Synthesis R. Amara et al. Paper

# Synthesis of *N*-Aryl and *N*-Heteroaryl γ-, δ-, and ε-Lactams Using Deprotometalation–Iodination and *N*-Arylation, and Properties Thereof

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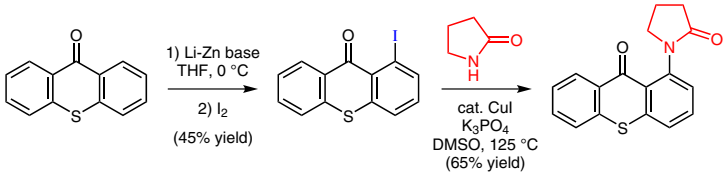


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**Abstract** Xanthone, thioxanthone, fluorenone, benzophenone, 2-benzoylpyridine, dibenzofuran, and dibenzothiophene were deprotonated using a base prepared in situ from $MCl_2$·TMEDA (M = Zn or Cd; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) and lithium 2,2,6,6-tetramethylpiperidide in a 1:3 ratio, as demonstrated by subsequent iodolysis. The different aryl halides were involved as partners in the *N*-arylation of pyrrolidin-2-one. In the presence of copper(I) iodide and tripotassium phosphate, and using dimethyl sulfoxide as solvent, the reactions could be performed in yields ranging from 40 to 70%. Most of the products were tested for their antimicrobial, antifungal, antioxidant, and cytotoxic (MCF-7) activity.

**Key words** C–N bond formation, deprotonative metalation, lactam, aromatic compound, antimicrobial activity, antifungal activity

Due to their presence in molecules of biological importance or in organic materials for various applications, aromatic compounds and notably heterocycles are essential, as well as the development of methods to functionalize them.

To regioselectively introduce substituents, deprotometalation has imposed itself as a powerful tool.[2] If alkyllithiums and hindered lithium dialkylamides have been largely employed, alternative approaches using lithium-metal combinations based on 2,2,6,6-tetramethylpiperidide (TMP) have recently emerged for performing reactions with sensitive substrates.[3] The 1:1 mixture of the homometallic amides LiTMP and $Zn(TMP)_2$, generated from LiTMP and $ZnCl_2$·TMEDA (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) in a 3:1 ratio, falls into this category.[4] With LiTMP-mediated deprotonation and in situ $Zn(TMP)_2$-induced transmetalation, this 'trans-metal trapping'[5] approach ensures both chemoselective and high-yielding reactions.[6]

Whereas secondary carboxamides are hardly compatible with the conditions required for their palladium-catalyzed *N*-arylation and *N*-heteroarylation (Goldberg reaction),[7] the corresponding copper-catalyzed reactions have benefited from the development of catalyst-base systems.[8] Copper(I) iodide is often used in the presence of a diamine (e.g., *trans*-cyclohexane-1,2-diamines or other 1,2-ethylenediamines, either *N*-alkylated or not) as ligand, and in combination with either a base ($K_3PO_4$, $K_2CO_3$, or $Cs_2CO_3$) or

CsF.[7,9] Ligand-free catalysis is also possible at moderate reaction temperatures provided that DMSO is used as solvent.[10]

We here describe the use of the lithium-zinc combination developed in the group to access aromatic iodides, as well as their conversion to *N*-arylated amides based on pyrrolidin-2-ones, piperidin-2-ones and hexahydro-2*H*-azepin-2-ones. The antimicrobial, antifungal, antioxidant, and cytotoxic activities of some of the prepared compounds were evaluated.

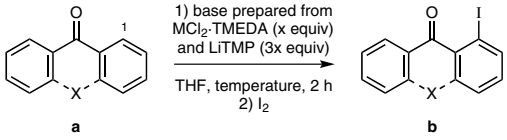
To subsequently access new *N*-aryl and *N*-heteroaryl lactams, we first involved xanthone (**1a**), thioxanthone (**2a**), fluorenone (**3a**), benzophenone (**4a**), and 2-benzoylpyridine (**5a**) in the reaction using mixed lithium-metal bases before interception with iodine (Table 1). Achieving the deprotometalation of such aromatic ketones represents a challenge due to their low compatibility toward lithium species.[11] Indeed, the method has so far been restricted to a few carbonyl-containing five-membered[12] and six-membered[13] aromatic compounds.

First, xanthone (**1a**) was reacted with a 1:1 mixture of LiTMP and $Zn(TMP)_2$ amides obtained by mixing $ZnCl_2$·TMEDA (0.5 equiv) and LiTMP (1.5 equiv).[4a] Conducting the reaction in tetrahydrofuran (THF) at 0 °C for 2 h provided, after interception with iodine, the 1-iodo derivative **1b** in 43% yield; a small amount (5% yield) of 1,9-diiodoxanthone (**1b′**) was also isolated (entry 1) and identified unambiguously (Figure 1). Increasing either the amount of base to 1 equiv of $ZnCl_2$·TMEDA and 3 equiv of LiTMP, or the reaction temperature to 20–25 °C, led to extended degradation due to the high reactivity of the ketone. In addition, replacing $ZnCl_2$·TMEDA (0.5 equiv) by $CdCl_2$·TMEDA[3d] (0.5 equiv) in the preparation of the base did not improve this result since a complex mixture was obtained.

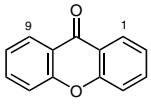
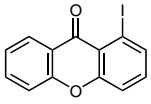
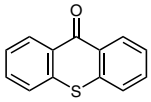
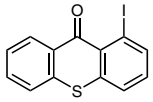
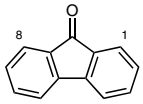
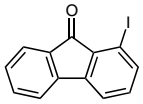
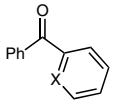
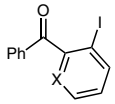
Starting from thioxanthone (**2a**), similar behavior was observed; using the 1:1 mixture of amides LiTMP and $Zn(TMP)_2$, this time obtained by mixing $ZnCl_2$·TMEDA (1 equiv) and LiTMP (3 equiv), furnished the 1-iodo derivative **2b** in 45% yield (entry 2, Figure 1).

In the case of fluorenone (**3a**), treatment by the base prepared from $ZnCl_2$·TMEDA (0.5 equiv) and LiTMP (1.5 equiv) in THF at room temperature for 2 h did not give any iodide; instead, the hydroxy ketone **3b′** was isolated in 63% yield (entry 3). Even if we did not observe the expected iodide **3b**, this result is of interest because it confirms that an aryllithium is first formed by reaction using this basic mixture (Scheme 1).[4] Indeed, trapping by the keto group would have been much more sluggish had an arylzinc (or zincate) been formed.[6c] By decreasing the reaction temperature to 0 °C, a complex mixture was noticed.

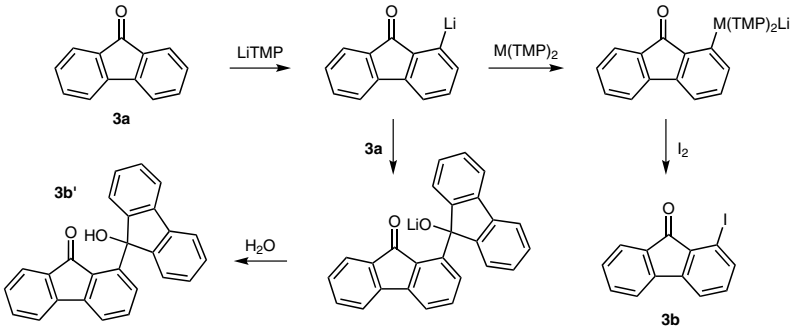
**Table 1** Deprotometalation-Iodination of the Ketones **1a–5a**




**a** **b**

| Entry | Ketone | | M, x | Temperature | Iodo ketone | Product, yield (%)[a] |
|---|---|---|---|---|---|---|
| 1 | **1a** |  | Zn, 0.5 | 0 °C |  | **1b**, 43[b] |
| 2 | **2a** |  | Zn, 1 | 0 °C |  | **2b**, 45 |
| 3 | **3a** |  | Zn, 0.5 | rt |  | **3b**, –[c] |
| 4 | | | Cd, 0.5 | | | **3b**, 80 |
| 5 | **4a** |  | X = CH | rt |  | **4b**, 66[d] |
| 6 | **5a** | | X = N | rt | | **5b**, –[e] |

[a] After purification by column chromatography.
[b] 1,9-Diiodoxanthone (**1b′**) was also isolated in 5% yield.
[c] The hydroxy ketone **3b′** was obtained instead in 63% yield (see Scheme 1).
[d] Using a protocol previously reported.[13]
[e] Complex mixtures were obtained under these conditions, and the ketone **5b** was prepared as described recently.[14]




**Scheme 1** Deprotometalation of fluorenone (**3a**)

To obtain the 1-iodo derivative **3b**, we efficiently turned to the corresponding lithium-cadmium base generated from $CdCl_2$·TMEDA (0.5 equiv) and LiTMP (1.5 equiv). After 2 h contact with **3a** in THF at room temperature and subsequent quenching with iodine, **3b** was this time obtained in 80% yield (Table 1, entry 4, Figure 1). This result (no detection of the hydroxy ketone **3b′**) suggests a lithium cadmate mediated deprotonation.[3d,13,15] Otherwise, if deprotolithiation followed by transmetalation (Scheme 1) would rather happen as proposed,[16] the latter could be considered as being faster with cadmium compared with zinc. Unfortunately, due to the lack of studies concerning compared kinetics/mechanisms of both lithium/zinc and lithium/cadmium transmetalations,[17] it is not possible to come to a conclusion. Nevertheless, the superiority of the lithium-cadmium base over the lithium-zinc one to solve chemoselectivity issues is a general trend, and was for example used to convert benzophenone (**4a**) into the iodide **4b** (entry 5).[13]

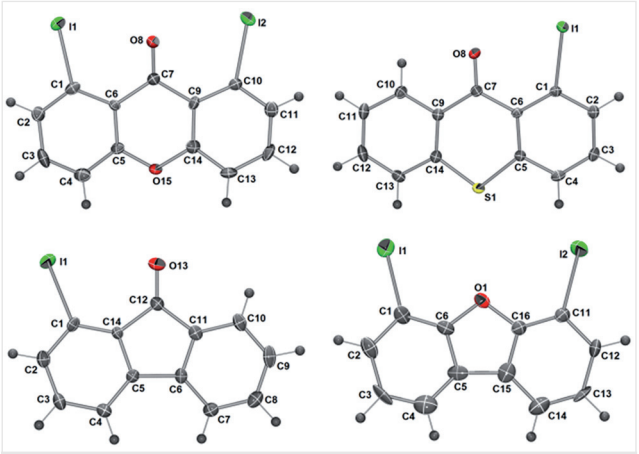
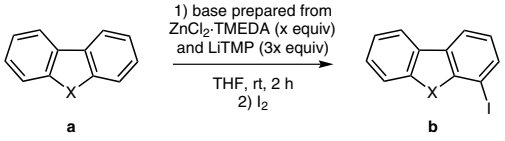
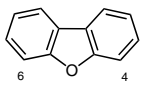
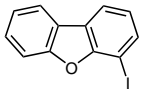
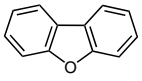
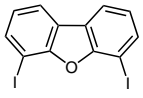
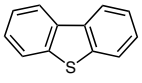
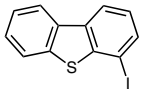


**Figure 1** ORTEP diagrams (50% probability) of the compounds **1b′**, **2b**, **3b**, and **6b′**

**Table 2** Deprotometalation–Iodination of the Substrates **6a** and **7a**




| Entry | Substrate | | x | Iodide/diiodide | Product, yield (%)[a] |
|---|---|---|---|---|---|
| 1 | **6a** |  | 0.5 |  | **6b**, 90[b] |
| 2 | **6a** |  | 1 |  | **6b′**, 79 |
| 3<br>4<br>5 | **7a** |  | 0.5<br>1<br>1.5 |  | **7b**, 47[c]<br>**7b**, 66[c]<br>**7b**, 85 |

[a] After purification by column chromatography.
[b] 4,6-Diiododibenzofuran (**6b′**) was also identified in the crude.
[c] The remainder was recovered starting material.

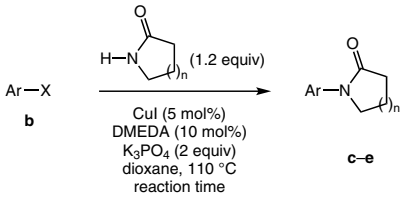
Our attempts to use the lithium-zinc base as before from 2-benzoylpyridine (**5a**) failed (entry 6). In a recent communication,[14] we showed it is possible to achieve its conversion to the 3-iodo derivative **5b** by using LiTMP in the presence of $ZnCl_2$·TMEDA, and used this protocol. These results suggest that the zinc chelate is a more efficient in situ trap than $Zn(TMP)_2$ to transmetalate the generated aryllithium.

We next turn to deprotometalation-iodolysis sequences starting from dibenzofuran (**6a**) and dibenzothiophene (**7a**) in order to generate either monoiodides or diiodides (Table 2). We chose the 1:1 mixture of amides LiTMP and $Zn(TMP)_2$ obtained by mixing $ZnCl_2$·TMEDA (x equiv) and LiTMP (3 x equiv) because it has been efficiently used to either monofunctionalize or difunctionalize depending on the amount of base.[6d,e,18]

Dibenzofuran (**6a**) can be either mono-[19] or dideprotonated[20] by using butyllithium, in the presence or not of TMEDA, at temperatures ranging from –75 °C to 60 °C. Using the base prepared from $ZnCl_2$·TMEDA (x equiv) and LiTMP (3x equiv) also led, at room temperature, to either the monometalated (x = 0.5) or the dimetalated (x = 1) derivatives in good yields, as evidenced by subsequent iodolysis (entries 1 and 2, Figure 1). Dibenzothiophene (**7a**) can be similarly mono-[19d,21] or dideprotonated[21c,22] using butyllithium. Surprisingly, whereas it was possible to achieve its monometalation using the lithium-zinc base, an efficient dimetalation proved impossible under the conditions tried (entries 3–5).

These iodides in hand, we considered their conversion to *N*-arylated amides. In search of an efficient method to achieve the C–N bond formation, we evaluated a protocol[9a,c,d] using copper(I) iodide (5 mol%) as transition metal source, DMEDA (10 mol%) as ligand (DMEDA = *N*,*N*′-dimethylethylenediamine), $K_3PO_4$ (2 equiv) as base and dioxane as solvent at 110 °C on different aryl halides (Table 3, Figure 2).

**Table 3** *N*-Arylation of Pyrrolidin-2-one, Piperidin-2-one, and Hexahydro-2*H*-azepin-2-one with Different Aryl Halides



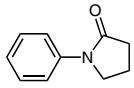
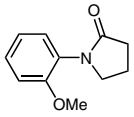
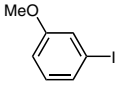
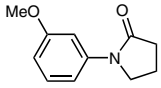
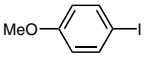
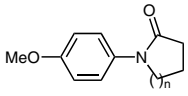
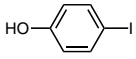
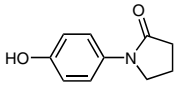
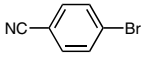
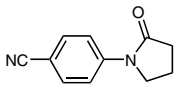
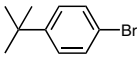
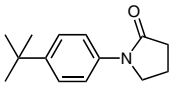
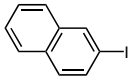
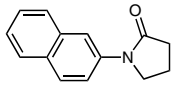
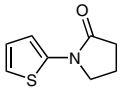
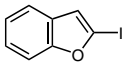
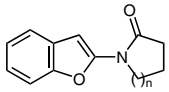
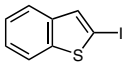
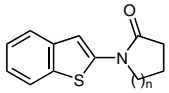
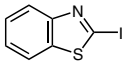
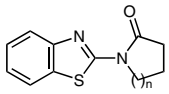

| Entry | Ar-X | | Time (h) | *N*-Arylamide | | Product, yield (%)[a] |
|---|---|---|---|---|---|---|
| 1 | **8b** |  | 24 |  | | **8c**, 95 |
| 2 | **9b** |  | 24 |  | | **9c**, 99 |
| 3 | **10b** |  | 24 |  | | **10c**, 99 |
| 4<br>5<br>6 | **11b** |  | 24<br>24<br>24 |  | n = 1<br>n = 2<br>n = 3 | **11c**, 85<br>**11d**, 73<br>**11e**, 99 |
| 7 | **12b** |  | 48 |  | | **12c**, 26[b], 20[c], 29[d] |
| 8 | **13b**′ |  | 24 |  | | **13c**, 89 |

Table 3 (continued)

| Entry | Ar-X | | Time (h) | *N*-Arylamide | | Product, yield (%)[a] |
|---|---|---|---|---|---|---|
| | **14b′** |  | 48 |  | | **14c**, 30 |
| 10 | **15b** |  | 72 |  | | **15c**, 45 |
| 11 | **16b** |  X = I | 24 |  | | **16c**, 93 |
| 12 | **16b′** | X = Br | | | | **16c**, 99 |
| 13 | |  | 48 |  | n = 1 | **17c**, 84 |
| 14 | **17b** | | 48 | | n = 2 | **17d**, 93 |
| 15 | | | 24 | | n = 3 | **17e**, 65 |
| 16 | |  | 48 |  | n = 1 | **18c**, 88 |
| 17 | **18b** | | | | n = 2 | **18d**, 81 |
| 18 | | | | | n = 3 | **18e**, 53 |
| 19 | |  | 24 |  | n = 1 | **19c**, 66 |
| 20 | **19b** | | 48 | | n = 2 | **19d**, 15 |
| 21 | | | 48 | | n = 3 | **19e**, 50 |

[a] After purification by column chromatography.
[b] A similar result was obtained by using $K_3PO_4$ (3 equiv) (reaction time: 72 h).
[c] Using DMSO instead of dioxane (48 h at 125 °C).
[d] Using CuI (10 mol%) and DMSO instead of dioxane (48 h at 125 °C).

The method works well with phenyl iodides provided that it is not substituted by a strong electron-donating group (entries 1–7). From phenyl bromides, these conditions are more suitable in the presence of electron-withdrawing substituents compared with electron-donating (entries 8 and 9). Whereas a moderate yield is noticed from 2-iodonaphthalene (**15b**, entry 10), both 2-iodo- and 2-bromothiophene (**16b** and **16b′**, entries 11 and 12) are converted efficiently. This encouraged us to involve in the reaction iodinated benzoazoles prepared by deprotometalation-iodolysis (entries 13–21).[23] The reactions proceed in correct to high yields from 2-iodobenzofuran (**17b**) and 2-iodobenzothiophene (**18b**) whereas 2-iodobenzothiazole (**19b**) is converted less efficiently.

Inspired by the study published by Güell and Ribas in 2014,[10] and in keeping with works recently developed in our group on azole *N*-arylation,[24] we next compared the previous protocol with a ligand-free one using DMSO as solvent. For this purpose, we employed 1-iodo-9-thioxanthone (**2b**) as substrate in the reaction with pyrrolidin-2-one, and demonstrated the superiority of the second protocol to arylate the lactam (Table 4).

These optimized conditions in hand, we first involved in the reaction the different aryl iodides **b** synthesized by deprotometalation-iodolysis. The expected *N*-functionalized lactams were obtained in yields ranging from 40 to 70% (Table 5, Figure 3).

Unfortunately, the double C–N bond formation performed on the aryl diiodide **6b′** proved less obvious (Scheme 2, Figure 3). Double functionalization did not take place at all, the monoamides either deiodinated (**6c**, 55% yield) or not (**6c′**, detected) being the only reaction products. Reacting **6c′** under the same reaction conditions also failed, only leading to loss of iodine.

This disappointing result led us to consider a more common substrate, 1,4-diiodobenzene (**8b′**), to attempt the same reaction. Even if more successful, the expected diamide **8c″** was isolated in a moderate 30% yield together with the iodinated amide **8c′** (7% yield). As already noticed for 4-iodophenol (**12b**) in Table 3 using similar conditions (entry 7, footnotes c and d), these results show that an electron-donating group (here, the introduced amide) tends to inhibit the reaction.

Because many pharmaceuticals are pyrrolidinone derivatives, e.g. cotinine (used to treat depression, Alzheimer's disease, post-traumatic stress disorder and schizophre-

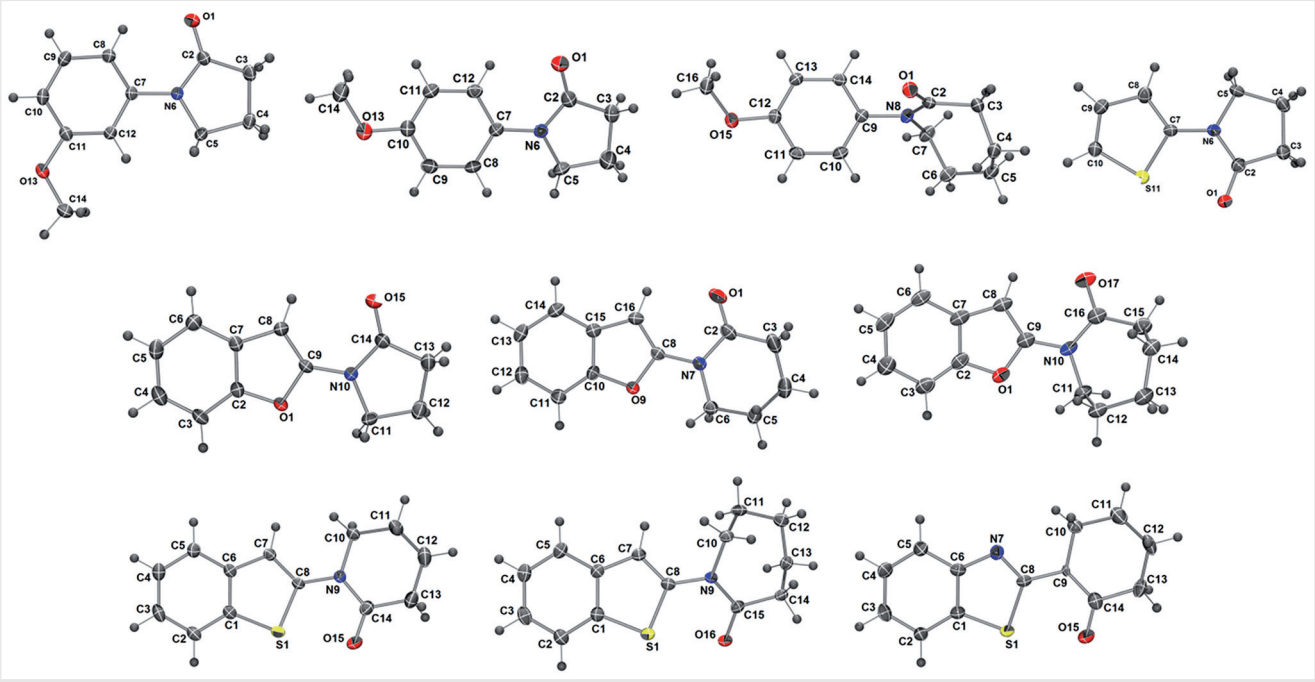


**Figure 2** ORTEP diagrams (50% probability) of the compounds **10c**, **11c**, **11e**, **16c**, **17c–e**, **18d**,**e**, and **19d**

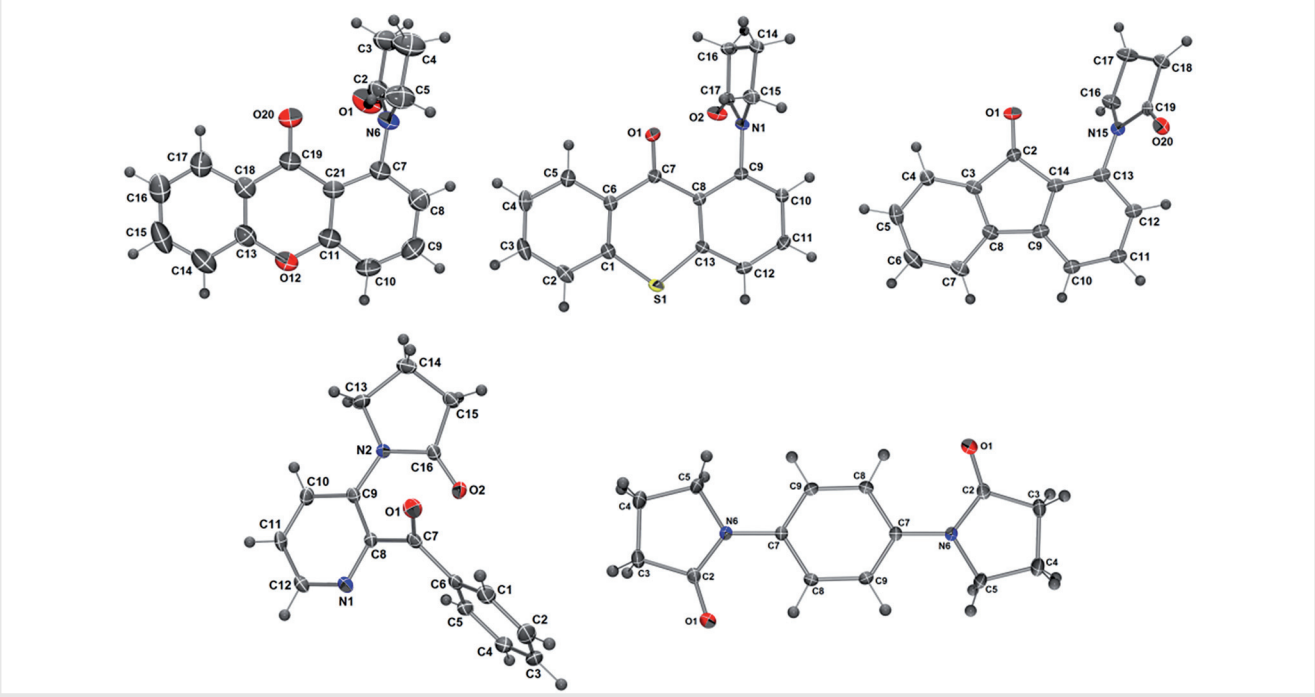
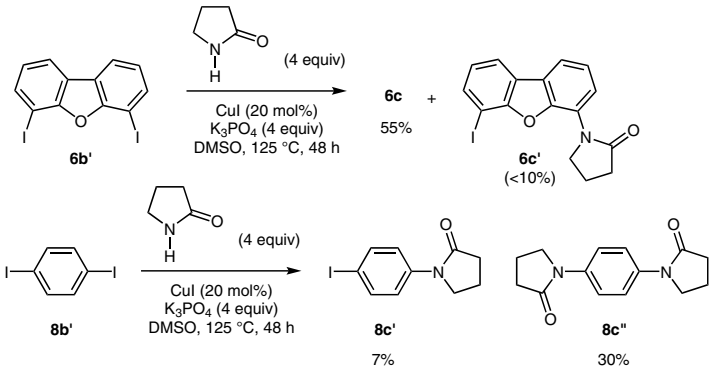


**Figure 3** ORTEP diagrams (50% probability) of compounds **1c**, **2c**, **3c**, **5c**, and **8c**′′




**Scheme 2** C–N Bond formation from diiodides

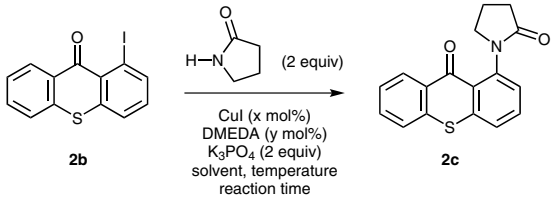
nia),[25] doxapram (a respiratory stimulant),[26] and piracetam (a cyclic derivative of γ-aminobutyric acid mainly used to treat myoclonus),[27] some of the synthesized compounds were evaluated for their biological properties.

The compounds **1c**, **2c**, **3c**, **4c**, **5c**, **6c**, **7c**, **8c**, **8c″**, **10c**, **11c–e**, **13c**, **15c**, **16c**, **17c–e**, **18c–e**, and **19c–e** were screened for their antimicrobial activity against bacteria and for their antifungal activity. An effect on the microbial growth of strains of bacteria was only noticed in the case of **4c**, **6c**, **7c**, and **8c″**. 1-(2-Benzoylphenyl)pyrrolidin-2-one (**4c**) has no significant inhibition effect on *L. monocytogenes*; it inhibits *E. coli*, *P. aeruginosa*, and *C. dubliniensis* at the same power while it strongly inhibits *S. aureus* and *E. faecium* compared to the positive control. 1-(Dibenzofuran-4-yl)pyrrolidin-2-one (**6c**) inhibits *S. aureus*, but above all *C. albicans*. The behavior of 1-(dibenzothiophen-4-yl)piperidin-2-one (**7c**) and 1,1′-(1,4-phenylene)bispyrrolidin-2-one (**8c″**) is even more interesting since both selectively inhibit *C. albicans* with a strength comparable to that of nystatin (Table 6).

As shown in Table 7, various compounds showed an average antioxidant activity around 40–50%. A study was also carried out in order to investigate the cytotoxic potential of the derivatives **8c**, **10c**, **11c**, **12c**, **13c**, and **16c** (Table 8). The antiproliferative activity of the derivatives was determined using breast cancer cell line MCF-7, which is an invasive differentiated mammary epithelial breast cancer cell line used worldwide to screen and compare the antiproliferative activity of new molecules vs standard anticancer compounds. None of the compounds synthesized can compete with the reference standard doxorubicin.

Thus, by combining deprotometalation-iodination of aromatic ketones with *N*-arylation of cyclic amides, we could access a large range of *N*-aryl and *N*-heteroaryl γ-, δ-, and ε-lactams. Whereas **4c** shows promising activity as antimicrobial and antifungal, compounds **6c** and, above all, **7c** and **8c″** exhibit interesting selective antifungal activity against *C. albicans*.

**Table 4** Comparison of Both Protocols for the *N*-Arylation of Pyrrolidin-2-one with 1-Iodo-9-thioxanthone (**2b**)

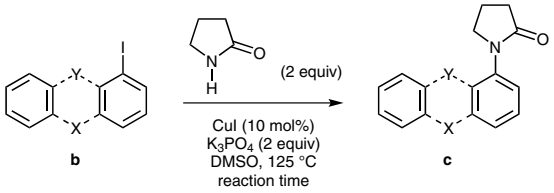



| Entry | CuI (mol%) | DMEDA (mol%) | Solvent | Temp (°C) | Time (h) | Yield (%)[a] |
|---|---|---|---|---|---|---|
| 1 | 5 | 10 | dioxane | 110 | 24 | 10 |
| 2 | 5 | 10 | dioxane | 110 | 72 | 32 |
| 3 | 5 | – | DMSO | 125 | 24 | 62 |
| 4 | 10 | – | DMSO | 125 | 24 | 65 |

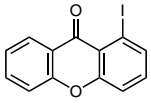
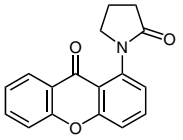
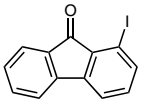
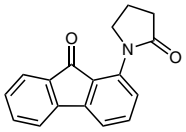
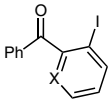
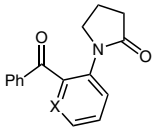
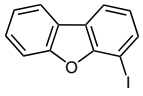
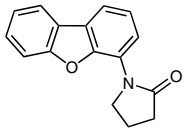
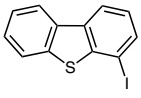
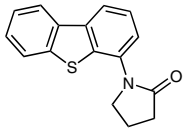
[a] After purification by column chromatography.

All reactions were performed under an argon atmosphere. THF was distilled over Na/benzophenone. Column chromatography separations were achieved on silica gel (40–63 μm). Melting points were measured on a Kofler apparatus. IR spectra were taken on a Perkin-Elmer Spectrum 100 spectrophotometer. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker Avance III spectrometer at 300 MHz and 75 MHz, respectively, $^{1}H$ NMR spectra relative to the solvent residual peak and $^{13}C$ NMR spectra are relative to the central peak of the solvent signal.[28] The structure of the new compounds was confirmed either by X-ray diffraction or through microanalysis.

**Table 5** *N*-Arylation of Pyrrolidin-2-one with Different Aryl Monoiodides




b c

| Entry | Ar-I | | | Time (h) | *N*-Arylamide | | Product, yield (%)[a] |
|---|---|---|---|---|---|---|---|
| 1 | **1b** |  | | 24 |  | | **1c**, 70 |
| 2 | **3b** |  | | 24 |  | | **3c**, 62 |
| 3<br>4 | **4b**<br>**5b** |  | X = CH<br>X = N | 24<br>72 |  | X = CH<br>X = N | **4c**, 56<br>**5c**, 40 |
| 5 | **6b** |  | | 48 |  | | **6c**, 50 |
| 6 | **7b** |  | | 48 |  | | **7c**, 54 |

[a] After purification by column chromatography.

**Table 6** Antimicrobial and Antifungal Activity of Compounds **4c**, **6c**, **7c**, and **8c′′**[a]

| Compound | Amount (μg) dissolved in DMSO | *Escherichia coli* | *Pseudomonas aeruginosa* | *Staphylococcus aureus* | *Enterococcus faecium* | *Listeria monocytogenes* | *Candida dubliniensis* | *Candida albicans* |
|---|---|---|---|---|---|---|---|---|
| **4c**[b] | 500 | 8 | 8 | 10 | 9 | ± | 8 | – |
| **6c**[c] | 150 | 0 | 0 | 4 | 0 | 0 | – | 14 |
| **7c**[c] | 150 | 0 | 0 | 0 | 0 | 0 | – | 14 |
| **8c′′**[c] | 150 | 0 | 0 | 0 | 0 | 0 | – | 15 |
| DMSO | – | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Reference compound | | 28 | 28 | 18 | 24 | 30 | 10 | 13 |
| | | Ceftazidime (30 μg) | | Vancomycin (30 μg) | | Ampicillin (25 μg) | Nystatin (416 UI) | |

[a] The diameters of zones of inhibition are given in mm.
[b] 10 μL/well.
[c] 30 μL/well.

**Table 7** Antioxidant Activity of Compounds **1c**, **2c**, **3c**, **4c**, **5c**, **6c**, **7c**, **8c**, **8c′′**, **10c**, **11c–e**, **13c**, **15c**, **16c**, **17c–e**, **18c–e**, and **19c–e**

| Compound | RSA (%)[a] at t = 0 min | RSA (%)[a] at t = 30 min |
|---|---|---|
| **1c** | 49 | 52 |
| **2c** | 53 | 52 |
| **3c** | 72 | 50 |
| **4c** | 54 | 54 |
| **5c** | 58 | 61 |
| **6c** | 63 | 64 |
| **7c** | 60 | 61 |
| **8c** | 44 | 51 |
| **8c′′** | 53 | 53 |
| **10c** | 12 | 50 |
| **11c** | 47 | 55 |
| **11d** | 46 | 46 |
| **11e** | 42 | 42 |
| **13c** | 41.5 | 49 |
| **15c** | 45 | 47 |
| **16c** | 43.5 | 49 |
| **17c** | 48 | 53 |
| **17d** | 50 | 55 |
| **17e** | 45.5 | 46 |
| **18c** | 44 | 47 |
| **18d** | 40 | 41 |
| **18e** | 41 | 42.5 |
| **19c** | 47 | 49 |
| **19d** | 51 | 53 |
| **19e** | 42 | 42 |

[a] Percentage of the radical scavenger activity.

**Table 8** Cytotoxic Activity on MCF-7 of the Compounds **8c**, **10c**, **11c**, **12c**, **13c**, and **16c**

| Compound | $IC_{50}$ (μg $mL^{-1}$)[a] |
|---|---|
| **8c** | 12.7 |
| **10c** | 12.4 |
| **11c** | 12.2 |
| **12c** | 11.9 |
| **13c** | 15.7 |
| **16c** | 13.0 |
| doxorubicin | 3.5 |

[a] $IC_{50}$ is defined as the concentration which results in a 50% decrease in the cell number as compared with that of the control structures in the absence of an inhibitor.

*Crystallography*: The samples were studied with graphite monochromatized Mo-Kα radiation (λ = 0.71073 Å). For compounds **1b′**, **2b**, **10c**, **11c**, **16c**, **17c–e**, **18d**,**e**, and **19d**, the X-ray diffraction data were collected at *T* = 150 K using an APEXII Bruker-AXS diffractometer. The structure was solved by direct methods using the SIR97 program,[29] and then refined with full-matrix least-square methods based on $F^2$ (SHELX-97)[30] with the aid of the WINGX program.[31] All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. H atoms were finally included in their calculated positions. For **3b**, **6b′**, **11e**, **1c**, **2c**, **3c**, **5c**, and **8c″**, the X-ray diffraction data were collected using a D8 VENTURE Bruker AXS diffractometer at the temperature given in the crystal data. The structure was solved by dual-space algorithm using the SHELXT program,[32] and then refined with full-matrix least-square methods based on $F^2$ (SHELXL-2014).[33] All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. H atoms were finally included in their calculated positions. The molecular diagrams were generated by ORTEP-3 (version 2.02).[34]

### 1-Iodo-9-xanthone (1b) and 1,8-Diiodo-9-xanthone (1b′); Typical Procedure

To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.5 mmol) in THF (2–3 mL) were successively added ca. 1.6 M BuLi in hexanes (1.5 mmol) and, after 5 min, $ZnCl_2$·TMEDA[35] (0.13 g, 0.50 mmol). The mixture was stirred for 15 min at 0 °C before introduction of xanthone (**1a**, 0.20 g, 1.0 mmol). After 2 h at this temperature, a solution of $I_2$ (0.38 g, 1.5 mmol) in THF (4 mL) was added. The mixture was stirred overnight before the addition of aq sat. $Na_2S_2O_3$ soln (4 mL). The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by chromatography (silica gel, heptane/$CH_2Cl_2$ 100:0 to 80:20) afforded the products.

### 1-Iodo-9-xanthone (1b)

Pale yellow powder; yield: 0.14 g (43%) ; mp 176 °C (Lit.[36] 172–173.5 °C).

IR (ATR): 663, 752, 777, 849, 903, 931, 1108, 1147, 1161, 1234, 1255, 1297, 1328, 1346, 1421, 1443, 1466, 1554, 1590, 1612, 1661, 3065 $cm^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 7.27 (dd, *J* = 8.4, 7.8 Hz, 1 H), 7.36 (ddd, *J* = 8.1, 7.2, 0.9 Hz, 1 H), 7.41 (dm, *J* = 9.0 Hz, 1 H), 7.48 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.70 (ddd, *J* = 8.7, 7.2, 1.8 Hz, 1 H), 8.00 (dd, *J* = 7.6, 1.1 Hz, 1 H), 8.31 (ddd, *J* = 8.1, 1.8, 0.5 Hz, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 91.3 (C), 117.7 (CH), 119.1 (CH), 120.1 (C), 121.3 (C), 124.3 (CH), 127.3 (CH), 134.7 (CH), 135.0 (CH), 138.6 (CH), 154.9 (C), 156.8 (C), 175.4 (C).

These data are similar to those reported previously.[36]

### 1,8-Diiodo-9-xanthone (1b′)

Yellow powder; yield: 22 mg (5%); mp 252 °C.

IR (ATR): 658, 777, 804, 868, 906, 1159, 1276, 1354, 1448, 1578, 1659, 2927 $cm^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 7.26 (dd, *J* = 8.1, 7.8 Hz, 2 H), 7.42 (dd, *J* = 8.3, 1.1 Hz, 2 H), 8.01 (dd, *J* = 7.5, 1.2 Hz, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 92.1 (C), 118.7 (CH), 120.3 (C), 124.8 (C), 134.6 (CH), 138.9 (CH), 155.6 (C).

*Crystal data for* **1b′**: $2(C_{13}H_6I_2O_2)$, *M* = 895.96, triclinic, *P* -1, *a* = 8.2003(2), *b* = 10.2204(2), *c* = 15.1904(3) Å, α = 86.8230(10), β = 74.5930(10), γ = 75.9650(10)°, *V* = 1190.67(4) $Å^3$, *Z* = 2, *d* = 2.499 g

cm$^{-3}$, μ = 5.267 mm$^{-1}$. A final refinement on $F^2$ with 5418 unique intensities and 307 parameters converged at ω$R(F^2)$ = 0.0725 ($R(F)$ = 0.0402) for 4325 observed reflections with $I > 2\sigma(I)$. CCDC 1544822.

### 1-Iodo-9-thioxanthone (2b)[37]

Following the typical procedure for **1b** using 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.5 mmol) in THF (2–3 mL) with ca. 1.6 M BuLi in hexanes (1.5 mmol) and then $ZnCl_2$·TMEDA[35] (0.13 g, 0.50 mmol) and 9-thioxanthone (**2a**, 0.11 g, 0.50 mmol), and finally $I_2$ (0.38 g, 1.5 mmol) in THF (4 mL). Purification by chromatography (silica gel, heptane/$CH_2Cl_2$ 100:0 to 80:20) afforded **2b** (75 mg, 45%) as a greenish powder; mp 156–158 °C.

IR (ATR): 664, 711, 745, 777, 923, 1080, 1159, 1241, 1300, 1425, 1537, 1573, 1589, 1641, 3062 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 7.10 (t, $J$ = 7.8 Hz, 1 H), 7.41–7.47 (m, 2 H), 7.52–7.60 (m, 2 H), 8.14 (dd, $J$ = 7.5, 1.2 Hz, 1 H), 8.47 (dm, $J$ = 8.1 Hz, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 94.8 (C), 125.5 (CH), 126.7 (CH), 126.8 (CH), 127.7 (C), 129.6 (C), 130.2 (CH), 131.8 (CH), 132.3 (CH), 135.0 (C), 138.7 (C), 141.8 (CH), 179.5 (C).

*Crystal data for* **2b**: $C_{13}H_7IOS$, $M$ = 338.15, monoclinic, $C2/c$, $a$ = 13.5793(4), $b$ = 8.3628(3), $c$ = 19.5623(6) Å, β = 101.6770(10)°, $V$ = 2175.54(12) Å$^3$, $Z$ = 8, $d$ = 2.065 g cm$^{-3}$, μ = 3.107 mm$^{-1}$. A final refinement on $F^2$ with 2491 unique intensities and 145 parameters converged at ω$R(F^2)$ = 0.0537 ($R(F)$ = 0.0249) for 2207 observed reflections with $I > 2\sigma(I)$. CCDC 1544824.

### 9′-Hydroxy-1,9′-bifluoren-9-one (3b′)

Following the typical procedure for **1b** using 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.5 mmol) in THF (2–3 mL) with ca. 1.6 M BuLi in hexanes (1.5 mmol) and then $ZnCl_2$·TMEDA[35] (0.13 g, 0.50 mmol) with addition of 9-fluorenone (**3a**, 0.18 g, 1.0 mmol) at 0–10 °C and stirring at rt for 2 h; finally $I_2$ (0.38 g, 1.5 mmol) in THF (4 mL) was added. Purification by chromatography (silica gel, heptane–$CH_2Cl_2$ 80:20) afforded **3b′** (0.11 g, 63%) as a beige powder; mp 222–224 °C (Lit.[38] 222–224 °C).

IR (ATR): 686, 728, 753, 771, 803, 909, 958, 1066, 1102, 1139, 1195, 1265, 1284, 1427, 1451, 1469, 1572, 1592, 1607, 1683, 2245, 3060, 3302 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 6.47 (dd, $J$ = 8.1, 0.9 Hz, 1 H), 7.11 (dd, $J$ = 8.1, 7.5 Hz, 1 H), 7.28 (td, $J$ = 7.5, 0.9 Hz, 2 H), 7.33–7.42 (m, 4 H), 7.47–7.57 (m, 4 H), 7.70 (d, $J$ = 7.2 Hz, 2 H), 7.78 (d, $J$ = 7.2 Hz, 1 H), 7.94 (s, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 85.5 (C), 119.9 (CH), 120.3 (2 CH), 120.3 (CH), 124.7 (2 CH), 125.3 (CH), 128.4 (CH), 128.4 (2 CH), 129.2 (2 CH), 129.6 (CH), 132.1 (C), 133.4 (C), 135.5 (CH), 136.0 (CH), 139.9 (2 C), 144.3 (C), 146.8 (C), 148.8 (C), 149.5 (2 C), 198.2 (C).

These data are as described previously.[14]

### 1-Iodo-9-fluorenone (3b)

Following the typical procedure for **1b** using 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.5 mmol) in THF (2–3 mL) with ca. 1.6 M BuLi in hexanes (1.5 mmol) and then $CdCl_2$·TMEDA[13] (0.15 g, 0.50 mmol) with addition of 9-fluorenone (**3a**, 0.18 g, 1.0 mmol) at 0–10 °C and stirring at rt for 2 h; finally $I_2$ (0.38 g, 1.5 mmol) in THF (4 mL) was added. Purification by chromatography (silica gel, heptane) afforded **3b** (0.24 g, 80%) as a yellow powder; mp 148 °C (Lit.[39] 144–145 °C).

IR (ATR): 733, 747, 784, 792, 918, 1056, 1085, 1126, 1149, 1186, 1257, 1281, 1295, 1437, 1563, 1588, 1606, 1715, 3048 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 7.15 (dd, $J$ = 8.1, 7.5 Hz, 1 H), 7.33 (ddd, $J$ = 10.2, 7.5, 4.8 Hz, 1 H), 7.49–7.56 (m, 3 H), 7.68–7.74 (m, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 91.6 (C), 120.1 (CH), 120.2 (CH), 124.7 (CH), 129.8 (CH), 134.0 (C), 134.1 (C), 135.0 (CH), 135.1 (CH), 140.6 (CH), 142.0 (C), 147.2 (C), 191.8 (C).

These data are as described previously.[14]

*Crystal data for* **3b**: $C_{13}H_7IO$, $M$ = 306.09, $T$ = 150 K, monoclinic, $P2_1$, $a$ = 7.5211(7), $b$ = 18.9683(18), $c$ = 7.6189(7) Å, β = 108.620(3)°, $V$ = 1030.04(17) Å$^3$, $Z$ = 4, $d$ = 1.974 g cm$^{-3}$, μ = 3.074 mm$^{-1}$. A final refinement on $F^2$ with 2426 unique intensities and 272 parameters converged at ω$R(F^2)$ = 0.0597 ($R(F)$ = 0.0248) for 2370 observed reflections with $I > 2\sigma(I)$. CCDC 1544826.

### 4-Iododibenzofuran (6b)

Following the typical procedure for **1b** using 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.5 mmol) in THF (2–3 mL) with ca. 1.6 M BuLi in hexanes (1.5 mmol) and then $ZnCl_2$·TMEDA[35] (0.13 g, 0.50 mmol) with addition of dibenzofuran (**6a**, 0.17 g, 1.0 mmol) and stirring at rt for 2 h; finally $I_2$ (0.38 g, 1.5 mmol) in THF (4 mL) was added. Purification by chromatography (silica gel, heptane) afforded **6b** (0.26 g, 90%) as a pale yellow powder; mp 72 °C (Lit.[40] 71–72 °C).

IR (ATR): 704, 722, 744, 785, 842, 851, 1022, 1100, 1192, 1303, 1382, 1432, 1444, 1470, 1539, 1570, 1788, 3048 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 7.09 (t, $J$ = 7.7 Hz, 1 H), 7.36 (td, $J$ = 7.5, 0.9 Hz, 1 H), 7.49 (ddd, $J$ = 8.1, 7.2, 1.2 Hz, 1 H), 7.65 (d, $J$ = 8.1 Hz, 1 H), 7.81 (dd, $J$ = 7.8, 1.2 Hz, 1 H), 7.86–7.92 (m, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 75.5 (C), 112.2 (CH), 120.6 (CH), 121.2 (CH), 123.3 (CH), 124.5 (CH), 124.6 (C), 124.7 (C), 127.8 (CH), 136.0 (CH), 155.8 (C), 156.5 (C).

These data are similar to those reported previously.[41]

### 4,6-Diiododibenzofuran (6b′)

Following the typical procedure using 2,2,6,6-tetramethylpiperidine (0.50 mL, 3.0 mmol) in THF (4 mL) with ca. 1.6 M BuLi in hexanes (3.0 mmol) and then $ZnCl_2$·TMEDA[35] (0.26 g, 1.0 mmol) and then dibenzofuran (**6a**, 0.17 g, 1.0 mmol) and stirring at rt for 2 h; finally $I_2$ (0.76 g, 3.0 mmol) in THF (7 mL) was added. Purification by chromatography (silica gel, heptane) afforded **6b′** (0.33 g, 79%) as a pale yellow powder; mp 155 °C (Lit.[42] 160 °C).

IR (ATR): 663, 672, 724, 749, 763, 853, 1024, 1051, 1174, 1403, 1413, 1458, 1570, 2852, 2922, 2953, 3061 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 7.12 (t, $J$ = 7.8 Hz, 2 H), 7.83–7.89 (m, 4 H).

$^{13}$C NMR ($CDCl_3$): δ = 75.7 (2 C), 121.1 (2 CH), 124.9 (2 CH), 125.0 (2 C), 136.7 (2 CH), 156.2 (2 C).

These data are similar to those reported previously.[43]

*Crystal data for* **6b′**: $C_{12}H_6I_2O$, $M$ = 419.97, $T$ = 150 K, monoclinic, $P2_1$, $a$ = 4.6869(8), $b$ = 13.973(3), $c$ = 17.703(3) Å, β = 92.702(7)°, $V$ = 1158.1(4) Å$^3$, $Z$ = 4, $d$ = 2.409 g cm$^{-3}$, μ = 5.400 mm$^{-1}$. A final refinement on $F^2$ with 4835 unique intensities and 266 parameters converged at ω$R(F^2)$ = 0.1172 ($R(F)$ = 0.0477) for 4447 observed reflections with $I > 2\sigma(I)$. CCDC 1544830.

### 4-Iododibenzothiophene (7b)

Following the typical procedure for **1b** using 2,2,6,6-tetramethylpiperidine (0.75 mL, 4.5 mmol) in THF (5 mL) with ca. 1.6 M BuLi in hexanes (4.5 mmol) and then $ZnCl_2$·TMEDA[35] (0.39 g, 1.5 mmol) with addition of dibenzothiophene (**7a**, 0.18 g, 1.0 mmol) and stirring at rt for 2 h; finally $I_2$ (1.1 g, 4.5 mmol) in THF (10 mL). Workup used aq

sat. $Na_2S_2O_3$ (10 mL) soln. Purification by chromatography (silica gel, heptane) afforded **7b** (0.26 g, 85%) as a pale yellow powder; mp 95–96 °C.

IR (ATR): 703, 729, 745, 785, 1010, 1022, 1100, 1302, 1382, 1432, 1539, 1789, 3047 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): δ = 7.18 (t, *J* = 7.8 Hz, 1 H), 7.47–7.50 (m, 2 H), 7.81 (dd, *J* = 7.5, 0.9 Hz, 1 H), 7.86–7.89 (m, 1 H), 8.06–8.09 (m, 1 H), 8.13 (dd, *J* = 7.8, 0.9 Hz, 1 H).

$^{13}C$ NMR ($CDCl_3$): δ = 88.3 (C), 121.2 (CH), 122.5 (CH), 122.9 (CH), 124.8 (CH), 125.8 (CH), 127.3 (CH), 135.8 (C), 136.0 (CH), 136.7 (C), 138.8 (C), 146.3 (C).

These data are similar to those reported previously.[44]

### *N*-Aryl Lactams 8c–10c, 11c–e, 12c–16c, 17c–g, 18c–e, 19c–e; General Procedure 1 (GP1)

A mixture of CuI (0.10 g, 0.50 mmol), lactam (12 mmol), $K_3PO_4$ (4.4 g, 20 mmol), halide (10 mmol), and DMEDA (0.11 mL, 1.0 mmol) in dioxane (5 mL) was degassed and heated under argon at 110 °C. After filtration over Celite (washing using EtOAc) and removal of the solvents, the crude product was purified by chromatography (silica gel).

### 1-Phenylpyrrolidin-2-one (8c)

Following GP1 using iodobenzene (**8b**, 1.1 mL) and pyrrolidin-2-one (1.0 g) with reaction time 24 h; chromatography (silica gel, hexane/EtOAc 50:50) gave **8c** (1.5 g, 95%) as a white powder; mp 67–68 °C (Lit.[45] 68–69 °C).

$^1H$ NMR ($CDCl_3$): δ = 2.16 (quint, *J* = 7.6 Hz, 2 H), 2.61 (t, *J* = 8.1 Hz, 2 H), 3.86 (t, *J* = 7.1 Hz, 2 H), 7.14 (tt, *J* = 7.6, 1.2 Hz, 1 H), 7.34–7.40 (m, 2 H), 7.59–7.63 (m, 2 H).

$^{13}C$ NMR ($CDCl_3$): δ = 18.2 ($CH_2$), 32.9 ($CH_2$), 48.9 ($CH_2$), 120.1 (2 CH), 124.6 (CH), 128.9 (2 CH), 139.5 (C), 174.4 (C).

### 1-(2-Methoxyphenyl)pyrrolidin-2-one (9c)

Following GP1 using 2-iodoanisole (**9b**, 2.3 g) and pyrrolidin-2-one (1.0 g) with reaction time 24 h; chromatography (silica gel, hexane/EtOAc 40:60) gave **9c** (1.9 g, 99%) as a pale yellow oil.

$^1H$ NMR ($CDCl_3$): δ = 2.17 (quint, *J* = 7.6 Hz, 2 H), 2.55 (t, *J* = 8.1 Hz, 2 H), 3.74 (t, *J* = 7.1 Hz, 2 H), 3.82 (s, 3 H), 6.93–7.00 (m, 2 H), 7.21–7.29 (m, 2 H).

$^{13}C$ NMR ($CDCl_3$): δ = 19.0 ($CH_2$), 31.2 ($CH_2$), 50.1 ($CH_2$), 55.6 ($CH_3$), 112.0 (CH), 120.9 (CH), 127.1 (C), 128.7 (CH), 128.8 (CH), 154.8 (C), 175.5 (C).

The spectral data are analogous to those described previously.[46]

### 1-(3-Methoxyphenyl)pyrrolidin-2-one (10c)

Following GP1 using 3-iodoanisole (**10b**, 2.3 g) and pyrrolidin-2-one (1.0 g) with reaction time 24 h; chromatography (silica gel, hexane/EtOAc 50:50) gave **10c** (1.9 g, 99%) as a pale yellow powder; mp 62–63 °C (Lit.[47] 56 °C).

$^1H$ NMR ($CDCl_3$): δ = 2.12 (quint, *J* = 7.7 Hz, 2 H), 2.59 (t, *J* = 8.1 Hz, 2 H), 3.80 (s, 3 H), 3.82 (t, *J* = 6.9 Hz, 2 H), 6.68 (ddd, *J* = 8.1, 2.4, 0.9 Hz, 1 H), 7.10 (dt, *J* = 8.1, 0.9 Hz, 1 H), 7.24 (t, *J* = 8.1 Hz, 1 H), 7.33 (t, *J* = 2.3 Hz, 1 H).

$^{13}C$ NMR ($CDCl_3$): δ = 18.0 ($CH_2$), 33.0 ($CH_2$), 48.9 ($CH_2$), 55.4 ($CH_3$), 106.0 (CH), 110.0 (CH), 112.0 (CH), 129.5 (CH), 140.6 (C), 159.9 (C), 174.4 (C).

*Crystal data for* **10c**: $C_{11}H_{13}NO_2$, *M* = 191.22, monoclinic, $P2_1/c$, *a* = 9.5486(8), *b* = 7.4520(8), *c* = 13.6565(14) Å, β = 103.073(3)°, *V* = 946.56(16) $Å^3$, *Z* = 4, *d* = 1.342 g $cm^{-3}$, μ = 0.093 $mm^{-1}$. A final refinement on $F^2$ with 2162 unique intensities and 128 parameters converged at $\omega R(F^2)$ = 0.1097 ($R(F)$ = 0.0414) for 1834 observed reflections with $I > 2\sigma(I)$. CCDC 1544832.

### 1-(4-Methoxyphenyl)pyrrolidin-2-one (11c)

Following GP1 using 4-iodoanisole (**11b**, 2.3 g) and pyrrolidin-2-one (1.0 g) with reaction time 24 h; chromatography (silica gel, hexane/EtOAc 40:60) gave **11c** (1.6 g, 85%) as a white powder; mp 119–120 °C (Lit.[48] 113–114 °C).

$^1H$ NMR ($CDCl_3$): δ = 2.13 (quint, *J* = 7.7 Hz, 2 H), 2.57 (t, *J* = 8.0 Hz, 2 H), 3.78 (s, 3 H), 3.81 (t, *J* = 6.9 Hz, 2 H), 6.89 (m, 2 H), 7.48 (m, 2 H).

$^{13}C$ NMR ($CDCl_3$): δ = 18.1 ($CH_2$), 32.6 ($CH_2$), 49.3 ($CH_2$), 55.5 ($CH_3$), 114.1 (2 CH), 121.9 (2 CH), 132.6 (C), 156.6 (C), 174.0 (C).

*Crystal data for* **11c**: $C_{11}H_{13}NO_2$, *M* = 191.22, orthorhombic, *Pcab*, *a* = 6.4531(9), *b* = 7.2771(11), *c* = 40.841(6) Å, *V* = 1917.9(5) $Å^3$, *Z* = 8, *d* = 1.325 g $cm^{-3}$, μ = 0.091 $mm^{-1}$. A final refinement on $F^2$ with 2206 unique intensities and 128 parameters converged at $\omega R(F^2)$ = 0.1947 ($R(F)$ = 0.0887) for 1434 observed reflections with $I > 2\sigma(I)$. CCDC 1544827.

### 1-(4-Methoxyphenyl)piperidin-2-one (11d)

Following GP1 using 4-iodoanisole (**11b**, 2.3 g) and piperidin-2-one (1.2 g) with reaction time 24 h; chromatography (silica gel, heptane/EtOAc 40:60) gave **11d** (1.5 g, 73%) as a pale yellow powder; mp 72 °C.

$^1H$ NMR ($CDCl_3$): δ = 1.92 (quint, *J* = 3.2 Hz, 4 H), 2.51–2.57 (m, 2 H), 3.56–3.61 (m, 2 H), 3.79 (s, 3 H), 6.90 (d, *J* = 9.0 Hz, 2 H), 7.14 (d, *J* = 9.0 Hz, 2 H).

$^{13}C$ NMR ($CDCl_3$): δ = 21.1 ($CH_2$), 23.1 ($CH_2$), 32.4 ($CH_2$), 51.6 ($CH_2$), 55.0 ($CH_3$), 114.0 (2 CH), 127.0 (2 CH), 135.9 (C), 157.6 (C), 169.7 (C).

The spectral data are analogous to those described previously.[49]

### 1-(4-Methoxyphenyl)hexahydro-2*H*-azepin-2-one (11e)[50]

Following GP1 using 4-iodoanisole (**11b**, 2.3 g) and hexahydro-2*H*-azepin-2-one (1.4 g) with reaction time 24 h; chromatography (silica gel, heptane/EtOAc 40:60) gave **11e** (2.2 g, 99%) as a pale yellow powder; mp 66 °C.

$^1H$ NMR ($CDCl_3$): δ = 1.76–1.85 (m, 6 H), 2.67–2.70 (m, 2 H), 3.69–3.72 (m, 2 H), 3.78 (s, 3 H), 6.88 (d, *J* = 9.0 Hz, 2 H), 7.11 (d, *J* = 9.0 Hz, 2 H).

$^{13}C$ NMR ($CDCl_3$): δ = 23.2 ($CH_2$), 28.5 ($CH_2$), 29.5 ($CH_2$), 37.2 ($CH_2$), 53.0 ($CH_2$), 55.1 ($CH_3$), 114.0 (2 CH), 127.0 (2 CH), 137.2 (C), 157.5 (C), 175.6 (C).

*Crystal data for* **11e**: $C_{13}H_{17}NO_2$, *M* = 219.27, monoclinic, $P2_1/c$, *a* = 6.0345(3), *b* = 19.2831(7), *c* = 10.1665(4) Å, β = 105.317(2)°, *V* = 1140.99(8) $Å^3$, *Z* = 4, *d* = 1.276 g $cm^{-3}$, μ = 0.086 $mm^{-1}$. A final refinement on $F^2$ with 2618 unique intensities and 147 parameters converged at $\omega R(F^2)$ = 0.0986 ($R(F)$ = 0.0387) for 2269 observed reflections with $I > 2\sigma(I)$. CCDC 1544833.

### 1-(4-Hydroxyphenyl)pyrrolidin-2-one (12c)

Following GP1 using 4-iodophenol (**12b**, 2.2 g) and pyrrolidin-2-one (1.0 g) with reaction time 48 h; chromatography (silica gel, hexane/EtOAc 40:60) gave **12c** (0.46 g, 26%) as a whitish powder; mp 168 °C (Lit.[51] 167 °C).

$^1$H NMR ($CDCl_3$): δ = 2.16 (quint, *J* = 7.6 Hz, 2 H), 2.61 (t, *J* = 8.1 Hz, 2 H), 3.82 (t, *J* = 7.1 Hz, 2 H), 6.19 (br s, 1 H), 6.78 (d, *J* = 9.0 Hz, 2 H), 7.32 (d, *J* = 9.0 Hz, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 18.2 ($CH_2$), 32.5 ($CH_2$), 49.9 ($CH_2$), 115.9 (2 CH), 122.9 (2 CH), 132.0 (C), 153.7 (C), 173.9 (C).

These data are analogous to those described previously.[51]

### 1-(4-Cyanophenyl)pyrrolidin-2-one (13c)[52]

Following GP1 using 4-bromobenzonitrile (**13b′**, 1.8 g) and pyrrolidin-2-one (1.0 g) with reaction time 24 h; chromatography (silica gel, hexane/EtOAc 70:30) gave **13c** (1.7 g, 89%) as a white powder; mp 115–116 °C.

IR (ATR): 748, 772, 984, 1007, 1029, 1091, 1220, 1257, 1308, 1334, 1407, 1455, 1589, 1703, 2911, 3332 $cm^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 2.19 (quint, *J* = 7.6 Hz, 2 H), 2.63 (t, *J* = 8.1 Hz, 2 H), 3.86 (t, *J* = 7.1 Hz, 2 H), 7.61 (d, *J* = 9.0 Hz, 2 H), 7.77 (d, *J* = 9.0 Hz, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 17.8 ($CH_2$), 32.9 ($CH_2$), 48.3 ($CH_2$), 107.0 (C), 119.0 (C), 119.3 (2 CH), 133.0 (2 CH), 143.2 (C), 175.0 (C).

### 1-(4-*tert*-Butylphenyl)pyrrolidin-2-one (14c)[53]

Following GP1 using 1-bromo-4-(*tert*-butyl)benzene (**14b′**, 2.1 g) and pyrrolidin-2-one (1.0 g) with reaction time 48 h; chromatography (silica gel, hexane/EtOAc 50:50) gave **14c** (0.65 g, 30%) as a pale yellow oil.

$^1$H NMR ($CDCl_3$): δ = 1.31 (s, 9 H), 2.15 (quint, *J* = 7.5 Hz, 2 H), 2.60 (t, *J* = 8.1 Hz, 2 H), 3.85 (t, *J* = 7.1 Hz, 2 H), 7.38 (d, *J* = 9.0 Hz, 2 H), 7.51 (d, *J* = 9.0 Hz, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 18.3 ($CH_2$), 29.8 ($CH_2$), 31.5 (3 $CH_3$), 32.8 (C), 49.0 ($CH_2$), 120.0 (2 CH), 125.8 (2 CH), 136.9 (C), 147.6 (C), 174.2 (C).

### 1-(2-Naphthyl)pyrrolidin-2-one (15c)

Following GP1 using 2-iodonaphthalene (**15b**, 2.5 g) and pyrrolidin-2-one (1.0 g) with reaction time 72 h; chromatography (silica gel, hexane/EtOAc 50:50) gave **15c** (0.95 g, 45%) as a yellow powder; mp 120 °C (Lit.[54] 125 °C).

$^1$H NMR ($CDCl_3$): δ = 2.27 (quint, *J* = 7.5 Hz, 2 H), 2.68 (t, *J* = 8.1 Hz, 2 H), 3.81 (t, *J* = 6.9 Hz, 2 H), 7.36 (dd, *J* = 7.2, 1.2 Hz, 1 H), 7.45–7.56 (m, 3 H), 7.74–7.90 (m, 3 H).

$^{13}$C NMR ($CDCl_3$): δ = 19.1 ($CH_2$), 31.4 ($CH_2$), 51.7 ($CH_2$), 122.6 (CH), 124.5 (CH), 125.5 (CH), 126.2 (CH), 126.6 (CH), 128.2 (CH), 128.4 (CH), 129.5 (C), 134.4 (C), 135.4 (C), 175.3 (C).

### 1-(2-Thienyl)pyrrolidin-2-one (16c)

Following GP1 using 2-iodothiophene (**16b**, 1.1 mL) [or 2-bromothiophene (**16b′**, 0.97 mL)] and pyrrolidin-2-one (1.0 g) with reaction time 24 h; chromatography (silica gel, hexane/EtOAc 50:50) gave **16c** [1.6 g, 93% (or 99%)] as a whitish powder; mp 118–119 °C (Lit.[9d] 116–117 °C).

$^1$H NMR ($CDCl_3$): δ = 2.22 (quint, *J* = 7.7 Hz, 2 H), 2.59 (t, *J* = 8.3 Hz, 2 H), 3.86 (t, *J* = 7.2 Hz, 2 H), 6.51 (dd, *J* = 3.6, 1.5 Hz, 1 H), 6.84–6.92 (m, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 17.9 ($CH_2$), 31.3 ($CH_2$), 48.8 ($CH_2$), 110.6 (CH), 118.0 (CH), 123.8 (CH), 140.5 (C), 172.1 (C).

*Crystal data for* **16c**: $C_8H_9NOS$, *M* = 167.22, monoclinic, $P2_1/n$, *a* = 7.6305(14), *b* = 8.928(2), *c* = 11.712(2) Å, β = 107.493(10)°, *V* = 761.0(3) Å$^3$, *Z* = 4, *d* = 1.46 g $cm^{-3}$, μ = 0.358 $mm^{-1}$. A final refinement on $F^2$ with 1732 unique intensities and 100 parameters converged at $\omega R(F^2)$ = 0.1199 ($R(F)$ = 0.0435) for 1379 observed reflections with $I > 2\sigma(I)$. CCDC 1544834.

### 1-(Benzofuran-2-yl)pyrrolidin-2-one (17c)

Following GP1 using 2-iodobenzofuran (**17b**, 2.4 g) and pyrrolidin-2-one (1.0 g) with reaction time 48 h; chromatography (silica gel, heptane/EtOAc 40:60) gave **17c** (1.7 g, 84%) as a white powder; mp 138 °C.

IR (ATR): 748, 772, 931, 984, 1007, 1029, 1091, 1220, 1308, 1334, 1407, 1455, 1589, 1703, 2911, 3332 $cm^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 2.24 (quint, *J* = 7.6 Hz, 2 H), 2.63 (t, *J* = 8.0 Hz, 2 H), 4.08 (t, *J* = 7.2 Hz, 2 H), 6.85 (d, *J* = 0.9 Hz, 1 H), 7.14–7.24 (m, 2 H), 7.36–7.40 (m, 1 H), 7.47–7.51 (m, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 18.4 ($CH_2$), 31.9 ($CH_2$), 46.8 ($CH_2$), 90.2 (CH), 110.5 (CH), 120.5 (CH), 122.8 (CH), 123.4 (CH), 129.5 (C), 148.9 (C), 150.0 (C), 172.9 (C).

*Crystal data for* **17c**: $C_{12}H_{11}NO_2$, *M* = 201.22, triclinic, *P*-1, *a* = 7.0061(4), *b* = 10.3157(7), *c* = 14.2592(9) Å, α = 70.602(3), β = 86.907(3), γ = 86.026(3)°, *V* = 969.19(11) Å$^3$, *Z* = 4, *d* = 1.379 g $cm^{-3}$, μ = 0.095 $mm^{-1}$. A final refinement on $F^2$ with 4400 unique intensities and 271 parameters converged at $\omega R(F^2)$ = 0.1157 ($R(F)$ = 0.0469) for 2847 observed reflections with $I > 2\sigma(I)$. CCDC 1544835.

### 1-(Benzofuran-2-yl)piperidin-2-one (17d)

Following GP1 using 2-iodobenzofuran (**17b**, 2.4 g) and piperidin-2-one (1.2 g) with reaction time 48 h; chromatography (silica gel, heptane/EtOAc 60:40) gave **17d** (2.0 g, 93%) as a white powder; mp 114–115 °C.

IR (ATR): 754, 774, 932, 985, 1008, 1092, 1182, 1221, 1335, 1408, 1455, 1489, 1567, 1591, 1668, 1704, 2955 $cm^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 1.87–1.98 (m, 4 H), 2.61 (t, *J* = 6.0 Hz, 2 H), 3.92 (t, *J* = 6.0 Hz, 2 H), 6.87 (d, *J* = 0.9 Hz, 1 H), 7.17–7.23 (m, 2 H), 7.35–7.40 (m, 1 H), 7.48–7.54 (m, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 20.7 ($CH_2$), 22.8 ($CH_2$), 33.3 ($CH_2$), 47.9 ($CH_2$), 95.0 (CH), 110.5 (CH), 120.7 (CH), 123.0 (CH), 123.1 (CH), 129.2 (C), 150.2 (C), 150.3 (C), 169.1 (C).

*Crystal data for* **17d**: $C_{13}H_{13}NO_2$, *M* = 215.24, monoclinic, $P2_1/n$, *a* = 6.2043(6), *b* = 13.6566(11), *c* = 12.3273(9) Å, β = 95.109(3)°, *V* = 1040.34(15) Å$^3$, *Z* = 4, *d* = 1.374 g $cm^{-3}$, μ = 0.093 $mm^{-1}$. A final refinement on $F^2$ with 2374 unique intensities and 145 parameters converged at $\omega R(F^2)$ = 0.1113 ($R(F)$ = 0.0437) for 1943 observed reflections with $I > 2\sigma(I)$. CCDC 1544855.

### 1-(Benzofuran-2-yl)hexahydro-2*H*-azepin-2-one (17e)

Following GP1 using 2-iodobenzofuran (**17b**, 2.4 g) and hexahydro-2*H*-azepin-2-one (1.4 g) with reaction time 24 h; chromatography (silica gel, heptane/EtOAc 60:40) gave **17e** (1.5 g, 65%) as a white powder; mp 76 °C.

IR (ATR): 746, 786, 806, 945, 970, 983, 1148, 1165, 1187, 1247, 1352, 1364, 1401, 1437, 1454, 1571, 1678, 2858, 2931 $cm^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 1.81–1.91 (m, 6 H), 2.73–2.77 (m, 2 H), 3.96–3.99 (m, 2 H), 6.73 (d, *J* = 0.9 Hz, 1 H), 7.17–7.23 (m, 2 H), 7.34–7.41 (m, 1 H), 7.46–7.53 (m, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 23.6 ($CH_2$), 28.8 ($CH_2$), 29.7 ($CH_2$), 38.0 ($CH_2$), 49.1 ($CH_2$), 95.5 (CH), 110.6 (CH), 120.7 (CH), 123.1 (CH), 123.2 (CH), 129.3 (C), 150.4 (C), 150.5 (C), 174.9 (C).

*Crystal data for* **17e**: $C_{14}H_{15}NO_2$, *M* = 229.27, monoclinic, *C*2/*c*, *a* = 15.2276(19), *b* = 10.4953(13), *c* = 14.7612(19) Å, β = 108.973(4)°, *V* = 2230.9(5) Å$^3$, *Z* = 8, *d* = 1.365 g cm$^{-3}$, μ = 0.091 mm$^{-1}$. A final refinement on $F^2$ with 2496 unique intensities and 154 parameters converged at ω*R*($F^2$) = 0.1127 (*R*(*F*) = 0.0465) for 1881 observed reflections with *I* > 2σ(*I*). CCDC 1544836.

### 1-(Benzothiophen-2-yl)pyrrolidin-2-one (18c)

Following GP1 using 2-iodobenzothiophene (**18b**, 2.6 g) and pyrrolidin-2-one (1.0 g) with reaction time 48 h; chromatography (silica gel, heptane/EtOAc 40:60) gave **18c** (1.9 g, 88%) as a white powder; mp 210 °C.

$^1$H NMR ($CDCl_3$): δ = 2.23 (quint, *J* = 7.7 Hz, 2 H), 2.64 (t, *J* = 8.1 Hz, 2 H), 3.91 (t, *J* = 7.2 Hz, 2 H), 6.65 (d, *J* = 0.6 Hz, 1 H), 7.22–7.35 (m, 2 H), 7.63 (dm, *J* = 7.8 Hz, 1 H), 7.76 (dm, *J* = 7.8 Hz, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 17.8 ($CH_2$), 31.5 ($CH_2$), 48.8 ($CH_2$), 106.1 (CH), 122.0 (CH), 122.2 (CH), 123.3 (CH), 124.5 (CH), 135.6 (C), 137.0 (C), 140.4 (C), 172.9 (C).

The spectral data are analogous to those described previously.[55]

### 1-(Benzothiophen-2-yl)piperidin-2-one (18d)

Following GP1 using 2-iodobenzothiophene (**18b**, 2.6 g) and piperidin-2-one (1.2 g) with reaction time 48 h; chromatography (silica gel, heptane/EtOAc 60:40) gave **18d** (1.9 g, 81%) as a yellow powder; mp 180 °C.

IR (ATR): 728, 741, 799, 1167, 1238, 1266, 1296, 1353, 1410, 1437, 1485, 1515, 1637, 2953, 3053 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 1.86–1.95 (m, 2 H), 1.99–2.08 (m, 2 H), 2.66 (t, *J* = 6.6 Hz, 2 H), 3.88 (t, *J* = 6.3 Hz, 2 H), 6.81 (s, 1 H), 7.25 (td, *J* = 7.2, 1.5 Hz, 1 H), 7.31 (td, *J* = 7.2, 1.2 Hz, 1 H), 7.65 (dm, *J* = 7.2 Hz, 1 H), 7.76 (dm, *J* = 7.8 Hz, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 20.5 ($CH_2$), 23.2 ($CH_2$), 33.2 ($CH_2$), 49.6 ($CH_2$), 107.0 (CH), 121.7 (CH), 122.2 (CH), 123.4 (CH), 124.3 (CH), 136.6 (C), 136.8 (C), 143.5 (C), 168.6 (C).

*Crystal data for* **18d**: $C_{13}H_{13}NOS$, *M* = 231.30, monoclinic, $P2_1/n$, *a* = 6.2311(4), *b* = 13.6241(8), *c* = 12.9733(7) Å, β = 97.711(2)°, *V* = 1091.39(11) Å$^3$, *Z* = 4, *d* = 1.408 g cm$^{-3}$, μ = 0.272 mm$^{-1}$. A final refinement on $F^2$ with 2493 unique intensities and 145 parameters converged at ω*R*($F^2$) = 0.1091 (*R*(*F*) = 0.0438) for 1983 observed reflections with *I* > 2σ(*I*). CCDC 1544837.

### 1-(Benzothiophen-2-yl)hexahydro-2*H*-azepin-2-one (18e)

Following GP1 using 2-iodobenzothiophene (**18b**, 2.6 g) and hexahydro-2*H*-azepin-2-one (1.4 g) with reaction time 48 h; chromatography (silica gel, heptane/EtOAc 70:30) gave **18e** (1.3 g, 53%) as a white powder; mp 143 °C.

IR (ATR): 744, 793, 979, 1195, 1217, 1242, 1267, 1303, 1397, 1439, 1522, 1659, 2857, 2930 cm$^{-1}$.

$^1$H NMR ($CDCl_3$): δ = 1.81–1.92 (m, 6 H), 2.78–2.82 (m, 2 H), 4.00–4.03 (m, 2 H), 6.87 (d, *J* = 0.3 Hz, 1 H), 7.24 (td, *J* = 7.5, 1.3 Hz, 1 H), 7.31 (td, *J* = 7.5, 1.3 Hz, 1 H), 7.64 (dm, *J* = 7.2 Hz, 1 H), 7.74 (dm, *J* = 7.5 Hz, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 23.4 ($CH_2$), 27.5 ($CH_2$), 29.3 ($CH_2$), 37.6 ($CH_2$), 51.4 ($CH_2$), 109.0 (CH), 121.7 (CH), 122.3 (CH), 123.4 (CH), 124.3 (CH), 136.7 (C), 136.9 (C), 144.5 (C), 174.4 (C).

*Crystal data for* **18e**: $C_{14}H_{15}NOS$, *M* = 245.33, orthorhombic, $Pbn2_1$, *a* = 6.2621(7), *b* = 9.9132(10), *c* = 19.3294(15) Å, *V* = 1199.9(2) Å$^3$, *Z* = 4, *d* = 1.358 g cm$^{-3}$, μ = 0.252 mm$^{-1}$. A final refinement on $F^2$ with 2458 unique intensities and 154 parameters converged at ω*R*($F^2$) = 0.0788 (*R*(*F*) = 0.0355) for 2294 observed reflections with *I* > 2σ(*I*). CCDC 1544838.

### 1-(Benzothiazol-2-yl)pyrrolidin-2-one (19c)

Following GP1 using 2-iodobenzothiazole (**19b**, 2.5 g) and pyrrolidin-2-one (1.0 g) with reaction time 24 h; chromatography (silica gel, heptane/EtOAc 60:40) gave **19c** (1.4 g, 66%) as a white powder; mp 180 °C.

$^1$H NMR ($CDCl_3$): δ = 2.30 (quint, *J* = 8.4 Hz, 2 H), 2.75 (t, *J* = 8.1 Hz, 2 H), 4.29 (t, *J* = 7.2 Hz, 2 H), 7.31 (ddd, *J* = 7.8, 7.2, 1.2 Hz, 1 H), 7.44 (ddd, *J* = 8.1, 7.5, 1.5 Hz, 1 H), 7.80–7.87 (m, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 18.1 ($CH_2$), 31.9 ($CH_2$), 48.2 ($CH_2$), 121.3 (CH), 121.4 (CH), 124.0 (CH), 126.1 (CH), 132.3 (C), 148.5 (C), 157.1 (C), 174.3 (C).

The spectral data are analogous to those described previously.[56]

### 1-(Benzothiazol-2-yl)piperidin-2-one (19d)

Following GP1 using 2-iodobenzothiazole (**19b**, 2.5 g) and piperidin-2-one (1.2 g) with reaction time 48 h; chromatography (silica gel, heptane/EtOAc 70:30) gave **19d** (0.35 g, 15%) as a beige powder; mp 143 °C.

$^1$H NMR ($CDCl_3$): δ = 1.92–2.06 (m, 4 H), 2.72 (t, *J* = 6.8 Hz, 2 H), 4.28 (t, *J* = 6.2 Hz, 2 H), 7.30 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.42 (td, *J* = 7.8, 1.4 Hz, 1 H), 7.82 (t, *J* = 7.7 Hz, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 20.3 ($CH_2$), 22.8 ($CH_2$), 33.2 ($CH_2$), 48.7 ($CH_2$), 121.2 (CH), 121.4 (CH), 124.0 (CH), 126.0 (CH), 133.5 (C), 148.2 (C), 159.4 (C), 170.5 (C).

The spectral data are analogous to those described previously.[55]

*Crystal data for* **19d**: $2(C_{13}H_{12}NOS)$, *M* = 460.59, tetragonal, *P*-4 $2_1/c$, *a* = 14.2662(9), *c* = 21.0404(18) Å, *V* = 4282.2(5) Å$^3$, *Z* = 8, *d* = 1.429 g cm$^{-3}$, μ = 0.277 mm$^{-1}$. A final refinement on $F^2$ with 4894 unique intensities and 289 parameters converged at ω*R*($F^2$) = 0.2382 (*R*(*F*) = 0.1) for 3133 observed reflections with *I* > 2σ(*I*). CCDC 1544839.

### 1-(Benzothiazol-2-yl)hexahydro-2*H*-azepin-2-one (19e)

Following GP1 using 2-iodobenzothiazole (**19b**, 2.5 g) and hexahydro-2*H*-azepin-2-one (1.4 g) with reaction time 48 h; chromatography (silica gel, heptane/EtOAc 60:40) gave **19e** (1.2 g, 50%) as a pale yellow powder; mp 130 °C.

$^1$H NMR ($CDCl_3$): δ = 1.83–1.90 (m, 6 H), 2.85–2.89 (m, 2 H), 4.57–4.61 (m, 2 H), 7.29 (ddd, *J* = 8.4, 7.4, 1.4 Hz, 1 H), 7.42 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1 H), 7.78–7.83 (m, 2 H).

$^{13}$C NMR ($CDCl_3$): δ = 23.5 ($CH_2$), 28.0 ($CH_2$), 29.4 ($CH_2$), 37.9 ($CH_2$), 47.8 ($CH_2$), 121.0 (CH), 121.1 (CH), 123.7 (CH), 125.9 (CH), 133.6 (C), 147.9 (C), 159.7 (C), 175.6 (C).

The spectral data are analogous to those described previously.[55]

### *N*-Arylated Pyrrolidin-2-ones 1c–7c; General Procedure 2 (GP2)

A mixture of CuI (19 mg, 0.10 mmol), $K_3PO_4$ (0.42 g, 2.0 mmol), pyrrolidin-2-one (0.17 g, 2.0 mmol), and iodide (1.0 mmol) in DMSO (2 mL) was degassed and stirred under argon at 125 °C. After cooling to rt, the mixture was filtered over Celite. $H_2O$ (25 mL) was added to the filtrate and it was extracted with $Et_2O$ (3 ×10 mL). The combined extracts were dried ($Na_2SO_4$), the solvent was removed, and the residue was purified by chromatography (silica gel).

**1-(9-Oxo-9*H*-xanthen-1-yl)pyrrolidin-2-one (1c)**

Following GP2 using 1-iodo-9-xanthone (**1b**, 0.32 g) with reaction time 24 h; chromatography (silica gel, EtOAc) gave **1c** (0.20 g, 70%) as a yellow powder; mp 236 °C.

IR (ATR): 671, 727, 767, 797, 925, 1139, 1233, 1252, 1306, 1333, 1351, 1416, 1438, 1470, 1604, 1615, 1653, 1683, 2974 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): δ = 2.33 (br s, 2 H), 2.68 (br s, 2 H), 3.82 (br s, 2 H), 7.19 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.35 (ddd, *J* = 8.1, 7.2, 1.2 Hz, 1 H), 7.45 (dd, *J* = 8.4, 0.6 Hz, 1 H), 7.51 (dd, *J* = 8.7, 1.2 Hz, 1 H), 7.70 (ddd, *J* = 8.4, 7.2, 1.5 Hz, 1 H), 7.72 (dd, *J* = 8.4, 7.5 Hz, 1 H), 8.24 (dd, *J* = 8.0, 1.4 Hz, 1 H).

$^{13}C$ NMR ($CDCl_3$): δ = 19.4 ($CH_2$), 31.6 ($CH_2$), 51.5 ($CH_2$), 117.7 (CH), 118.4 (C), 118.8 (CH), 122.6 (C), 124.2 (CH), 125.1 (CH), 126.8 (CH), 134.6 (CH), 134.9 (CH), 138.8 (C), 155.3 (C), 157.9 (C), 176.3 (C), 176.3 (C).

*Crystal data for* **1c**: $C_{17}H_{13}NO_3$, *M* = 279.28, *T* = 295 K, orthorhombic, *Pna*$2_1$, *a* = 18.9134(17), *b* = 5.5288(5), *c* = 12.5988(9) Å, *V* = 1317.44(19) $Å^3$, *Z* = 4, *d* = 1.408 g $cm^{-3}$, μ = 0.097 $mm^{-1}$. A final refinement on $F^2$ with 2959 unique intensities and 190 parameters converged at ω*R*($F^2$) = 0.1398 (*R*(*F*) = 0.0628) for 2150 observed reflections with *I* > 2σ(*I*). CCDC 1544823.

**1-(9-Thioxo-9*H*-xanthen-1-yl)pyrrolidin-2-one (2c)**

Following GP2 using 1-iodo-9-thioxanthone (**2b**, 0.34 g) with reaction time 24 h; chromatography (silica gel, EtOAc) gave **2c** (0.19 g, 65%) as a yellow powder; mp 192 °C.

IR (ATR): 673, 728, 755, 791, 918, 1079, 1122, 1160, 1249, 1308, 1409, 1449, 1591, 1641, 1691, 2975 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): δ = 2.33 (quint, *J* = 7.5 Hz, 2 H), 2.64 (t, *J* = 8.1 Hz, 2 H), 3.90 (t, *J* = 6.8 Hz, 2 H), 7.26 (dd, *J* = 6.9, 1.8 Hz, 1 H), 7.44 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1 H), 7.49–7.63 (m, 4 H), 8.40 (ddd, *J* = 8.7, 1.5, 0.6 Hz, 1 H).

$^{13}C$ NMR ($CDCl_3$): δ = 19.4 ($CH_2$), 31.9 ($CH_2$), 51.6 ($CH_2$), 125.4 (CH), 126.0 (C), 126.3 (CH), 122.6 (CH), 127.4 (CH), 129.9 (CH), 131.3 (C), 132.1 (CH), 132.3 (CH), 135.7 (C), 139.5 (C), 140.5 (C), 175.8 (C), 180.8 (C).

*Crystal data for* **2c**: $C_{17}H_{13}NO_2S$, *M* = 295.34, *T* = 150 K, monoclinic, *P*$2_1$/*c*, *a* = 13.3409(9), *b* = 5.4022(5), *c* = 18.5865(15) Å, β = 100.595(3)°, *V* = 1316.70(18) $Å^3$, *Z* = 4, *d* = 1.490 g $cm^{-3}$, μ = 0.249 $mm^{-1}$. A final refinement on $F^2$ with 2988 unique intensities and 190 parameters converged at ω*R*($F^2$) = 0.0889 (*R*(*F*) = 0.0394) for 2290 observed reflections with *I* > 2σ(*I*). CCDC 1544825.

**1-(9-Oxo-9*H*-fluoren-1-yl)pyrrolidin-2-one (3c)**

Following GP2 using 1-iodo-9-fluorenone (**3b**, 0.31 g) with reaction time 24 h; chromatography (silica gel, EtOAc) gave **3c** (0.16 g, 62%) as a yellow powder; mp 124 °C.

IR (ATR): 676, 757, 802, 911, 1148, 1188, 1239, 1308, 1398, 1455, 1484, 1591, 1607, 1700, 2973 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): δ = 2.27 (quint, *J* = 7.4 Hz, 2 H), 2.63 (t, *J* = 8.0 Hz, 2 H), 3.90 (t, *J* = 6.9 Hz, 2 H), 7.22 (dd, *J* = 7.7, 1.1 Hz, 1 H), 7.29 (td, *J* = 7.2, 1.2 Hz, 1 H), 7.43–7.54 (m, 4 H), 7.61 (dt, *J* = 7.5, 1.7 Hz, 1 H).

$^{13}C$ NMR ($CDCl_3$): δ = 19.3 ($CH_2$), 31.7 ($CH_2$), 50.4 ($CH_2$), 119.2 (CH), 120.4 (CH), 124.4 (CH), 127.9 (C), 128.2 (CH), 129.5 (CH), 134.2 (C), 134.7 (CH), 135.7 (CH), 137.1 (C), 143.7 (C), 146.2 (C), 175.4 (C), 191.7 (C).

*Crystal data for* **3c**: 2($C_{17}H_{10}NO_2$), *M* = 520.52, monoclinic, *P*$2_1$/*c*, *a* = 7.0380(3), *b* = 22.3046(13), *c* = 16.6958(9) Å, β = 104.886(2)°, *V* = 2532.9(2) $Å^3$, *Z* = 4, *d* = 1.365 g $cm^{-3}$, μ = 0.090 $mm^{-1}$. A final refinement on $F^2$ with 5301 unique intensities and 331 parameters converged at ω*R*($F^2$) = 0.3050 (*R*(*F*) = 0.1373) for 4131 observed reflections with *I* > 2σ(*I*). CCDC 1544828.

**1-(2-Benzoylphenyl)pyrrolidin-2-one (4c)**

Following GP2 using 2-iodobenzophenone (**4b**, 0.31 g) with reaction time 24 h; chromatography (silica gel, EtOAc/heptane 80:20) gave **4c** (0.15 g, 56%) as a yellow oil.

IR (ATR): 701, 756, 921, 1137, 1236, 1316, 1397, 1454, 1484, 1599, 1664, 1698, 2961 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): δ = 1.88 (quint, *J* = 7.4 Hz, 2 H), 2.21 (t, *J* = 8.0 Hz, 2 H), 3.77 (t, *J* = 6.9 Hz, 2 H), 7.29 (dd, *J* = 8.0, 0.7 Hz, 1 H), 7.34 (td, *J* = 7.8, 1.2 Hz, 1 H), 7.40–7.47 (m, 2 H), 7.49–7.58 (m, 3 H), 7.78–7.83 (m, 2 H).

$^{13}C$ NMR ($CDCl_3$): δ = 18.7 ($CH_2$), 31.4 ($CH_2$), 50.8 ($CH_2$), 125.4 (CH), 126.5 (CH), 128.3 (2 CH), 129.9 (2 CH), 130.2 (CH), 131.7 (CH), 132.9 (CH), 135.7 (C), 137.4 (C), 137.5 (C), 174.6 (C), 195.9 (C).

The spectral data are analogous to those described previously.[57]

**1-(2-Benzoyl-3-pyridyl)pyrrolidin-2-one (5c)**

Following GP2 using 2-benzoyl-3-iodopyridine[14] (**5b**, 0.31 g) with reaction time 72 h; chromatography (silica gel, EtOAc/heptane 60:40) gave **5c** (0.11 g, 40%) as a pale yellow powder; mp 132 °C.

IR (ATR): 664, 693, 711, 781, 804, 815, 920, 946, 1022, 1066, 1151, 1225, 1241, 1296, 1315, 1328, 1397, 1457, 1666, 1692, 2888, 2923, 2968, 3063 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): δ = 2.14 (quint, *J* = 7.2 Hz, 2 H), 2.39 (t, *J* = 8.0 Hz, 2 H), 3.88 (t, *J* = 6.9 Hz, 2 H), 7.42–7.49 (m, 3 H), 7.55 (td, *J* = 7.4, 1.2 Hz, 1 H), 7.67 (d, *J* = 8.1 Hz, 1 H), 7.92–7.96 (m, 2 H), 8.53 (d, *J* = 4.5 Hz, 1 H).

$^{13}C$ NMR ($CDCl_3$): δ = 18.8 ($CH_2$), 31.4 ($CH_2$), 50.2 ($CH_2$), 125.4 (CH), 128.3 (2 CH), 130.7 (2 CH), 132.9 (CH), 133.2 (CH), 134.1 (C), 135.8 (C), 146.0 (CH), 152.4 (C), 174.6 (C), 193.1 (C).

*Crystal data for* **5c**: $C_{16}H_{14}N_2O_2$, *M* = 266.29, *T* = 150 K, monoclinic, *P*$2_1$/*c*, *a* = 10.8301(10), *b* = 8.2056(6), *c* = 14.9205(14) Å, β = 91.168(4)°, *V* = 1325.7(2) $Å^3$, *Z* = 4, *d* = 1.334 g $cm^{-3}$, μ = 0.090 $mm^{-1}$. A final refinement on $F^2$ with 3012 unique intensities and 181 parameters converged at ω*R*($F^2$) = 0.1349 (*R*(*F*) = 0.0550) for 2432 observed reflections with *I* > 2σ(*I*). CCDC 1544829.

**1-(Dibenzofuran-4-yl)pyrrolidin-2-one (6c)**

Following GP2 using 4-iododibenzofuran (**6b**, 0.29 g) with reaction time 48 h; chromatography (silica gel, heptane/EtOAc 60:40) gave **6c** (0.13 g, 50%) as a beige powder; mp 85 °C.

IR (ATR): 675, 740, 753, 832, 1019, 1192, 1250, 1265, 1299, 1318, 1392, 1424, 1451, 1503, 1602, 1688, 2895, 2924, 2985 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): δ = 2.27 (quint, *J* = 7.6 Hz, 2 H), 2.65 (t, *J* = 8.0 Hz, 2 H), 4.12 (t, *J* = 6.9 Hz, 2 H), 7.31–7.38 (m, 2 H), 7.45 (td, *J* = 7.8, 1.4 Hz, 1 H), 7.57 (d, *J* = 8.1 Hz, 1 H), 7.67 (dd, *J* = 8.0, 1.1 Hz, 1 H), 7.81 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.93 (dd, *J* = 7.5, 0.6 Hz, 1 H).

$^{13}C$ NMR ($CDCl_3$): δ = 19.0 ($CH_2$), 31.5 ($CH_2$), 49.9 ($CH_2$), 111.8 (CH), 118.7 (CH), 120.8 (CH), 123.1 (CH), 123.1 (CH), 123.7 (C), 123.9 (CH), 124.0 (C), 126.0 (C), 127.5 (CH), 149.5 (C), 156.0 (C), 174.8 (C).

**1-(Dibenzothiophen-4-yl)pyrrolidin-2-one (7c)**

Following GP2 using 4-iododibenzothiophene (**7b**, 0.31 g) with reaction time 48 h; chromatography (silica gel, heptane/EtOAc 60:40) gave **7c** (0.14 g, 54%) as a beige powder; mp 98 °C.

IR (ATR): 704, 744, 837, 848, 888, 1067, 1120, 1206, 1229, 1243, 1270, 1305, 1410, 1443, 1466, 1569, 1606, 1682, 1729, 2901, 2972, 2988, 3675 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): δ = 2.25 (quint, *J* = 7.5 Hz, 2 H), 2.64 (t, *J* = 8.1 Hz, 2 H), 3.90 (t, *J* = 6.9 Hz, 2 H), 7.36–7.50 (m, 4 H), 7.79–7.83 (m, 1 H), 8.06 (dd, *J* = 7.8, 1.2 Hz, 1 H), 8.09–8.13 (m, 1 H).

$^{13}C$ NMR ($CDCl_3$): δ = 19.4 ($CH_2$), 31.5 ($CH_2$), 49.8 ($CH_2$), 120.5 (CH), 121.9 (CH), 122.8 (CH), 124.2 (CH), 124.6 (CH), 125.3 (CH), 127.2 (CH), 133.8 (C), 135.6 (C), 136.1 (C), 137.6 (C), 139.3 (C), 174.4 (C).

***N*-Iodoarylated Pyrrolidines 6c′ and 8c′; General Procedure 3 (GP3)**

A mixture of CuI (38 mg, 0.20 mmol), $K_3PO_4$ (0.84 g, 4.0 mmol), pyrrolidin-2-one (0.34 g, 4.0 mmol), and iodide (1.0 mmol) in DMSO (2 mL) was degassed and stirred under argon at 125 °C. After cooling to rt, the mixture was filtered over Celite. $H_2O$ (25 mL) was added to the filtrate and it was extracted with $Et_2O$ (3 × 10 mL). The combined extracts were dried ($Na_2SO_4$), the solvent was removed, and the residue was purified by chromatography (silica gel).

**1-(Dibenzofuran-4-yl)pyrrolidin-2-one (6c) and 1-(6-Iododibenzofuran-4-yl)pyrrolidin-2-one (6c′)**

Following GP3 using 4,6-diiododibenzofuran (**6b′**, 0.42 g) with reaction time 48 h; chromatography (silica gel, heptane/EtOAc 60:40) gave **6c** (0.21 g, 55%) and **6c′**, which was also detected in the crude product, and identified by NMR.

**1-(6-Iododibenzofuran-4-yl)pyrrolidin-2-one (6c′)**

$^1H$ NMR ($CDCl_3$): δ = 2.32 (quint, *J* = 7.5 Hz, 2 H), 2.68 (t, *J* = 8.0 Hz, 2 H), 4.28 (t, *J* = 7.1 Hz, 2 H), 7.13 (t, *J* = 7.7 Hz, 1 H), 7.39 (t, *J* = 7.8 Hz, 1 H), 7.78 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.79–7.84 (m, 2 H), 7.90 (dd, *J* = 7.7, 1.1 Hz, 1 H).

$^{13}C$ NMR ($CDCl_3$): δ = 19.3 ($CH_2$), 31.7 ($CH_2$), 50.0 ($CH_2$), 75.5 (C), 118.8 (CH), 120.8 (CH), 123.8 (CH), 124.2 (CH), 124.2 (C), 124.4 (C), 124.9 (CH), 126.3 (C), 136.2 (CH), 148.4 (C), 156.4 (C), 175.1 (C).

**1,1′-(1,4-Phenylene)bispyrrolidin-2-one (8c″) and 1-(4-Iodophenyl)pyrrolidin-2-one (8c′)**

Following GP3 using 1,4-diiodobenzene (**8b′**, 0.33 g) with reaction time 24 h; chromatography (silica gel, EtOAc/MeOH 90:10) gave **8c″** and **8c′**

**1,1′-(1,4-Phenylene)bispyrrolidin-2-one (8c″)**

Beige powder; yield: 73 mg (30%) as a beige powder; mp 255 °C (Lit.[58] 251–253 °C).

IR (ATR): 832, 1223, 1300, 1387, 1425, 1456, 1512, 1674, 2340, 2894 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): δ = 2.14 (quint, *J* = 7.5 Hz, 4 H), 2.59 (t, *J* = 8.1 Hz, 4 H), 3.83 (t, *J* = 6.9 Hz, 4 H), 7.59 (s, 4 H).

$^{13}C$ NMR ($CDCl_3$): δ = 18.0 (2 $CH_2$), 32.7 (2 $CH_2$), 48.8 (2 $CH_2$), 120.3 (4 CH), 135.9 (2 C), 174.2 (2 C).

*Crystal data for* **8c″**: $C_{14}H_{16}N_2O_2$, *M* = 244.29, *T* = 150 K, monoclinic, $P2_1/c$, *a* = 12.2154(6), *b* = 7.2772(3), *c* = 6.5169(3) Å, β = 91.436(2)°, *V* = 579.13(5) $Å^3$, *Z* = 2, *d* = 1.401 g $cm^{-3}$, μ = 0.095 $mm^{-1}$. A final refinement on $F^2$ with 1315 unique intensities and 82 parameters converged at $\omega R(F^2)$ = 0.1134 ($R(F)$ = 0.0425) for 1202 observed reflections with $I > 2\sigma(I)$. CCDC 1544831.

**1-(4-Iodophenyl)pyrrolidin-2-one (8c′)**

White powder; yield: 20 mg (7%); mp 140 °C (Lit.[59] 140–142 °C).

IR (ATR): 694, 735, 765, 812, 836, 1001, 1034, 1068, 1126, 1189, 1224, 1303, 1386, 1403, 1484, 1583, 1598, 1678, 2854, 2924, 2955, 3101, 3349 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$): δ = 2.15 (quint, *J* = 7.5 Hz, 2 H), 2.59 (t, *J* = 8.1 Hz, 2 H), 3.81 (t, *J* = 7.1 Hz, 2 H), 7.37–7.42 (m, 2 H), 7.62–7.67 (s, 2 H).

$^{13}C$ NMR ($CDCl_3$): δ = 18.0 ($CH_2$), 32.8 ($CH_2$), 48.6 ($CH_2$), 88.0 (C), 121.6 (2 CH), 128.9 (C), 137.8 (2 CH), 174.4 (C).

The spectral data are analogous to those described previously.[59]

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