

# Synthesis of biaryl imino/keto carboxylic acid *via* aryl amide directed C-H activation reaction

Nana Zhang,<sup>a,c</sup> Qingzhen Yu,<sup>a</sup> Ruixue Chen,<sup>b</sup> Jianhui Huang,<sup>\*a,c</sup> Yeqing Xia<sup>a</sup> and Kang  
Zhao<sup>\*a</sup>

<sup>a</sup>Tianjin Key Laboratory for Modern Drug Delivery & High-Efficiency,  
School of Pharmaceutical Science and Technology, Tianjin University,  
92 Weijin Road, Nankai District, Tianjin, P. R. China, 300072  
email: [jhuang@tju.edu.cn](mailto:jhuang@tju.edu.cn) and [kangzhao@tju.edu.cn](mailto:kangzhao@tju.edu.cn)

<sup>b</sup>Tianjin University of Traditional Chinese Medicine

<sup>c</sup>Synergetic Innovation Center of Chemical Science and Engineering(Tianjin)

## Supporting Information

### Content

## General Information

Flash chromatography was performed on silica gel 100-200 m. The solvent system used was a gradient of petroleum ether/ethyl acetate, increasing in polarity to ethyl acetate. Thin layer chromatography (TLC) was performed on glass backed plates pre-coated with silica (GF254), which were developed using standard visualizing agents.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a 600 MHz BRUKER AVANCE spectrometer at 25 °C.  $^1\text{H}$ : Chemical shifts are reported in ppm with the solvent resonance as the internal standard ( $\text{CHCl}_3$ :  $\delta$  7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet, sept = septet), integration, coupling constants ( $J$ ) in Hz.  $^{13}\text{C}$  NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ( $\text{CDCl}_3$ :  $\delta$  77.0 ppm). High-resolution mass spectra (HRMS) recorded for accurate mass analysis, were performed on either a Q-TOF micro (Waters) spectrometer. Melting points were performed on recrystallised solids and recorded on a national standard melting point apparatus and are uncorrected.

**Table 1 Reaction condition screening**

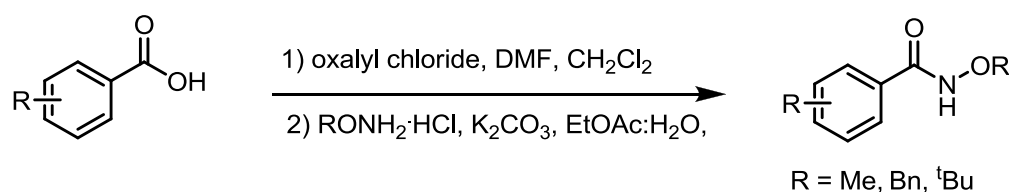
Entry	Catalyst	Oxidant	Additive	Solvent	Yield
1	Pd(OAc) <sub>2</sub>	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	-	DMSO	0%
2	Pd(OAc) <sub>2</sub>	<i>m</i> -CPBA	-	DMSO	0%
3	Pd(OAc) <sub>2</sub>	BQ	-	DMSO	<5%
4	Pd(OAc) <sub>2</sub>	Ag <sub>2</sub> O	-	DMSO	0%
5	Pd(OAc) <sub>2</sub>	TBHP	-	DMSO	67%
6	Pd(OAc) <sub>2</sub>	H <sub>2</sub> O <sub>2</sub>	-	DMSO	0%
7	Pd(OAc) <sub>2</sub>	TBHP	-	DMSO/Diglyme	53%
8	Pd(OAc) <sub>2</sub>	TBHP	-	DMSO/MeCN	40%
9	Pd(OAc) <sub>2</sub>	TBHP	-	DMSO/Dioxane	73%
10	Pd(OAc) <sub>2</sub>	TBHP	I <sub>2</sub>	DMSO/Dioxane	0%
11	Pd(OAc) <sub>2</sub>	TBHP	NaCl	DMSO/Dioxane	0%
12	Pd(OAc) <sub>2</sub>	TBHP	NaI	DMSO/Dioxane	0%
13	Pd(OAc) <sub>2</sub>	TBHP	NaBr	DMSO/Dioxane	0%
14	Pd(OAc) <sub>2</sub>	TBHP	CuCl <sub>2</sub>	DMSO/Dioxane	0%
15	Pd(OAc) <sub>2</sub>	TBHP	CuBr <sub>2</sub>	DMSO/Dioxane	0%
16	Pd(OAc) <sub>2</sub>	TBHP	Cu(OAc) <sub>2</sub>	DMSO/Dioxane	0%
17	Pd(OAc) <sub>2</sub>	TBHP	<sup>a</sup> BF <sub>3</sub> ·OEt <sub>2</sub>	DMSO/Dioxane	84%
18	PdCl <sub>2</sub>	TBHP	<sup>a</sup> BF <sub>3</sub> ·OEt <sub>2</sub>	DMSO/Dioxane	<5%
19	Pd(TFA) <sub>2</sub>	TBHP	<sup>a</sup> BF <sub>3</sub> ·OEt <sub>2</sub>	DMSO/Dioxane	76%
20	Pd <sub>2</sub> dba <sub>3</sub>	TBHP	<sup>a</sup> BF <sub>3</sub> ·OEt <sub>2</sub>	DMSO/Dioxane	29%

Reaction conditions: benzamide **1** (0.3 mmol), aldehyde **2** (0.9 mmol), Pd(cat) (10 mol%), TBHP (70% in H<sub>2</sub>O) (5.0 equiv), additive (1.0 equiv) at 130 °C in DMSO:dioxane 4:1 (1.5 mL, 0.2 M), 5-12 h. <sup>a</sup>0.4 equiv of BF<sub>3</sub>·OEt<sub>2</sub> was used.

## General Procedures

All the known amides were prepared following literature procedure<sup>1-4</sup> and the analytical data are agreed with those data which have been reported previously.

### General Procedure A: Synthesis of *N*-alkoxybenzamides

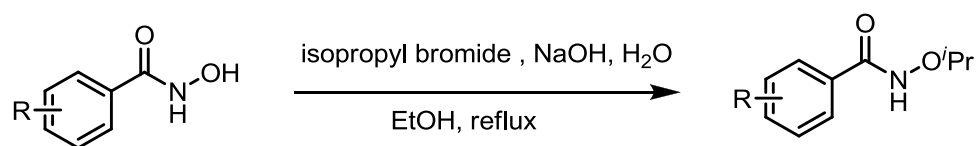


Following same procedure by Guimond *et. al*<sup>1</sup>

To a solution of the carboxylic acid (10 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.3 M) at 0 °C under N<sub>2</sub> was added dropwise oxalyl chloride (12 mmol) followed by a catalytic amount of DMF (2 drops). The reaction was allowed to stir at room temperature until completion (typically 4h). The solvent was then removed under reduce pressure to afford the corresponding crude acid chloride. Alkoxyamine hydrochloride (11 mmol) was added to a biphasic mixture of K<sub>2</sub>CO<sub>3</sub> (20 mmol) in a 2:1 mixture of EtOAc:H<sub>2</sub>O (0.2 M). The resulting solution was cooled to 0°C followed by addition of a solution unpurified acid chloride in a minimum amount of EtOAc dropwise. The flask containing the acid chloride was then rinsed with additional EtOAc. The reaction was stirring for 4h and slowly warmed up to room temperature. The two layers were separated and extracted with EtOAc (40 mL x 2). The combined organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel.

### General Procedure B: Synthesis of *N*-isopropoxybenzamides

The amide was prepared by following the procedure reported by A. Nickon *et al*<sup>5</sup>, and the analytical data are consistently agreed with those ones are reported in the literature.

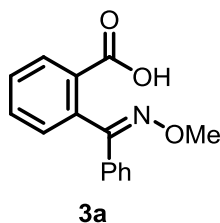


Following similar procedure reported by Nickon *et. al*<sup>5</sup>

Benzohydroxamic acid<sup>6</sup> (3 mmol) was added into a solution of sodium hydroxide (4.5 mmol) in 1.5 mL H<sub>2</sub>O, the mixture was warmed to 50 °C until the solids were dissolved, the resulting solution was added to isopropyl bromide (15 mmol) in absolute ethanol (6 mL), and the mixture was heated to reflux for 5 h. After the reaction was completed, the solvents were removed under reduced pressure. The residue was dissolved in EtOAc (20 mL), washed with H<sub>2</sub>O (15 mL x 2). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel.

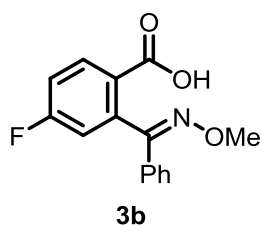
### General Procedure C: Synthesis of imino carboxylic acid and analogues

A solution of amide (0.3 mmol), aldehyde (1.2 mmol), Pd(OAc)<sub>2</sub> (10 mol%), TBHP (1.5 mmol) and BF<sub>3</sub>·OEt<sub>2</sub> (40 mol%) in DMSO/Dioxane (V:V = 4:1, 1.5 mL) was heated at 130 °C under air. The reaction was monitored by TLC. After the reaction was completed, the reaction mixture was allowed to cool down to room temperature and EtOAc (20 mL) was added. The resulting mixture was washed with water (10 mL x 3). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was removed under reduced pressure to provide the crude product. The purification was performed by flash column chromatography on silica gel.



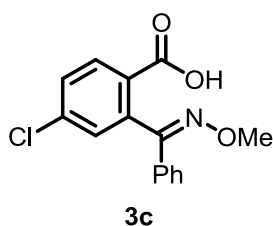
2-((Methoxyimino)(phenyl)methyl)benzoic acid (3a)

Following the general procedure C, imino carboxylic acid **3a** was isolated (64 mg, 84%) as a white solid: Mp 108-110 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 10.94 (br s, 1H, COOH), 8.14 (d, *J* = 7.5 Hz, 1H, ArH), 7.64 (td, *J* = 7.5, 1.0 Hz, 1H, ArH), 7.51 (td, *J* = 8.0, 1.0 Hz, 1H, ArH), 7.48 (d, *J* = 7.5 Hz, 2H, ArH), 7.35-7.30 (m, 3H, ArH), 7.23 (d, *J* = 7.5 Hz, 1H, ArH), 3.90 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 171.5, 156.6, 135.8, 135.7, 133.0, 130.9, 129.6, 129.2, 129.0, 128.7, 128.3, 127.2, 62.3; FTIR (KBr) 3064 (w), 2940 (w), 2826 (w), 1721 (s), 1573 (m), 1486 (m), 1443 (m), 1382 (m), 1328 (m), 1230 (s), 1139 (m), 1055 (s), 763 (m), 693 (s) cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>15</sub>H<sub>13</sub>NO<sub>3</sub>Na [M+Na]<sup>+</sup> 278.0793; found 278.0790.



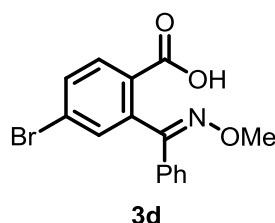
#### 4-Fluoro-2-((methoxyimino)(phenyl)methyl)benzoic acid (**3b**)

Following the general procedure C, imino carboxylic acid **3b** was isolated (42 mg, 51%) as an off-white solid: Mp 124-125 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 11.05 (br s, 1H, COOH), 8.16 (dd, *J* = 8.5, 5.5 Hz, 1H, ArH), 7.44 (d, *J* = 7.5 Hz, 2H, ArH), 7.35-7.30 (m, 3H, ArH), 7.18 (td, *J* = 8.0, 2.5 Hz, 1H, ArH), 6.94 (dd, *J* = 8.5, 2.5 Hz, 1H, ArH), 3.90 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 170.3, 165.0 (*J*<sub>C-F</sub> = 212.5 Hz), 155.3, 138.8 (*J*<sub>C-F</sub> = 7.5 Hz), 135.1, 133.7 (*J*<sub>C-F</sub> = 7.5 Hz), 129.4, 128.3, 127.0, 124.9 (*J*<sub>C-F</sub> = 2.5 Hz), 117.0 (*J*<sub>C-F</sub> = 18.0 Hz), 115.7 (*J*<sub>C-F</sub> = 18.0 Hz), 62.5; FTIR (KBr) 3045 (w), 2931 (w), 2813 (w), 1696 (s), 1580 (s), 1421 (m), 1304 (s), 1282 (s), 1226 (s), 1059 (s), 869 (m), 766 (m), 689 (s), 602 (s) cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>15</sub>H<sub>12</sub>FNO<sub>3</sub> [M+Na]<sup>+</sup> 296.0699; found 278.0700.



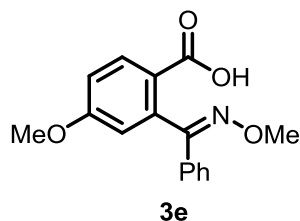
#### 4-Chloro-2-((methoxyimino)(phenyl)methyl)benzoic acid (**3c**)

Following the general procedure C, imino carboxylic acid **3c** was isolated (50 mg, 58%) as a brown solid: Mp 182-183 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 10.60 (br s, 1H, COOH), 8.06 (d, *J* = 8.5 Hz, 1H, ArH), 7.47 (d, *J* = 8.5 Hz, 1H, ArH), 7.43 (d, *J* = 7.0 Hz, 2H, ArH), 7.34-7.30 (m, 3H, ArH), 7.21 (s, 1H, ArH), 3.89 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 170.4, 155.1, 139.6, 137.5, 135.1, 132.4, 129.6, 129.4, 128.9, 128.4, 127.2, 127.0, 62.5; FTIR (KBr) 2931 (w), 2813 (w), 1696 (s), 1559 (m), 1422 (m), 1300 (s), 1274 (m), 1113 (m), 1058 (s), 841 (m), 691 (m) cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>15</sub>H<sub>12</sub><sup>35</sup>ClNO<sub>3</sub> [M+Na]<sup>+</sup> 312.0403; found 312.0406.



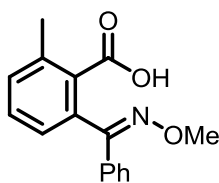
#### 4-Bromo-2-((methoxyimino)(phenyl)methyl)benzoic acid (**3d**)

Following the general procedure C, imino carboxylic acid **3d** was isolated (62 mg, 62%) as an off-white solid: Mp 195-197 °C; <sup>1</sup>H NMR (600 MHz, DMSO): δ 13.03 (br s, 1H, COOH), 7.92 (d, *J* = 8.5 Hz, 1H, ArH), 7.77 (dd, *J* = 8.5, 2.0 Hz, 1H, ArH), 7.43 (d, *J* = 2.0 Hz, 1H, ArH), 7.39-7.35 (m, 5H, ArH), 3.83 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, DMSO): δ 166.0, 155.0, 136.6, 134.9, 132.0, 131.8, 131.5, 129.6, 129.3, 128.3, 126.5, 125.9, 61.9; FTIR (KBr) 3058 (w), 2931 (w), 2814 (w), 1697 (s), 1584 (m), 1567 (m), 1421 (m), 1301 (s), 1272 (m), 1058 (s), 989 (m), 846 (m), 691 (s) cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>15</sub>H<sub>12</sub><sup>79</sup>BrNO<sub>3</sub> [M+Na]<sup>+</sup> 355.9898; found 355.9895.



#### 4-Methoxy-2-((methoxyimino)(phenyl)methyl)benzoic acid (**3e**)

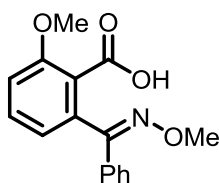
Following the general procedure C, imino carboxylic acid **3e** was isolated (60 mg, 70%) as a white solid: Mp 171-173 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 10.98 (br s, 1H, COOH), 8.11 (d, *J* = 9.0 Hz, 1H, ArH), 7.46 (d, *J* = 8.0 Hz, 2H, ArH), 7.33-7.28 (m, 3H, ArH), 6.97 (dd, *J* = 9.0, 3.0 Hz, 1H, ArH), 6.69 (d, *J* = 2.5 Hz, 1H, ArH), 3.90 (s, 3H, OCH<sub>3</sub>), 3.85 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 170.6, 163.3, 156.4, 138.3, 135.5, 133.4, 129.1, 128.2, 127.0, 120.6, 114.9, 113.7, 62.4, 55.6; FTIR (KBr) 2933 (w), 2812 (w), 1682 (s), 1597 (s), 1304 (m), 1242 (s), 1060 (s), 1030 (m), 768 (m), 602 (m) cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>16</sub>H<sub>15</sub>NO<sub>4</sub> [M+Na]<sup>+</sup> 308.0899; found 308.0899.



**3f**

### 2-((Methoxyimino)(phenyl)methyl)-6-methylbenzoic acid (**3f**)

Following the general procedure C, imino carboxylic acid **3f** was isolated (52 mg, 64%) as a brown solid: Mp 143-145 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 10.75 (br s, 1H, COOH), 7.47 (d, *J* = 7.0 Hz, 2H, ArH), 7.42 (t, *J* = 7.5 Hz, 1H, ArH), 7.33 (d, *J* = 7.0 Hz, 1H, ArH), 7.32-7.30 (m, 3H, ArH), 7.01 (d, *J* = 7.5 Hz, 1H, ArH), 3.90 (s, 3H, OCH<sub>3</sub>), 2.54 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 172.8, 156.6, 137.7, 135.9, 133.9, 131.5, 131.0, 130.7, 129.3, 128.2, 127.6, 126.7, 62.2, 21.0; FTIR (KBr) 3050 (w), 2947 (w), 1704 (s), 1587 (m), 1425 (m), 1266 (s), 1050 (s), 1038 (m), 914 (m), 787 (m), 772 (m), 693 (s) cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>16</sub>H<sub>15</sub>NO<sub>3</sub> [M+Na]<sup>+</sup> 292.0950; found 292.0949.

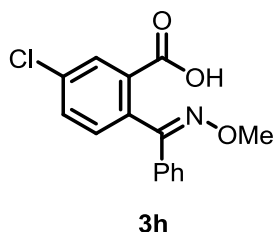


**3g**



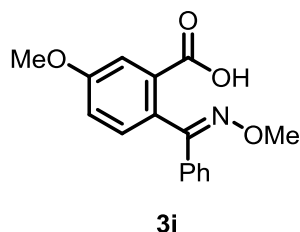
### 2-Methoxy-6-((methoxyimino)(phenyl)methyl)benzoic acid (**3g**)

Following the general procedure C, imino carboxylic acid **3g** was isolated (45 mg, 53%) as a white solid: Mp 134-135 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 7.55 (t, *J* = 8.0 Hz, 1H, ArH), 7.47 (d, *J* = 8.0 Hz, 2H, ArH), 7.32-7.28 (m, 3H, ArH), 7.08 (d, *J* = 8.5 Hz, 1H, ArH), 6.85 (d, *J* = 7.5 Hz, 1H, ArH), 4.01 (s, 3H, OCH<sub>3</sub>), 3.92 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 167.2, 157.6, 156.2, 136.9, 135.5, 132.7, 129.3, 128.2, 127.2, 122.1, 119.7, 111.9, 62.3, 56.5; FTIR (KBr) 2931 (w), 2818 (w), 1686 (s), 1587 (m), 1467 (m), 1309 (m), 1274 (s), 1056 (s), 765 (m), 687 (m) cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>16</sub>H<sub>15</sub>NO<sub>4</sub> [M+Na]<sup>+</sup> 308.0899; found 308.0904.



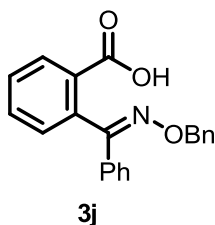
### 5-Chloro-2-((methoxyimino)(phenyl)methyl)benzoic acid (**3h**)

Following the general procedure C, imino carboxylic acid **3h** was isolated (47 mg, 54%) as an off-white solid: Mp 148-150 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 9.83 (br s, 1H, COOH), 8.10 (d, *J* = 2.0 Hz, 1H, ArH), 7.61 (dd, *J* = 8.0, 2.0 Hz, 1H, ArH), 7.43 (d, *J* = 8.0 Hz, 2H, ArH), 7.35-7.30 (m, 3H, ArH), 7.16 (d, *J* = 8.0 Hz, 1H, ArH), 3.89 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 170.1, 155.5, 135.03, 134.8, 133.9, 133.1, 131.0, 130.9, 130.6, 129.4, 128.4, 127.0, 62.4; FTIR (KBr) 3099 (w), 2935 (w), 2816 (w), 1697 (s), 1568 (m), 1406 (m), 1293 (m), 1248 (s), 1056 (s), 883 (m), 692 (s) cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>15</sub>H<sub>12</sub><sup>35</sup>ClNO<sub>3</sub>Na [M+Na]<sup>+</sup> 312.0403; found 312.0399.



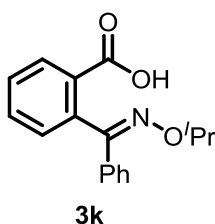
### 5-Methoxy-2-((methoxyimino)(phenyl)methyl)benzoic acid (**3i**)

Following the general procedure C, imino carboxylic acid **3i** was isolated (62 mg, 72%) as a white solid: Mp 145-146 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 10.55 (br s, 1H, COOH), 7.60 (d, *J* = 2.5 Hz, 1H, ArH), 7.45 (d, *J* = 7.0 Hz, 2H, ArH), 7.33-7.28 (m, 3H, ArH), 7.16-7.11 (m, 2H, ArH), 3.89 (s, 3H, OCH<sub>3</sub>), 3.88 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 171.1, 159.5, 156.3, 136.1, 130.9, 130.4, 129.1, 128.2, 127.6, 127.2, 119.1, 115.3, 62.2, 55.6; FTIR (KBr) 2932 (w), 1689 (s), 1606 (m), 1502 (m), 1420 (m), 1286 (s), 1235 (m), 1054 (s), 834 (m), 693 (m) cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>16</sub>H<sub>15</sub>NO<sub>4</sub> [M+Na]<sup>+</sup> 308.0899; found 308.0901.



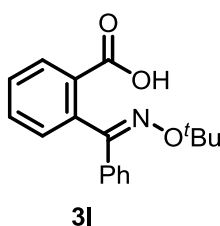
### 2-((Benzyloxyimino)(phenyl)methyl)benzoic acid (**3j**)

Following the general procedure C, imino carboxylic acid **3j** was isolated (76 mg, 77%) as an off-white solid: Mp 108-110 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 10.07 (br s, 1H, COOH), 8.11 (d, *J* = 7.5 Hz, 1H, ArH), 7.62 (t, *J* = 7.5 Hz, 1H, ArH), 7.49 (t, *J* = 7.5 Hz, 1H, ArH), 7.43 (d, *J* = 7.0 Hz, 2H, ArH), 7.32-7.28 (m, 3H, ArH), 7.26-7.14 (m, 6H, ArH), 5.14 (s, 2H, CH<sub>2</sub>), <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 170.9, 156.9, 138.1, 136.0, 135.8, 133.0, 131.0, 129.5, 129.2, 128.7, 128.6, 128.2, 128.1, 127.9, 127.5, 127.1, 76.4; FTIR (KBr) 3030 (w), 2923 (w), 1695 (s), 1597 (w), 1453 (m), 1302 (m), 978 (m), 768 (m), 694 (s) cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>21</sub>H<sub>17</sub>NO<sub>3</sub> [M+Na]<sup>+</sup> 354.1106; found 354.1111.



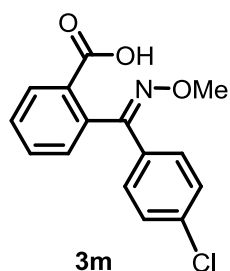
### 2-((Isopropoxyimino)(phenyl)methyl)benzoic acid (**3k**)

Following the general procedure C, imino carboxylic acid **3k** was isolated (65 mg, 76%) as a white solid: Mp 119-120 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 11.38 (br s, 1H, COOH), 8.07 (d, *J* = 7.5 Hz, 1H, ArH), 7.60 (t, *J* = 7.0 Hz, 1H, ArH), 7.49-7.47 (m, 3H, ArH), 7.32-7.29 (m, 3H, ArH), 7.18 (d, *J* = 7.5 Hz, 1H, ArH), 4.43-4.39 (m, 1H, OCH), 1.16 (d, *J* = 6.0 Hz, 6H, CH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 171.7, 155.2, 136.4, 135.9, 132.7, 130.5, 129.6, 129.5, 128.8, 128.3, 128.2, 127.2, 76.1, 21.5; **3k** FTIR (KBr) 3060 (w), 2975 (m), 1698 (s), 1573 (m), 1409 (m), 1297 (s), 1278 (s), 977 (s), 768 (s), 695 (s) cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>17</sub>H<sub>17</sub>NO<sub>3</sub> [M+Na]<sup>+</sup> 306.1106; found 306.1108.



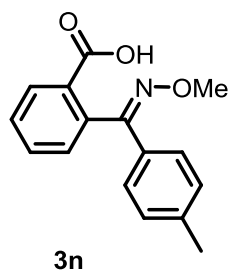
### 2-((*tert*-Butoxyimino)(phenyl)methyl)benzoic acid (**3l**)

Following the general procedure C, imino carboxylic acid **3l** was isolated (41 mg, 46%) as a white solid: Mp 158-159 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 11.32 (br s, 1H, COOH), 8.03 (d, *J* = 8.0 Hz, 1H, ArH), 7.59 (t, *J* = 7.5 Hz, 1H, ArH), 7.49 (d, *J* = 7.5 Hz, 2H, ArH), 7.46 (t, *J* = 7.5 Hz, 1H, ArH), 7.31-7.30 (m, 3H, ArH), 7.16 (d, *J* = 7.5 Hz, 1H, ArH), 1.23 (s, 9H, CH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 171.6, 154.1, 136.8, 135.8, 132.5, 130.3, 129.9, 129.6, 128.7, 128.1, 128.1, 127.1, 79.4, 27.5; FTIR (KBr) 3066 (w), 2975 (m), 1692 (s), 1679 (s), 1596 (m), 1414 (m), 1301 (m), 1281 (m), 961 (m), 768 (m), 695 (m) cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>18</sub>H<sub>19</sub>NO<sub>3</sub> [M+Na]<sup>+</sup> 320.1263; found 320.1265.



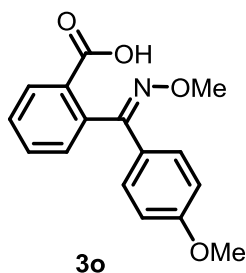
### 2-((4-Chlorophenyl)(methoxyimino)methyl)benzoic acid (**3m**)

Following the general procedure C, imino carboxylic acid **3m** was isolated (49 mg, 56%) as an off-white solid: Mp 162-164 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 10.79 (br s, 1H, COOH), 8.03 (d, *J* = 7.5 Hz, 1H, ArH), 7.55 (t, *J* = 7.0 Hz, 1H, ArH), 7.42 (t, *J* = 7.5 Hz, 1H, ArH), 7.29 (d, *J* = 8.5 Hz, 2H, ArH), 7.18 (d, *J* = 8.5 Hz, 2H, ArH), 7.11 (d, *J* = 7.5 Hz, 1H, ArH), 3.79 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 171.3, 155.6, 135.3, 135.2, 134.3, 133.2, 131.1, 129.5, 128.9, 128.7, 128.5, 128.3, 62.4; FTIR (KBr) 3015 (w), 2946 (w), 1693 (s), 1571 (m), 1490 (m), 1412 (m), 1298 (m), 1274 (m), 1046 (s), 830 (m), 772 (m) cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>15</sub>H<sub>12</sub><sup>35</sup>ClNO<sub>3</sub>Na [M+Na]<sup>+</sup> 312.0403; found 312.0398.



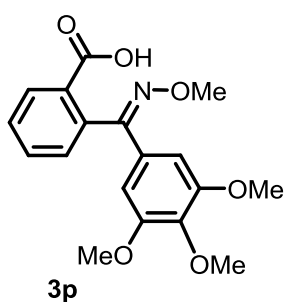
### 2-((Methoxyimino)(p-tolyl)methyl)benzoic acid (**3n**)

Following the general procedure C, imino carboxylic acid **3n** was isolated (64 mg, 79%) as an off-white solid: Mp 148-150 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 10.66 (br s, 1H, COOH), 8.12 (d, *J* = 8.0 Hz, 1H, ArH), 7.64 (t, *J* = 7.5 Hz, 1H, ArH), 7.50 (t, *J* = 7.5 Hz, 1H, ArH), 7.36 (d, *J* = 8.0 Hz, 2H, ArH), 7.22 (d, *J* = 7.5 Hz, 1H, ArH), 7.12 (d, *J* = 8.0 Hz, 2H, ArH), 3.89 (s, 3H, OCH<sub>3</sub>), 2.35 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 171.4, 156.6, 139.2, 135.9, 133.0, 133.0, 130.9, 129.6, 129.0, 129.0, 128.6, 127.1, 62.2, 21.3; FTIR (KBr) 3007 (w), 2934 (w), 1692 (s), 1574 (m), 1450 (m), 1408 (m), 1303 (s), 1273 (m), 1050 (s), 977 (m), 822 (m), 736 (m) cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>16</sub>H<sub>15</sub>NO<sub>3</sub> [M+Na]<sup>+</sup> 292.0950; found 292.0947.



### 2-((Methoxyimino)(4-methoxyphenyl)methyl)benzoic acid (**3o**)

Following the general procedure C, imino carboxylic acid **3o** was isolated (69 mg, 81%) as a white solid: Mp 134-136 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 10.49 (br s, 1H, COOH), 8.11 (dd, *J* = 8.0, 1.0 Hz, 1H, ArH), 7.63 (td, *J* = 7.5, 1.0 Hz, 1H, ArH), 7.49 (td, *J* = 8.0, 1.0 Hz, 1H, ArH), 7.38 (d, *J* = 9.0 Hz, 2H, ArH), 7.22 (dd, *J* = 7.5, 1.0 Hz, 1H, ArH), 6.83 (d, *J* = 9.0 Hz, 2H, ArH), 3.87 (s, 3H, OCH<sub>3</sub>), 3.80 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 171.3, 160.5, 156.2, 135.9, 132.9, 130.8, 129.5, 129.0, 128.6, 128.5, 128.4, 113.7, 62.1, 55.3; FTIR (KBr) 3045 (w), 2929 (w), 1693 (s), 1605 (s), 1511 (s), 1416 (w), 1302 (s), 1249 (s), 1162 (m), 1035 (m), 1023 (m), 841 (m), 765 (m), 589 (m) cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>16</sub>H<sub>15</sub>NO<sub>4</sub> [M+Na]<sup>+</sup> 308.0899; found 308.0903.

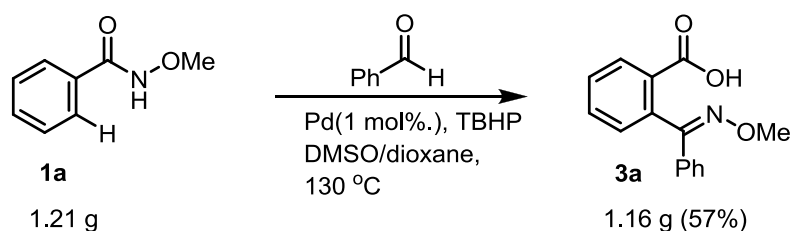


### 2-((Methoxyimino)(3,4,5-trimethoxyphenyl)methyl)benzoic acid (**3p**)

Following the general procedure C, imino carboxylic acid **3p** was isolated (85 mg, 82%) as a white solid: Mp 173-175 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 11.46 (br s, 1H, COOH), 8.11 (d, *J* = 8.0 Hz, 1H, ArH), 7.64 (t, *J* = 7.5 Hz, 1H, ArH), 7.51 (t, *J* = 7.5 Hz, 1H, ArH), 7.21 (d, *J* = 7.5 Hz, 1H, ArH), 6.68 (s, 2H, ArH), 3.88 (s, 3H,

OCH<sub>3</sub>), 3.84 (s, 3H, OCH<sub>3</sub>), 3.77 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 171.3, 156.2, 153.0, 139.3, 135.3, 132.9, 131.3, 130.8, 129.6, 129.1, 128.8, 104.7, 62.3, 60.9, 56.1; FTIR (KBr) 3010 (w), 2935 (w), 1693 (s), 1575 (s), 1505 (s), 1462 (m), 1410 (s), 1351 (s), 1143 (s), 1048 (s), 1009 (s), 767 (m), 717 (m) cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>18</sub>H<sub>19</sub>NO<sub>6</sub> [M+Na]<sup>+</sup> 368.1110; found 368.1103.

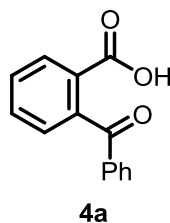
#### General procedure D: Gram-scale synthesis of imino benzoic acid



A solution of amide **1a** (8 mmol, 1.2 g), aldehyde (32 mmol, 3.2 mL), Pd(OAc)<sub>2</sub> (1 mol%, 18 mg), TBHP (40 mmol) and BF<sub>3</sub>·OEt<sub>2</sub> (40 mol%, 404 μl) in DMSO/Dioxane (V:V = 4:1, 40 mL) was heated at 130 °C under air for 7 h. The reaction mixture was allowed to cool down to room temperature and EtOAc (100 mL) was added. The resulting mixture was washed with water (50 mL x 3). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was removed under reduced pressure to provide the crude product. The purification was performed by flash column chromatography on silica gel. Following the above procedure C, acid **3a** was obtained (1.16 g, 57%) as a white solid.

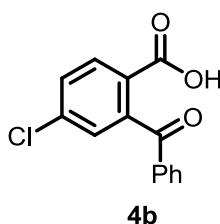
#### General procedure E: Synthesis of ketobenzoic acid

A solution of amide (0.3 mmol), aldehyde (1.2 mmol), Pd(OAc)<sub>2</sub> (10 mol%), TBHP (1.5 mmol) and BF<sub>3</sub>·OEt<sub>2</sub> (40 mol%) in DMSO/Dioxane (V:V = 4:1, 1.5 mL) was heated at 130 °C under air. After the reaction completed, conc. HCl (250 μL, 10.0 eq.) was added at 100 °C. Then the mixture was continually heated at 100 °C until completion. After cooling to room temperature, H<sub>2</sub>O (30 mL) was added and extracted with EtOAc (20 mL x 3). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated and purified by column chromatography on silica gel to give the carboxyl acid.



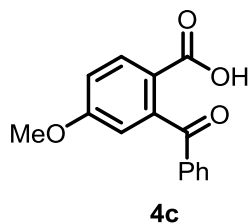
### 2-Benzoylbenzoic acid (4a)

Following the general procedure E, acid **4a** was obtained (55 mg, 81% from **3a** and 48 mg, 71% from **3k** as a white solid: Mp 131-133 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 10.37 (br s, 1H, COOH), 8.06 (d, *J* = 8.0 Hz, 1H, ArH), 7.70 (d, *J* = 8.0 Hz, 2H, ArH), 7.65 (t, *J* = 7.5 Hz, 1H, ArH), 7.55 (t, *J* = 7.5 Hz, 1H, ArH), 7.52 (t, *J* = 7.5 Hz, 1H, ArH), 7.39 (t, *J* = 7.5 Hz, 2H, ArH), 7.36 (d, *J* = 7.5 Hz, 1H, ArH); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 197.1, 170.9, 142.6, 137.0, 133.21, 133.19, 130.9, 129.5, 129.4, 128.5, 128.0, 127.7; HRMS (ESI) *m/z* calcd for C<sub>14</sub>H<sub>10</sub>NO<sub>3</sub> [M+Na]<sup>+</sup> 249.0528; found 249.0528.



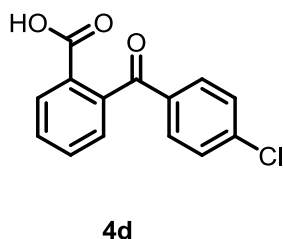
### 2-Benzoyl-4-chlorobenzoic acid (4b)

Following the general procedure E, acid **4b** was obtained (39 mg, 50%) as a white solid: Mp 175-177 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 8.50 (br s, COOH), 8.01 (d, *J* = 8.5 Hz, 1H, ArH), 7.70 (d, *J* = 7.5 Hz, 2H, ArH), 7.56 (t, *J* = 7.0 Hz, 1H, ArH), 7.52 (d, *J* = 8.5 Hz, 1H, ArH), 7.42 (t, *J* = 7.5 Hz, 2H, ArH), 7.34 (s, 1H, ArH); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 195.3, 169.7, 144.2, 140.1, 136.4, 133.5, 132.4, 129.7, 129.4, 128.6, 127.9, 126.1; The analytical data are consistently agreed with those have been previously reported in the literature.<sup>7</sup>



### 2-Benzoyl-4-methoxybenzoic acid (4c)

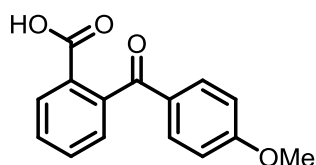
Following the general procedure E, acid **4c** was obtained (43 mg, 56%) as a white solid: Mp 179-180 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 9.15 (br s, 1H, COOH), 8.02 (d, *J* = 8.5 Hz, 1H, ArH), 7.70 (d, *J* = 7.5 Hz, 2H, ArH), 7.52 (t, *J* = 7.5 Hz, 1H, ArH), 7.39 (t, *J* = 7.5 Hz, 2H, ArH), 7.00 (dd, *J* = 8.5, 2.5 Hz, 1H, ArH), 6.81 (d, *J* = 2.5 Hz, 1H, ArH), 3.85 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 196.7, 170.2, 163.5, 145.1, 136.8, 133.2, 133.1, 129.4, 128.4, 119.7, 114.7, 112.9, 55.7; FTIR (KBr) 2924 (w), 2853 (w), 1683 (s), 1596 (s), 1428 (m), 1332 (m), 1313 (m), 1244 (s), 1022 (m), 852 (m), 703 (m), 606 (m) cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>15</sub>H<sub>12</sub>NO<sub>4</sub> [M+Na]<sup>+</sup> 279.0633; found 279.0636.



### 2-(4-Chlorobenzoyl)benzoic acid (4d)

Following the general procedure E, acid **4d** was obtained (42 mg, 54%) as a white solid: Mp 142-144 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 8.09 (d, *J* = 8.0 Hz, 1H, ArH), 7.68 (t, *J* = 7.5 Hz, 1H, ArH), 7.65 (d, *J* = 8.5 Hz, 2H, ArH), 7.58 (t, *J* = 7.5 Hz, 1H, ArH), 7.38 (d, *J* = 8.5 Hz, 2H, ArH), 7.35 (d, *J* = 7.5 Hz, 1H, ArH); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 195.9, 170.4, 142.1, 139.7, 135.4, 133.4, 131.0, 130.7, 129.8, 128.8, 127.8, 127.6; The analytical data are consistently agreed with those have been previously reported in the literature.<sup>7</sup>





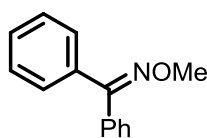
**4e**

### 2-(4-Methoxybenzoyl)benzoic acid (**4e**)

Following the general procedure E, acid **4e** was obtained (61 mg, 80%) as a white solid: Mp 153-155 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 9.80 (br s, 1H, COOH), 8.06 (d, *J* = 8.0 Hz, 1H, ArH), 7.68 (d, *J* = 8.5 Hz, 2H, ArH), 7.63 (t, *J* = 7.5 Hz, 1H, ArH), 7.53 (t, *J* = 7.5 Hz, 1H, ArH), 7.33 (d, *J* = 7.5 Hz, 1H, ArH), 6.87 (d, *J* = 8.5 Hz, 2H, ArH), 3.83 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 195.9, 170.8, 163.7, 142.8, 133.0, 131.9, 130.9, 130.7, 129.3, 127.9, 127.7, 113.8, 55.5; The analytical data are consistently agreed with those have been previously reported in the literature.<sup>7</sup>

### General procedure F: Synthesis of biaryl imino **5a**

To a solution of (*E*)-2-((methoxyimino)(phenyl)methyl)benzoic acid (77 mg, 0.3 mmol) in NMP (N-Methylpyrrolidone, 0.6 mL) was added Cu<sub>2</sub>O (11 mg, 25 mol%) and 1,10-Phenanthroline (27 mg, 50 mol%). Then the mixture was heated at 170 °C for 0.5 h. After cooling to room temperature, H<sub>2</sub>O (30 mL) was added and extracted with EtOAc (20 mL x 3). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated and purified by column chromatography on silica gel to give the decarboxylated product **5a** as a colorless oil (56 mg, 83%).



**5a**

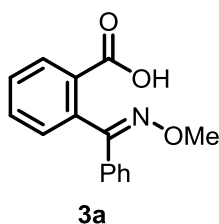
### Benzophenone *O*-methyl oxime (**5a**)

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 7.48 (d, *J* = 7.0 Hz, 2H, ArH), 7.43-7.40 (m, 3H, ArH), 7.34-7.28 (m, 5H, ArH), 3.97 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): 156.7,

136.4, 133.3, 129.3, 129.2, 128.8, 128.3, 128.1, 127.9, 62.4; The analytical data are consistently agreed with those have been previously reported in the literature.<sup>8</sup>

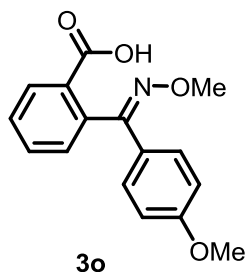
### General Procedure G: Synthesis of imino carboxylic acid and analogues using alcohols

A solution of amide (0.3 mmol), alcohol (1.8 mmol), Pd(OAc)<sub>2</sub> (10 mol%), TBHP (2.4 mmol) and BF<sub>3</sub>·OEt<sub>2</sub> (40 mol%) in DMSO/Dioxane (V:V = 4:1, 1.5 mL) was heated at 130 °C under air. The reaction was monitored by TLC. After the reaction was completed, the reaction mixture was allowed to cool down to room temperature and EtOAc (20 mL) was added. The resulting mixture was washed with water (10 mL x 3). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was removed under reduced pressure to provide the crude product. The purification was performed by flash column chromatography on silica gel.



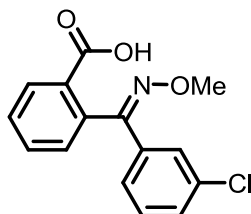
### 2-((methoxyimino)(phenyl)methyl)benzoic acid (3a)

Following the general procedure G, imino carboxylic acid **3a** was isolated (41 mg, 54%) as a white solid: Mp 108-110 °C. The analytical data are consistently agreed with those have been reported previously.



### 2-((Methoxyimino)(4-methoxyphenyl)methyl)benzoic acid (3o)

Following the general procedure G, imino carboxylic acid **3o** was isolated (51 mg, 60%) as a white solid: Mp 134-136 °C. The analytical data are consistently agreed with those have been reported previously.



**3s**

### 2-((3-Chlorophenyl)(methoxyimino)methyl)benzoic acid (**3s**)

Following the general procedure G, imino carboxylic acid **3s** was isolated (28 mg, 32%) as an off-white solid: Mp 105-106 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.08 (br s, 1H, COOH), 8.15 (d,  $J = 8.0$  Hz, 1H, ArH), 7.66 (t,  $J = 7.5$  Hz, 1H, ArH), 7.53 (t,  $J = 7.5$  Hz, 1H, ArH), 7.50 (s, 1H, ArH), 7.31-7.29 (m, 2H, ArH), 7.24-7.20 (m, 2H, ArH), 3.90 (s, 3H,  $\text{OCH}_3$ );  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.1, 155.4, 137.6, 135.1, 134.4, 133.2, 131.1, 129.5, 129.5, 129.2, 129.0, 128.7, 126.9, 125.3, 62.5; FTIR (KBr) 2962 (w), 2932 (w), 1686 (s), 1573 (m), 1417 (m), 1307 (m), 1279 (m), 1055 (m), 994 (m), 895 (m), 727 (m), 696 (m)  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{12}^{35}\text{ClNO}_3\text{Na}$   $[\text{M}+\text{Na}]^+$  312.0403; found 312.0407.

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## Spectroscopic data

