Palladium-Free Copper-Catalyzed Sonogashira Cross-Coupling at Room Temperature

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Abstract: We have developed an efficient method for the palladium-free copper-catalyzed Sonogashira cross-coupling of o-iodoacetanilide derivatives with alkynes at room temperature; the corresponding coupling products were obtained in good to excellent yields using copper(I) iodide/N-methylpyrrolidine-2-carboxamide as the catalyst. This inexpensive catalyst system has high tolerance towards various functional groups in the substrates. This represents the lowest reaction temperatures for copper-catalyzed Sonogashira cross-coupling thus far.

Key words: Sonogashira reaction, cross-coupling, copper catalysis, N,N-ligand, room temperature

Many antimycotics,1 antibiotics,2 liquid crystals, polymers, and optical or electronic materials3 have been synthesized via the Sonogashira reaction4 of terminal alkynes and aryl or vinyl halides; this palladium and copper cocatalyzed coupling is a popular strategy for the construction of C(sp2)–C(sp) bonds. However, the drawbacks of the catalyst systems, such as air sensitivity, high cost, and toxicity, limit their applications for industrial processes, hence it is highly desirable to develop readily available and inexpensive catalyst systems instead of palladium catalysts to promote the coupling of terminal alkynes and aryl or vinyl halides.

During the last decade, several examples involving nickel-5 and copper-catalyzed6 Sonogashira reactions have been reported, but high temperatures (80–130 °C) and long times were required. In particular, cyclic indoles were the major products and only small amounts of o-alkynyltrifluoroacetanilides were obtained when o-halo trifluoroacetanilides were used as the starting materials [Scheme 1 (a)].6e–h In fact, the o-alkynyltrifluoroacetanilides are important intermediates for the construction of diverse novel molecules, for example palladium-catalyzed

Scheme 1 (a) Copper-catalyzed coupling of o-halotrifluoroacetanilides with terminal alkynes; palladium-catalyzed synthesis of (b) 2-substituted 3-alkynylindoles or 2-substituted 3-acylindoles7a and (c) 12-acylindolo[1,2-c]quinazolines7b using o-alkynyltrifluoroacetanilides as the starting materials

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Table 1  Copper-Catalyzed Sonogashira Cross-Coupling Reaction of \(N\)-(2-Iodophenyl)trifluoro- (1a) and \(N\)-(2-Iodophenyl)acetamide (1d) with Phenylacetylene (2a): Optimization of the Catalysis Conditions\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Catalyst</th>
<th>Ligand</th>
<th>Base</th>
<th>Isolated yield (%)</th>
<th>3a</th>
<th>4a</th>
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<td>CF(_3)</td>
<td>CuI</td>
<td>A</td>
<td>Cs(_2)CO(_3)</td>
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<td>0</td>
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<tr>
<td>2</td>
<td>CF(_3)</td>
<td>CuI</td>
<td>B</td>
<td>Cs(_2)CO(_3)</td>
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<td>0</td>
<td></td>
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<tr>
<td>3</td>
<td>CF(_3)</td>
<td>CuI</td>
<td>C</td>
<td>Cs(_2)CO(_3)</td>
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<td>0</td>
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<td>Cs(_2)CO(_3)</td>
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<tr>
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<td>CF(_3)</td>
<td>CuI</td>
<td>E</td>
<td>Cs(_3)CO(_3)</td>
<td>75</td>
<td>trace</td>
<td></td>
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<tr>
<td>6</td>
<td>CF(_3)</td>
<td>CuI</td>
<td>F</td>
<td>Cs(_2)CO(_3)</td>
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<td>0</td>
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<tr>
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<td>G</td>
<td>Cs(_2)CO(_3)</td>
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<td>0</td>
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<td>8</td>
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<td>CuI</td>
<td>G</td>
<td>Cs(_2)CO(_3)</td>
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<tr>
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<td>CF(_3)</td>
<td>CuI(^c)</td>
<td>G(^d)</td>
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<td>G(^d)</td>
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<td>K(_3)PO(_4)</td>
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<tr>
<td>18</td>
<td>CF(_3)</td>
<td>CuI</td>
<td>G</td>
<td>K(_2)CO(_3)</td>
<td>61</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: \(o\)-iodoacetanilide derivative 1 (0.5 mmol), phenylacetylene (2a, 0.75 mmol), catalyst (0.15 mmol), ligand (0.5 mmol), base (1.25 mmol), solvent (2 mL), \(N_2\), 25 °C, 6 h.

\(^b\) Reaction temperature: 40 °C.

\(^c\) Catalyst (0.05 mmol), ligand (0.1 mmol).

\(^d\) Reaction time: 12 h.

\(^e\) Reaction temperature: 80 °C.
N-phenyl-3-alkynyltrifluoroacetanilides and inhibit the cyclization of the internal alkynes to indoles, hence, we initialized the optimization of the catalysis conditions as shown in Table 1. Several ligands, N,N′-dimethylethylendiamine A (entry 1),8 amino acids B–E (entries 2–5),9 rac-BINOL F (entry 6),10 and N-methylpyrrolidine-2-carboxamide hydrochloride G11 (entry 7) (1 equiv relative to o-iodotrifluoroacetanilide) were screened using 30 mol% copper(I) iodide as the copper source, cesium carbonate as the base and N,N-dimethylformamide as the solvent. N-Methylpyrrolidine-2-carboxamide exhibited the best activity (90% yield of 3a, entry 7). No cyclic product 4a was observed in the reaction of N-(2-iophenyl)trifluoroacetanamide (1a) with phenylacetylene (2a) even when the reaction time was extended to 12 hours under the same conditions (entry 7). The coupling yield greatly decreased to 10% when the NHCOClF3 group in o-iodotrifluoroacetanilide 1a was replaced with NHCOMe to give o-iodotrifluoroacetanilide 1b (90% yield of 3a, entry 7).

We studied the effect of copper salts (compare entries 7 and 11–15) and copper(I) iodide was found to be the best catalyst. The base also influences the reaction process and cesium carbonate provided the highest yields (compare entries 7 and 16–18). Other solvents (DMSO, toluene, dioxane, and THF) were also investigated and the results showed that an increase in temperature, extended time, and reduction in the amount of catalyst/ligand improved the yield of cyclic product 4a. In contrast, a reasonable amount of catalyst/ligand, lower temperatures, and shorter reaction times could inhibit transformation of 3a to 4a. We studied the effect of copper salts (compare entries 7 and 11–15) and copper(I) iodide was found to be the best catalyst. The base also influences the reaction process and cesium carbonate provided the highest yields (compare entries 7 and 16–18). Other solvents (DMSO, toluene, dioxane, and THF) were also investigated and the results showed that an increase in temperature, extended time, and reduction in the amount of catalyst/ligand improved the yield of cyclic product 4a. In contrast, a reasonable amount of catalyst/ligand, lower temperatures, and shorter reaction times could inhibit transformation of 3a to 4a.
products when one equivalent of ligand was used. However, the coupling rate of o-iodotrifluoroacetanilide 1a with cyclopropylacetylene (2e) was very fast in the presence of two equivalents of the ligand and the reaction was complete within 30 minutes giving 3e together with a small amount of cyclization product 4e (entry 5). Unfortunately, o-bromoacetanilide 1e reacted with phenylacetylene (2a) and oct-1-yn (2d) to provide lower yields of 3a and 3d even at 40 °C (entries 13 and 14); the yield of the corresponding cyclic products gradually increased when temperature was continuously raised. We investigated the ortho effect of o-halotrifluoroacetanilides; the coupling of 2,4-diodotrifluoroacetanilide derivative 1b with alkynes selectively occurred at the ortho position (entries 6 and 7), and these result showed that the NHCOCF 3 group in 2,4-diodotrifluoroacetanilide derivative 1b could promote the Sonogashira cross-coupling. We also attempted the coupling of 2,6-diodotrifluoroacetanilide derivative 1c with phenylacetylene (2a), pent-1-yn-3-ol (2b), and 1-ethynylcyclohexene (2c), in all cases this gave the corresponding monosubstituted products 3h, 3j, and 3k as the major product with small amount of disubstituted products (entries 8–10). The result showed that addition of the first alkyne to 2,6-diodotrifluoroacetanilide derivative 1c decreased the activity of the second C–I bond in the monosubstituted products. The monosubstituted product 3k could be coupled with another alkyne to give internal dialkyne 5 under palladium catalysis (Scheme 2), which provides an opportunity for the construction of diverse molecules. In addition, the inexpensive catalyst system (CuI/N-methylpyrrolidine-2-carboxamide) has a high tolerance towards various functional groups in the substrates, for example ester, amide, and hydroxy groups.

A possible coupling mechanism of N-methylpyrrolidine-2-carboxamide-promoted copper-catalyzed Sonogashira cross-coupling of o-haloacetanilides with alkynes has been suggested (Scheme 3). The reaction of a terminal alkyne with copper(I) iodide in the presence of a base (Cs2CO3) formed copper acetylide I, the complex of I with the ligand (Pro-NHMe) yields II, oxidative addition of II to the haloacetanilide gives III. Release of copper(I) iodide provides the target product 3. The ortho-substituent effect was previously identified by Ma’s group.12

Table 2  N-Methylpyrrolidine-2-carboxamide-Promoted Copper-Catalyzed Sonogashira Cross-Coupling of Substituted o-Haloacetanilide Derivatives with Alkynes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl halide</th>
<th>Acetylene</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>R3 = Ph</td>
<td>6</td>
<td>3a</td>
<td>90</td>
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<tr>
<td>2</td>
<td>1a</td>
<td>R3 = CH(OH)Et</td>
<td>6</td>
<td>3b</td>
<td>82</td>
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<tr>
<td>3</td>
<td>1a</td>
<td>R3 = cyclohex-1-enyl</td>
<td>6</td>
<td>3c</td>
<td>78</td>
</tr>
</tbody>
</table>
Table 2  N-Methylpyrrolidine-2-carboxamide-Promoted Copper-Catalyzed Sonogashira Cross-Coupling of Substituted o-Haloacetanilide Derivatives with Alkynes^a (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl halide</th>
<th>Acetylene</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>1a</td>
<td>R³ = n-hexyl</td>
<td>6</td>
<td><img src="image" alt="" /></td>
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<td>5</td>
<td>1a</td>
<td>R³ = cyclopropyl</td>
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<td>60(^c)</td>
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<tr>
<td>6</td>
<td>1b</td>
<td>2a</td>
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<td>8</td>
<td>1c</td>
<td>2a</td>
<td>20</td>
<td><img src="image" alt="" /></td>
<td>46</td>
</tr>
</tbody>
</table>

^a Reaction conditions: Cul (30 mol\%) and L (100 mol\%) in DMF, Cs₂CO₃, r.t.
Table 2  \(N\)-Methylpyrrolidine-2-carboxamide-Promoted Copper-Catalyzed Sonogashira Cross-Coupling of Substituted \(o\)-Haloacetanilide Derivatives with Alkynes\(^a\) (continued)

<table>
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<tr>
<th>Entry</th>
<th>Aryl halide</th>
<th>Acetylene</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield(^b) (%)</th>
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<td>1c</td>
<td>2b</td>
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<td><img src="image" alt="Product 3i" /></td>
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<tr>
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<td><img src="image" alt="Product 3j" /></td>
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<tr>
<td>11</td>
<td>1d</td>
<td>2a</td>
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<td><img src="image" alt="Product 3m" /></td>
<td>93(^d)</td>
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</table>
The trifluoroacetyl group in the \(o\)-alkynyltrifluoroacetanilides is readily removed to yield \(o\)-alkynylanilides.\(^{13}\) For example, treatment of 2,2,2-trifluoro-\(N\)-(2-(phenylethynyl)phenyl)acetamide (3a) with methanol–water/sodium carbonate at 70 °C for 12 hours gave 2-(phenylethynyl)aniline (6) in 71% yield (Scheme 4). \(o\)-Alkynylanilides are important intermediates in organic synthetic chemistry and medicinal chemistry\(^{14}\) and they provide many opportunities for the synthesis of diverse compounds.

In summary, we have developed an efficient method for synthesis of \(o\)-alkynylacetanilides; this protocol used inexpensive copper(I) iodide/\(N\)-methylpyrrolidine-2-carboxamide as the catalyst and various \(o\)-haloacetanilide derivatives as the substrates. The coupling reactions were carried out at room temperature and increasing the amount of the catalyst (CuI) and the ligand (\(N\)-methylpyrrolidine-2-carboxamide) improved the efficiency of the Sonogashira cross-coupling of \(o\)-haloacetanilide derivatives with alkynes and inhibited the cyclization of the \(o\)-alkynylacetanilides. The inexpensive catalyst system has a high tolerance towards various functional groups in the substrates. This convenient and efficient approach to \(o\)-alkynylacetanilides provides opportunities for the synthesis of diverse molecules.

All reactions were carried out under an \(N_2\) atmosphere. DMF was dried over CaH\(_2\) and freshly distilled before use. \(^1\)H and \(^13\)C NMR spectra were recorded with TMS as internal standard in CDCl\(_3\) (\(^1\)H NMR: TMS, \(\delta = 0.00\), CDCl\(_3\), \(\delta = 7.24\); \(^13\)C NMR: CDCl\(_3\), \(\delta = 77.0\)). Compounds \(1a\)–\(c\) were synthesized according to the known literature.\(^{15}\)

\(^1\)H and \(^13\)C NMR spectra were recorded with TMS as internal standard in CDCl\(_3\) (\(^1\)H NMR: TMS, \(\delta = 0.00\), CDCl\(_3\), \(\delta = 7.24\); \(^13\)C NMR: CDCl\(_3\), \(\delta = 77.0\)). Compounds \(1a\)–\(c\) were synthesized according to the known literature.\(^{15}\)

### Table 2 \(N\)-Methylpyrrolidine-2-carboxamide-Promoted Copper-Catalyzed Sonogashira Cross-Coupling of Substituted \(o\)-Haloacetanilide Derivatives with Alkynes\(^{a}\) (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl halide</th>
<th>Acetylene</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield(^b) (%)</th>
</tr>
</thead>
<tbody>
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<td>12</td>
<td>1d</td>
<td>2b</td>
<td>6</td>
<td>![Product Image]</td>
<td>78(^d)</td>
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<tr>
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<td>![Aryl halide Image]</td>
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<td>1e</td>
<td>2d</td>
<td>20</td>
<td>3d</td>
<td>33</td>
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</table>

\(^a\) Reaction conditions: \(o\)-haloacetanilide 1 (0.5 mmol), acetylene 2 (0.75 mmol, 1.25 mmol for entry 10), CuI (0.15 mmol), ligand (0.5 mmol), Cs\(_2\)CO\(_3\) (1.25 mmol), DMF (2 mL), \(N_2\).

\(^b\) Isolated yield.

\(^c\) Ligand (2 equiv) was used.

\(^d\) Reaction temperature (40 °C).

### Scheme 4 Deprotection of the trifluoroacetyl group in 2,2,2-trifluoro-\(N\)-(2-(phenylethynyl)phenyl)acetamide (3a) to give 2-(phenylethynyl)aniline (6)

A flask was charged with CuI (29 mg, 0.15 mmol), \(N\)-methylpyrrolidine-2-carboxamide hydrochloride (83 mg, 0.5 mmol), Cs\(_2\)CO\(_3\) (407 mg, 1.25 mmol), haloacetanilide 1 (0.5 mmol), acetylene 2 (0.75 mmol for all examples in Tables 1 and 2 except Table 2, entry 10, 1.25 mmol), and DMF (2 mL). The mixture was stirred under \(N_2\) at r.t. (25 °C or 40 °C) for the period indicated in Tables 1 and 2. After completion of the coupling reaction (TLC), the mixture was diluted with EtOAc, the soln was filtered, and the inorganic salts were re-
moved. The solvent of the filtrate was removed with the aid of a rotary evaporator, and the residue was purified by flash column chromatography (silica gel, petroleum ether–EtOAc, 40:1 to 4:1) to provide the desired product.

2,2,2-Trifluoro-N-[2-(phenylethynyl)phenyl]acetamide (3a)

White solid; yield: 90%; mp 121–122 °C.

\[ \delta = 8.87 \text{ (s, 1 H), 8.35 (d, } J = 8.2 \text{ Hz, 1 H), 7.50–7.53 \text{ (m, 4 H), 7.37–7.39 \text{ (m, 3 H), } 7.18 \text{ (t, } J = 8.1 \text{ Hz, 1 H).} \]

\[ \text{HRMS: } [M + H]^+ \text{ calcd for C}_{16}H_{15}F_3NO: 294.1106; \text{ found: 294.1107}. \]

2,2,2-Trifluoro-N-[2-(3-hydroxy-1-ynyl)phenyl]acetamide (3b)

White solid; yield: 82%; mp 90–91 °C.

\[ \delta = 8.71 \text{ (s, 1 H), 8.31 (d, } J = 8.2 \text{ Hz, 1 H), 7.35–7.45 \text{ (m, 2 H), 7.16 (t, } J = 8.5 \text{ Hz, 1 H), 4.62 (t, } J = 6.5 \text{ Hz, 1 H), 2.17 \text{ (s, 1 H), 1.86 (m, 2 H), 1.09 \text{ (t, } J = 7.3 \text{ Hz, 3 H).} \]

\[ \text{HRMS: } [M + H]^+ \text{ calcd for C}_{16}H_{11}F_3NO: 290.0793; \text{ found: 290.0794}. \]

2,2,2-Trifluoro-N-[2-(oct-1-ynyl)phenyl]acetamide (3d)

White solid; yield: 82%; mp 121–122 °C.

\[ \delta = 8.78 \text{ (s, 1 H), 8.30 (d, } J = 8.3 \text{ Hz, 1 H), 7.40 (d, } J = 7.6 \text{ Hz, 1 H), 7.33 (t, } J = 8.2 \text{ Hz, 1 H), 7.14 (t, } J = 7.6 \text{ Hz, 1 H), 1.53 \text{ (m, 1 H), 0.98–0.84 \text{ (m, 4 H).} \]

\[ \text{HRMS: } [M + H]^+ \text{ calcd for C}_{16}H_{19}F_3NO: 298.1419; \text{ found: 298.1417}. \]

2,2,2-Trifluoro-N-[2-(phenylethynyl)phenyl]-2,2,2-trifluoroacetamide (3e)

White solid; yield: 60%; mp 66–67 °C.

\[ \delta = 8.78 \text{ (s, 1 H), 8.30 (d, } J = 8.3 \text{ Hz, 1 H), 7.40 (d, } J = 7.6 \text{ Hz, 1 H), 7.33 (t, } J = 8.2 \text{ Hz, 1 H), 7.14 (t, } J = 7.6 \text{ Hz, 1 H), 1.53 \text{ (m, 1 H), 0.98–0.84 \text{ (m, 4 H).} \]

\[ \text{HRMS: } [M + H]^+ \text{ calcd for C}_{18}H_{19}F_3NO: 294.1140; \text{ found: 294.1140}. \]

N-[2-(Cyclohex-1-ynyl)phenyl]-2,2,2-trifluoroacetamide (3f)

White solid; yield: 78%; mp 75–76 °C.

\[ \delta = 8.80 \text{ (s, 1 H), 8.32 (d, } J = 8.2 \text{ Hz, 1 H), 7.42 (d, } J = 7.9 \text{ Hz, 1 H), 7.34 (t, } J = 7.6 \text{ Hz, 1 H), 7.14 \text{ (t, } J = 7.6 \text{ Hz, 1 H), 6.27 \text{ (s, 1 H), 2.16–2.22 \text{ (m, 4 H), 1.61–1.72 \text{ (m, 4 H).} \]

\[ \text{HRMS: } [M + H]^+ \text{ calcd for C}_{18}H_{12}F_3INO_3: 473.9814; \text{ found: 473.9812}. \]

N-[2-(Cyclopropylthynyl)phenyl]-2,2,2-trifluoroacetamide (3g)

White solid; yield: 46%; mp 124–126 °C.

\[ \delta = 8.38–8.42 \text{ (m, } J = 8.2 \text{ Hz, 3 H), 7.33–7.45 \text{ (m, } J = 6.2 \text{ Hz, 5 H), 3.92 \text{ (s, 3 H).} \]

\[ \text{HRMS: } [M + H]^+ \text{ calcd for C}_{18}H_{12}F_3INO_3: 473.9814; \text{ found: 473.9812}. \]

Methyl 3-(3-Hydroxy-1-ynyl)-5-iodo-2-(trifluoroacetamido)benzoate (3i)

White solid; yield: 83%; mp 129–130 °C.

\[ \delta = 8.22 (d, J = 7.9 \text{ Hz, 1 H), 7.19 (t, } J = 7.6 \text{ Hz, 1 H), 6.25 (s, 1 H), 2.16–2.22 \text{ (m, 4 H), 1.61–1.72 \text{ (m, 4 H).} \]

\[ \text{HRMS: } [M + H]^+ \text{ calcd for C}_{18}H_{12}F_3INO_3: 473.9814; \text{ found: 473.9812}. \]
Methyl 3-(Cyclohex-1-enylethynyl)-5-iodo-4-(trifluoroacetamido)benzoate (3k)
White solid; yield: 53%.
\[^1^H\] NMR (300 MHz, CDCl₃): \( \delta = 8.32–8.37 \) (m, 1 H), 8.00–8.18 (m, 2 H), 6.22 (s, 1 H), 3.92 (s, 3 H), 2.14 (m, 4 H), 1.64 (m, 4 H).
\[^{13}C\] NMR (300 MHz, CDCl₃): \( \delta = 164.4, 154.5 \) (J = 19.7 Hz), 149.9, 139.3, 137.8, 133.3, 130.8, 123.9, 119.8, 118.5 (J = 143.1 Hz), 99.4, 96.5, 81.2, 52.6, 28.5, 25.8, 22.0, 21.2.

Methyl 3,5-Bis(cyclohex-1-enylethynyl)-4-(trifluoroacetamido)benzoate (3l)
White solid; yield: 29%; mp 179–180 °C.
\[^1^H\] NMR (300 MHz, CDCl₃): \( \delta = 8.05–8.22 \) (m, 3 H), 7.33–7.48 (m, 5 H), 6.25 (s, 1 H), 3.9 (s, 3 H), 2.16–2.18 (m, 4 H), 1.62–1.67 (m, 4 H).
\[^{13}C\] NMR (300 MHz, CDCl₃): \( \delta = 165.1, 154.2 \) (J = 19.0 Hz), 138.4, 137.5, 132.9, 132.7, 131.6, 129.4, 129.1, 124.8, 121.9, 121.7, 121.1, 129.9, 115.4 (J = 143.6 Hz), 99.6, 97.0, 83.8, 81.1, 52.5, 28.6, 25.8, 22.1, 21.2.

2-(Phenylethynyl)aniline (6)
White solid; yield: 71%; mp 80–82 °C (Lit. 85–87 °C).
\[^1^H\] NMR (300 MHz, CDCl₃): \( \delta = 7.31–7.52 \) (m, 7 H), 6.67–6.69 (m, 2 H), 4.13 (s, 2 H).
\[^{13}C\] NMR (300 MHz, CDCl₃): \( \delta = 147.6, 132.0, 131.4, 129.6, 128.3, 128.1, 123.2, 117.9, 114.3, 107.8, 94.6, 85.8.

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