHz, $CDCl_3$): δ = 7.51–7.48 (m, 2H), 7.35–7.28 (m, 3H), 7.23–7.17 (m, 1H), 6.64 (d, 1H, *J* = 8.37 Hz), 6.51 (t, 1H, *J* = 8.06 Hz), 5.99 (s, 2H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 197.6, 150.9, 138.3, 137.2, 134.4, 134.1 130.5, 128.3, 117.7, 117.0, 115.5 ppm. IR (ATR): ν_{max} = 3474, 3367, 1579, 1545, 1239, 1090, 923, 757, 661 cm^{-1} MS (EI, 70 eV): *m/z* (%):230 (100, [M^+]), 214 (15), 196 (23), 139 (25), 120 (50), 111 (45), 92 (42), 65 (47), 75 (20), 65 (47).

(2-aminophenyl)(3-chlorophenyl)-methanone[15] **(5d)** Method A. Yellow, solid; 130 mg (0.57 mmol, yield: 51%). m.p. 82-87 °C Rf: 0.64 (Hexane:EtOAc = 2:1) ^1H NMR (250 MHz, $CDCl_3$): δ = 7.52 (s, 1H), 7.42–7.17 (m, 5H), 6.64 (d, 1H, *J* = 8.37 Hz), 6.51 (t, 1H, *J* = 8.06 Hz), 6.06 (br s, 2H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 197.3, 151.1, 141.7, 134.6, 134.3, 134.2, 130.9, 129.4, 128.9, 127.1, 117.4, 117.0, 115.6 ppm. IR (ATR): ν_{max} = 3440, 3331, 1610, 1541, 1442, 1305, 1241, 944, 746, 709 cm^{-1} MS (EI, 70 eV): *m/z* (%): 230 (80, [M^+]), 196 (55), 167 (20), 139 (25), 120 (100), 111 (45), 92 (57), 65 (60).

(2-amino-3-methoxyphenyl)(4-chlorophenyl)-methanone (5e) Method B. Yellow, solid; 68 mg (0.26 mmol, yield: 26%). m.p. 82-88 °C Rf: 0.68 (Hexane:EtOAc = 2:1) ^1H NMR (250 MHz,

$CDCl_3$): δ = 7.59 (d, 2H, *J* = 8.37 Hz), 7.42 (d, 2H, *J* = 8.53 Hz), 7.02 (dd, 1H, J_1 = 8.21 Hz J_2 = 1.11 Hz), 6.88 (d, 1H, *J* = 7.74 Hz), 6.53 (t, 1H, J = 8.06 Hz), 6.39 (br s, 2H), 3.90 (s, 3H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 197.5, 147.2, 142.2, 138.5, 137.1, 130.5, 128.2, 125.5, 117.0, 113.9, 112.9, 55.7 ppm. IR (ATR): ν_{max} = 3455, 3342, 1545, 1449, 1221, 1082, 959, 730 cm^{-1} MS (EI, 70 eV): *m/z* (%): 261 (100, [M^+]), 246 (45), 211 (63), 183 (26), 139 (48), 11 (50). HRMS: *m/z* $[M + H]^+$ calcd for $C_{14}H_{13}ClNO_2$: 262.0635; found: 262.0633.

(2-amino-4-fluorophenyl)(phenyl)-methanone[16] (5f) Method B**.** Yellow, oil; 56 mg (0.26 mmol, yield: 26%). Rf: 0.52 (Hexane:EtOAc = 2:1) ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.61–7.43 (m, 5H), 6.42–6.26 (m, 3H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 198.0, 168.5 (d, J_{CF} = 253.2 Hz), 153.4 (d, J_{CF} = 12.9 Hz), 140.0, 137.5 (d, J_{CF} = 11.5 Hz), 131.0, 128.9, 128.1, 115.0, 103.6 (d, J_{CF} = 22.5 Hz), 102.4 (d, J_{CF} = 24.4 Hz) ppm. IR (ATR): ν_{max} = 3386, 2964, 1602, 1241, 931, 714, 658 cm^{-1} MS (EI, 70 eV): *m/z* (%): 214 (100, [M+]), 138 (73), 110 (18), 105 (116), 83 (20), 77 (45).

1-(2-aminophenyl)butan-1-one[17] (5g) Method B. Off-white, solid; 56 mg (0.34 mmol, yield: 34%). m.p. 40-45 °C Rf: 0.73 (Hexane:EtOAc = 2:1) ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.66 (dd, 1H, J_1 = 8.53 Hz J_2 = 1.58 Hz), 7.20–7.13 (m, 1H), 6.58-6.52 (m, 2H), 6.20 (s, 2H), 2.83 (t, 2H, *J* = 7.27 Hz), 1.67 (sextet, 2H, *J* = 7.42 Hz), 0.92 (t, 3H, *J* = 7.42 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 202.9, 150.2, 134.0, 131.2, 117.9, 117.3, 115.6, 41.1, 18.2, 13.9 ppm. IR (ATR): ν_{max} = 3436, 3323, 2956, 1616, 1204, 1160, 747 cm^{-1} MS (EI, 70 eV): *m/z* (%): 163 (30, [M+]), 120 (100), 92 (33), 65 (30).

(2-aminophenyl)(thiophen-2-yl)methanone[18] (5h) Method B. brown, oil; 49 mg (0.24 mmol, yield: 24%). Rf: 0.73 (Hexane:EtOAc = 2:1) ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.77 (dd, 1H, J_1 = 8.06 Hz J_2 = 1.58 Hz), 7.65 (dd, 1H, J_1 = 5.06 Hz J_2 = 1.11 Hz), 7.57 (dd, 1H, J_1 = 3.63 Hz J_2 = 0.95 Hz), 7.34–7.26 (m, 1H), 7.15–7.11 (m, 1H), 6.75–6.66 (m, 2H), 5.71 (s, 2H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 189.4, 149.8, 144.7, 133.8, 133.7, 132.8, 132.7, 127.5, 119.0, 116.9, 115.9 ppm. IR (ATR): ν_{max} = 3350, 2915, 1578, 1249, 1161, 719, 649 cm^{-1} MS (EI, 70 eV): *m/z* (%): 202 (100, [M+]), 170 (50), 119 (47), 111 (48), 92 (49), 65 (47).

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Supporting information

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

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