METHODS FOR FORMING ARYL CARBON-NITROGEN BONDS USING LIGHT AND PHOTOREACTORS USEFUL FOR CONDUCTING SUCH REACTIONS

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The disclosure relates to a dual catalytic method for forming aryl carbon-nitrogen bonds. The method comprises contacting an aryl halide with an amine in the presence of a dual catalytic solution comprising a Ni(II) salt catalyst, a photocatalyst, and an optional base, thereby forming a reaction mixture; exposing the reaction mixture to light under reaction condition sufficient to produce the aryl carbon-nitrogen bonds. In certain embodiments, the amine may be present in a molar excess to the aryl halide. In certain embodiment, the photocatalyst may be [Ru(bpy)$_3$]Cl$_2$ or an organic phenoxazine. In certain embodiments, the Ni salt catalyst solution includes a Ni(II) salt and a polar solvent, wherein the Ni(II) salt is dissolved in the polar solvent.
Previous Methods:

Heat-driven
a) Cu, ligand, high T, mild base
b) Pd, ligand, high T, strong base
c) Ni(0), ligand, high T, strong base

Light or electricity-driven
d) Cu(I), rt, UV light (e.g. 254 nm), strong base
e) Ni(II)/Ir PC, rt, blue LED, mild base
f) Ni(II)/organic PC, rt, white LED, mild base
g) Ni(II), ligand, rt, electricity, no added base

Methods of the Disclosure:

h) NiBr$_2$ 3H$_2$O, rt, light driven, e.g., 365 nm LED, blue or green visible light
   - economical and abundant Ni source
   - rt, ligand-free and optional added base
   - optional added photoredox catalyst
   - tolerant to O$_2$ and H$_2$O
   - broad scope

![Chemical reaction](image)

FIG. 1
5 mol% NiBr₂•3H₂O 1.5 equiv. quinuclidine
DMAC (0.4 M), N₂, rt, 3 h
13 W 365 nm LED

95% (91%) c

1.0 equiv.

1.5 equiv.
FIG. 3A
FIG. 3B

Chemical structures and their corresponding yields are shown in the figure. The yields are indicated in parentheses next to each structure. The structures are numbered from 1 to 15, with specific conditions for each reaction step also mentioned.
Conversion = \frac{1}{(1+3.10)} = 24\%
Fig. 14A

NIRb3-3HbO (5 mol %) LED

[Diagram showing chemical structures and data]

Fig. 14C

C-N cross coupling through E,T

[Graph showing normalized emission and absorption spectra]

Fig. 14E

Normalized emission

[Table showing parameters and values]
FIG. 16A

[NIBr₂(quinuclidine)]

[A] [NIBr₂(morpholine)]

FIG. 16B

[NIBr₂(propylamine)]

[B] [NIBr₂(morpholine)]

FIG. 16C

[C] Ni-amine Complex Bond

<table>
<thead>
<tr>
<th>Wavelength (nm)</th>
<th>Dist. (Å)</th>
<th>Value (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>550</td>
<td>2.105(2)</td>
<td>85.54(8)</td>
</tr>
<tr>
<td>560</td>
<td>2.148(2)</td>
<td>94.46(8)</td>
</tr>
<tr>
<td>800</td>
<td>2.616(2)</td>
<td>180.</td>
</tr>
<tr>
<td>800</td>
<td>2.0317(18)</td>
<td>112.31(10)</td>
</tr>
<tr>
<td>800</td>
<td>2.3852(3)</td>
<td>126.32(2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wavelength (nm)</th>
<th>Dist. (Å)</th>
<th>Value (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>550</td>
<td>2.099(4)</td>
<td>107.5(2)</td>
</tr>
<tr>
<td>560</td>
<td>2.050(4)</td>
<td>110.71(3)</td>
</tr>
<tr>
<td>800</td>
<td>2.5359(9)</td>
<td>128.11(10)</td>
</tr>
<tr>
<td>800</td>
<td>2.0317(18)</td>
<td>112.31(10)</td>
</tr>
<tr>
<td>800</td>
<td>2.3852(3)</td>
<td>126.32(2)</td>
</tr>
</tbody>
</table>
C-N Cross Coupling Scope

NIBI, 34,0 (5 mol %), blue LED R, PC 1 or 2 (0.2 mol %), DMAC, 15 hrs.

3.5 eq.

PATENT APPLICATION PUBLICATION

FIG. 17
METHODS FOR FORMING ARYL CARBON-NITROGEN BONDS USING LIGHT AND PHOTOREACTORS USEFUL FOR CONDUCTING SUCH REACTIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application is a continuation-in-part of U.S. application Ser. No. 16/404,255, filed May 6, 2019, which claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 62/688,515 filed May 8, 2018, the contents of which are hereby incorporated by reference in their entireties.

GOVERNMENTAL RIGHTS

[0002] This invention was made with government support under F32GM122392 and R35GM119702 awarded by the National Institutes of Health and DE-AR0000881 awarded by the Defense Advanced Research Projects Agency. The government has certain rights in the inventions disclosed.

FIELD OF THE INVENTION

[0003] The present disclosure relates to methods for forming aryl carbon-nitrogen bonds and to photoreactors useful for conducting these and other light-driven reactions.

BACKGROUND OF THE INVENTION

[0004] C—N cross-coupling is an important class of reactions with far-reaching impacts across chemistry, materials science, biology, and medicine. Transition metal complexes can elegantly orchestrate diverse assemblies of aminations, however they typically require harsh reaction conditions, precious metal catalysts, or oxygen sensitive procedures.

[0005] What is needed, therefore, is a method for forming aryl carbon-nitrogen bonds that form under less extreme conditions and utilize an environmentally friendly catalyst.

[0006] Photochemistry comprises chemical reactions of atoms or molecules that have been electronically excited by absorption of light with wavelength typically in the range of 200 nm to about 700 nm. However, photoreactors used in connection with such photochemistry are often inefficient.

[0007] What is needed, therefore, are improved photoreactors for use in connection with photochemistry.

SUMMARY OF THE INVENTION

[0008] A dual catalytic method for forming an aryl carbon-nitrogen bond, the method comprising contacting an aryl halide with an amine in the presence of a dual catalytic solution comprising a Ni(n) salt catalyst, a photocatalyst, and an optional base, thereby forming a reaction mixture, and exposing the reaction mixture to light under reaction conditions sufficient to form the aryl carbon-nitrogen bond.

[0009] In certain embodiments, the amine may be present in a molar excess to the aryl halide.

[0010] In certain embodiments, the photocatalyst may be [Ru(bpy)3]Cl2 or an organic phenoxyazine.

[0011] In certain embodiments, the Ni salt may be a nickel bromide salt such as NiBr3.H2O salt.

[0012] In certain embodiments, the optional base may be an amine containing base such as quinoline.

[0013] In certain embodiments, the Ni salt catalyst solution includes a polar solvent, where the Ni salt is in the polar solvent. In other embodiments, the reaction mixture includes a polar solvent. In certain embodiments, the polar solvent may be N,N-dimethylacetamide.

[0014] In certain embodiments, the light may be visible light or UV light, e.g., 365 nm, 405 nm, 457 nm, 523 nm, etc.

[0015] These and other aspects and iterations of the disclosure are described in more detail below.

BRIEF DESCRIPTION OF THE FIGURES

[0016] The patent application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of necessary fee.


[0018] FIG. 2 depicts an exemplary C—N cross-coupling reaction of the disclosure.

[0019] FIG. 3A, FIG. 3B, and FIG. 3C describe an exemplary C—N cross-coupling via direct photoexcitation of nickel-amine complex (FIG. 3A): amine (FIG. 3B) and aryl halide scope (FIG. 3C) in accordance with embodiments of the disclosure.

[0020] FIG. 4 depicts a schematic of a photoreactor of the disclosure.

[0021] FIG. 5 depicts the conversion of the C—N coupled product determined from 1H NMR in accordance with embodiments of the disclosure.

[0022] FIG. 6 depicts the molar absorptivity vs. wavelength for 4-bromobenzotrifluoride and morpholine individually and combined in DMAc, 0.4 M in 4-bromobenzotrifluoride and 1.4 M in morpholine in accordance with embodiments of the disclosure.

[0023] FIG. 7 depicts the molar absorptivity vs. wavelength for NiBr2.3H2O and its combinations with 4-bromobenzotrifluoride and morpholine in DMAc in accordance with embodiments of the disclosure.

[0024] FIG. 8 depicts the absorption spectra of NiBr2.3H2O at concentrations ranging from 0.02-0.004 M in DMAc. Inset: a photo of the solution and linear regressions at 657 nm and 473 nm in accordance with embodiments of the disclosure.

[0025] FIG. 9 depicts the absorption spectra of NiBr2.3H2O+4-BrBzCF3 at concentrations ranging from 0.02-0.004 M (NiBr2.3H2O) and 0.4-0.08 M (4-BrBzCF3) in DMAc. Inset: linear regressions at 657 nm and 473 nm in accordance with embodiments of the disclosure.

[0026] FIG. 10 depicts the absorption spectra of NiBr2.3H2O+morpholine at concentrations ranging from 0.02-0.004 M (NiBr2.3H2O) and 1.4-0.28 M (morpholine) in DMAc. Inset: a photo of the mixture and linear regressions at 736 nm and 427 nm in accordance with embodiments of the disclosure.

[0027] FIG. 11 depicts the absorption spectra of NiBr2.3H2O+morpholine+4-BrBzCF3 at concentrations ranging from 0.02-0.004 M (NiBr2.3H2O)+1.4-0.28 M (morpholine), and 0.4-0.08 M (4-BrBzCF3) in DMAc. Inset: linear regressions at 736 nm and 427 nm in accordance with embodiments of the disclosure.

[0028] FIG. 12A and FIG. 12B depict synthetic applications in accordance with embodiments of the disclosure.
Right axis: solid-state UV-visible absorption spectra of single crystals of complexes shown in (FIG. 16A). Inset: photographs of single crystals of each complex. (FIG. 16C) Selected bond distances and angles.

[0033] FIG. 17. Scope of C—N coupling reactions using PC 1 and PC 2; PC 1 = [Ru(bpy)3]Cl2 and PC 2 = 3,7-di[1,1’-biphenyl]-1-[4-yl]-10-(naphthalen-1-yl)-10H-phthalazinone. Yields were determined using 19F NMR where possible. Isolated yields are reported in parentheses. X−Br unless otherwise indicated. ai eq. KBr was used as an additive. bi 1.5 eq. of the amine was used with 1.5 eq. added quinuclidine. cAn aryl iodide was used. tr-trace product isolated. Reactions were performed with 0.4 mmol of aryl halide at room temperature. The blue LED emission $\lambda_{max} = 457$ nm.

[0034] FIG. 18. Proposed Mechanism. Values in black were calculated by density functional theory. Values shown in blue were measured experimentally. It is noted that that multiple pathways are possible for the first additions of morpholine, with the most likely hypothesized pathway shown in FIG. 18 involving ligand substitution of the tetrabromonickelate anion.

DETAILED DESCRIPTION OF THE INVENTION

[0035] Provided herein are methods for forming aryl carbon-nitrogen bonds. Suitable reaction components and parameters for forming aryl carbon-nitrogen bonds are detailed below. In accordance with certain aspects, the present disclosure provides a nickel-catalyzed C—N cross-coupling methodology that operates at room temperature using an inexpensive nickel source (e.g., a Ni bromide salt). In other aspects, the reaction is tolerant to oxygen and proceeds through direct irradiation of the Ni complex.

[0036] Certain aspects of the disclosure encompass a method for forming an aryl carbon-nitrogen bond. The method comprises contacting an aryl halide with an amine in the presence of a Ni salt catalyst solution and an optional base, thereby forming a reaction mixture, and exposing the reaction mixture to light under reaction conditions sufficient to produce the aryl carbon-nitrogen bond. In some aspects, the methods may include the addition of an optional photocatalyst (PC) to the reaction mixture.

[0037] In certain embodiments, the method is a dual catalytic method comprising contacting an aryl halide with an amine in the presence of a dual catalytic solution comprising a Ni(II) salt catalyst, a photocatalyst, and an optional base, thereby forming a reaction mixture; and exposing the reaction mixture to light under reaction conditions sufficient to form the aryl carbon-nitrogen bond.

[0038] In certain embodiments, the light is visible light or UV light. In certain embodiments, the amine is present in a molar excess to the aryl halide. In certain embodiments, the Ni salt catalyst solution includes a Ni salt and a polar solvent, wherein the Ni salt is dissolved in the polar solvent. In other embodiments, the reaction mixture includes a polar solvent. In yet other embodiments, the reaction mixture may include an optional PC.

[0039] In certain embodiments, the reactions conditions include holding the reaction mixture at suitable temperatures, e.g., between about room temperature and about 100°C, between room temperature and about 90°C, between about room temperature and about 80°C, etc., for between about 30 minutes and about 20 hours, for between about 1
hour and about 20 hours, etc., such that at least about 50% yield, at least about 55% yield, at least about 60% yield, etc., is obtained.

[0040] Aryl carbon-nitrogen (C—N) bonds are ubiquitous across a wide range of natural products and medicinally-relevant compounds, making amations one of the most important and frequently used reactions in medicinal chemistry. Discov...ed in the early 1900s, copper-catalyzed Ullmann condensations constitute one of the oldest methods to construct an aryl C—N bond, however commonly require elevated temperatures that can limit reaction scope. The field of transition metal catalyzed C—N bond formation has since evolved to provide a plethora of approaches for efficient aminations (Fig. 1). For example, palladium-catalyzed Buchwald-Hartwig C—N cross-coupling has become the predominant method for constructing aryl C—N bonds. However, the use of palladium as well as the requirements for high temperatures (e.g., 800°C or more) and strong alkoxide bases (e.g., NaOtBu) presents toxicity concerns and can limit functional group tolerance. As such, the potential to use abundant nickel in place of palladium has received significant interest. The widespread use of the Ni(0) system is, however, hampered by the required use of high temperatures, strong alkoxide bases, and air-sensitive Ni(0) compounds (e.g., bis(cyclooctadiene)nickel) and although methods that implement air-stable Ni(II) complexes have been developed, they do not address all of the challenges. In recent years a new paradigm has arisen in aryl C—N bond formations that are driven by light or electricity in preference to heat. In 2012, a photoinduced Ullmann C—N cross-coupling was reported. Deprotonated amine (e.g., carbazole) and Cu(I) species form a Cu-amine complex (e.g., Cu-carbazole complex). Upon light irradiation, the Cu-amine complex and an aryl halide participated in a single electron transfer event to facilitate aryl C—N bond formation at room temperature. This reaction, nevertheless, typically requires a strong alkoxide base, high energy UV irradiation (e.g., 254 nm), and has a restricted substrate scope. In 2016, dual photoredox systems driven by light and Ni catalysis for C—N cross-couplings were reported. A Ni(II) salt (e.g., NiBr2-glyme), in conjunction with an iridium-based photocatalyst (PC) proved successful in constructing aryl C—N bonds under blue LED irradiation and mild conditions (e.g., ligand-free, room temperature, and a mild organic base). In an ensuing report, it was demonstrated that ditydrophenazine and phenoxazine organic PCs as sustainable replacements for the precious metal iridium PC, achieving dual Ni/photocatalysis for aryl C—N bond formation under similar mild reaction conditions. In addition to light, electricity was recently employed to alter the redox state of Ni to achieve aryl C—N bond formation, although electrochemical aryl amination involving anilines has not yet been demonstrated and the use of ligands is required. Nevertheless, mild and oxygen tolerant C—N bond forming reactions not requiring precious metals are still in need to be developed for this important chemical transformation.

[0042] In certain aspects, the present disclosure provides a light-driven, Ni-catalyzed C—N cross-coupling methodology that does not use an added photocatalyst and operates via direct photoexcitation of a reaction mixture. Without intending to be bound by theory, the present disclosure provides that the catalytically active Ni state for C—N cross-coupling can be accessed through an electronically excited nickel-amine complex without the aid of a supplementary photocatalyst to affect electron or energy transfer.

[0043] In other aspects, the present disclosure provides a light-driven, dual catalyzed C—N cross-coupling methodology that proceeds under conditions with a dual catalyst solution comprising a Ni salt catalyst and a photocatalyst. Without intending to be bound by theory, the present disclosure provides that, in the absence of an added PC, the catalytically active Ni state for C—N cross-coupling can be accessed directly through electron transfer (ET) from photoexcitation. Similarly, in a dual catalytic system, an analogous (but possibly distinct) Ni excited state can be accessed through energy transfer (EnT) from a PC. In this regard, a dual catalytic system with a Ni salt catalyst and a photocatalyst enables mild visible light irradiation. Thus, addition of an PC can enable use of UV-sensitive substrates.

[0044] Again, without intending to be bound by theory, in certain embodiments of the disclosure, spectroscopic evidence in support of EnT from an excited state PC to Ni-amine complexes under conditions relevant for dual catalytic C—N cross-coupling driven by visible light is provided. In particular, using nanosecond transient absorption (TA) spectroscopy, the excited state of [Ru(bpy)3]Cl2 (bpy = 2,2'-bipyridine) reacting with Ni-amine complexes formed in situ in C—N coupling reaction mixtures was observed. The spectral data is consistent with an EnT pathway proceeding primarily through a Förster type mechanism, a result that is notably distinct from the Dexter type pathway typically invoked in the literature in catalytic cycles involving EnT that results in substrate sensitization. Next, speciation studies elucidated the Ni-amine complexes that serve as EnT acceptors (or as light absorbers in the direct excitation method). Finally, these mechanistic insights were utilized in conjuction with quantitative Förster theory to select an organic phenoxazine PC that proved to be more effective than [Ru(bpy)3]Cl2 in the C—N coupling of various substrate pairs.

[0045] In accordance with certain aspects of the disclosure, as described in the Examples below, it has been determined that efficient C—N cross-coupling at high yields can be achieved between an aryl halide (e.g., 4-bromobenzotriazolide) and an amine (e.g., morpholine) when irradiated with visible or ultraviolet LED (e.g., 365 nm, 405 nm, 457 nm, 523 nm, etc.) in the presence of a Ni(II) salt catalyst solution (e.g., Ni DMAC solution containing 5 mol % NiBr2·3H2O and 1.5 equivalent quinhydrone) under an oxygen atmosphere at room temperature (Table 1, FIG. 2). After 3 hours of irradiation, C—N coupled product 1 (FIG. 2) was obtained in 95% yield (determined from 1H-NMR), and was isolated at 91% yield. Control experiments revealed that no reaction occurred in the absence of light at either room temperature or 800°C (Table 1, entry 1). Irradiation using a visible blue light (405 nm) LED was similarly effective at promoting aryl C—N bond formation (93%, Table 1, entry 2) although proceeding at a slower rate. The nickel salt is crucial for amination as no reaction was observed in its absence (Table 1, entry 3). At 95% yield, both hydrated nickel salts NiBr2·3H2O and NiCl2·6H2O (Table 1, entry 5) gave identical yield to NiBr2-glyme (Table 1, entry 4), which was used in previous light or electrochemically driven C—N cross-coupling reactions (FIG. 1, schemes e, f, and g). Markedly, hydrated nickel salts are at least two orders
of magnitude cheaper than NiBr₂·glyme, thus rendering the aryl C–N cross-coupling methodology of the disclosure economically attractive.

### Table 1
Reaction development and control experiments.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from conditions above</th>
<th>Yield[^a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No light (rt or 80°C)</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>13 W 405 nm LED</td>
<td>93%</td>
</tr>
<tr>
<td>3</td>
<td>No nickel salt</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>5 mol % NiBr₂·glyme</td>
<td>95%</td>
</tr>
<tr>
<td>5</td>
<td>5 mol % NiCl₂·6H₂O</td>
<td>95%</td>
</tr>
<tr>
<td>6</td>
<td>No quinuclidine base</td>
<td>55%</td>
</tr>
<tr>
<td>7</td>
<td>No quinuclidine, 3.5 equiv.</td>
<td>94% (87%)[^b]</td>
</tr>
<tr>
<td>8</td>
<td>1.5 equiv. DBU base</td>
<td>2%</td>
</tr>
<tr>
<td>9</td>
<td>Same as entry 7 with presence of oxygen[^c]</td>
<td>91%</td>
</tr>
<tr>
<td>10</td>
<td>1 hour</td>
<td>72%</td>
</tr>
</tbody>
</table>

[^a]: 0.4 mmol scale; DMAC: N,N-dimethylacetamide; rt: room temperature; LED: light-emitting diode; DBU: 1,8-diazabicyclo[5.4.0]octene
[^b]: Yield determined by ¹H-NMR
[^c]: Isolated yield.

[^d]: Deoxygenated reaction mixture sparged with air for two minutes prior to light irradiation.

(I) Definitions

[0046] When introducing elements of the present disclosure or the preferred aspects thereof, the articles “a,” “an,” “the,” and “said” are intended to mean that there are one or more of the elements. The terms “comprising,” “including,” and “having” are intended to be inclusive and mean that there may be additional elements other than the listed elements.

(I) Methods

[0047] Certain aspects of the disclosure encompass a method for forming aryl carbon-nitrogen bonds. The method comprises contacting an aryl halide with an amine in the presence of a Ni salt catalyst solution and an optional base, thereby forming a reaction mixture; exposing the reaction mixture to visible or UV light under reaction condition sufficient to produce the aryl carbon-nitrogen bonds. In some embodiments, an optional PC is added to the reaction mixture.

[0048] Another aspect of the present disclosure is directed to a method for forming aryl carbon-nitrogen bonds. The method comprising contacting an aryl halide with an amine in the presence of a Ni(II) salt, quinuclidine, and N,N-dimethylacetamide, thereby forming a reaction mixture, and exposing the reaction mixture to visible or UV light under reaction conditions sufficient to form the aryl carbon-nitrogen bond. Again, in some embodiments, an optional PC is added to the reaction mixture.

[0049] In certain embodiments, the amine may be present in a molar excess to the aryl halide. In certain embodiments, the Ni salt catalyst solution includes a Ni(II) salt and a polar solvent, wherein the Ni(II) salt is dissolved in the polar solvent. In other embodiments, the reaction mixture may include a polar solvent. In certain embodiments, the reactions conditions include holding the reaction mixture at between about room temperature and about 80°C for between about 1 hour and about 20 hours such that at least about 50% yield is obtained.

[0050] In other aspects, the method comprises contacting an aryl halide with an amine in the presence of a Ni(II) salt, a base, and a polar solvent, thereby forming a reaction mixture, and exposing the reaction mixture to visible or UV light under reaction condition sufficient to produce the aryl carbon-nitrogen bonds. Again, in some embodiments, an optional PC is added to the reaction mixture.

[0051] In certain embodiments, the reactions conditions may be those described herein, e.g., holding the reaction mixture at between about room temperature and about 100°C, between room temperature and about 90°C, between about room temperature and about 80°C, etc., for between about 30 minutes and about 20 hours, for between about 1 hour and about 20 hours, etc., such that at least about 50% yield, at least about 55% yield, at least about 60% yield, etc. is obtained.

[0052] In certain aspects, the present disclosure provides a light-driven and nickel-catalyzed C–N cross-coupling methodology that proceeds via direct photoexcitation of a nickel-amine complex. Again, without intending to be limited by theory, the catalytically active nickel states can be efficiently accessed without requiring energy or electron transfer mechanisms from an added photoredox catalyst (PC).

[0053] In other aspects, the present disclosure provides a light-driven, Ni-catalyzed C–N cross-coupling methodology that proceeds under conditions with an optional added photoredox catalyst (PC). Without intending to be bound by theory, the present disclosure provides that, in the absence of an added PC, the catalytically active Ni state for C–N cross-coupling can be accessed directly through electron transfer (ET) from photo-excitation. Similarly, in a dual catalytic system, an analogous (but possibly distinct) Ni excited state can be accessed through energy transfer (ET) from a PC.

[0054] Secondary, primary alkyl, and primary (hetero)aryl amines can be effectively coupled to aryl halides with diverse electronics (see Examples) at room temperature without added ligand and, in many cases, without added base. The use of inexpensive hydrated nickel salts (e.g., NiBr₂·3H₂O) in preference to considerably more expensive NiBr₂·glyme significantly lowers the cost of this C–N cross-coupling methodology of the disclosure. The effectiveness of the methodology of the disclosure is highlighted by the successive use of light-driven C–S/C–N cross-couplings to synthesize complex structures as well as the synthesis of flavanocin and structurally related derivatives, discussed further herein.

[0055] The application of this reaction methodology to various aryl halide, amine, and nickel salt catalyst solutions was investigated, as described herein.

[0056] In one embodiment, an exemplary C–N cross-coupling via direct photoexcitation of nickel-amine complex of the disclosure is illustrated in FIG. 3A, including a depiction of an exemplary photoreactor equipped with a visible or UV LED (e.g., 365 nm LED, 405 nm LED, 457 nm LED, 523 nm LED, etc.) as described herein (DMAC: N,N-dimethylacetamide; rt: room temperature; LED: light-emitting diode; Boc: tert-butyloxycarbonyl) a 3.5 equiv. amine used with no added base. b 6.4 mmol scale reaction. c Dimethyl sulfide (DMSO) used as solvent. d 1.5 equiv. amine used with 1.5 equiv. quinuclidine base.) In FIG. 3B and FIG. 3C discussed below, unless otherwise specified, reactions were generally conducted at 0.4 mmol scale and
aryl bromide was used as the coupling partner. Percent isolated yield are reported next to the product number (bolded).

(a) Aryl Halide

[0057] In general, the reaction comprises an aryl halide. In regards to the scope of aryl halides, the C—N cross-coupling methodology of the disclosure is compatible with any suitable aryl halide which provides sufficient reactivity to form the carbon-nitrogen bond. Without intending to be limited by theory, generally, aryl halides containing electron-withdrawing groups are more reactive than their electron-neutral or electron-donating counterparts. For example, when comparing substituents in the para position of an aryl bromide under similar reaction conditions, the yield of cyano (FIG. 3C, species 27a, 53%)-methoxy (FIG. 3C, species 29a, 7%), the use of aryl iodides such as iodobenzene (FIG. 3C, species 27b, 66%), 4-iodoanisole (FIG. 3C, species 29b, 26%), and 3-iodopyridine (FIG. 3C, species 35b, 47%), resulted in increased yields relative to using aryl bromides.

[0058] In certain embodiments, the aryl halide may include trifluoromethyl (FIG. 3B, species 1-20), fluoro (FIG. 3C, species 21-24), chloro (FIG. 3C, species 25), amide (FIG. 3C, species 26), methyl (FIG. 3C, species 28), methoxy (FIG. 3C, species 29-31), cyano (FIG. 3C, species 32), ester (FIG. 3C, species 33), and carbonyl (FIG. 3C, species 34) functional groups. In other embodiments, the aryl halide may include heteroaryl halides including pyridine (FIG. 3C, species 35) and pyrimidine (FIG. 3C, species 36).

[0059] In accordance with aspects of the disclosure, the aryl halide may be an aryliodide, an aryl chloride, or an aryl iodide. By way of example, suitable aryl halides include, without limit, aryl bromide (e.g., bromobenzene; 4-bromobenzotrifluoride; 3-bromobenzotrifluoride; 1-bromo-3,5-difluorobenzene; 4-bromobenzotrifluoride; 1-bromo-3-(trifluoromethyl)benzene; 1-bromo-3-chlorobenzene; 4-bromobenzamide; 1-bromo-4-methoxybenzene; 1-bromo-4-methoxybenzene; 1-bromo-3,5-dimethoxybenzene; 4-chlorobenzonitrile; methyl 4-chlorobenzonitrile; 1-(4-bromophenyl)ethan-1-one; 3-bromopyrididine; 5-bromopyrimidine, and the like), aryl chloride (e.g., chlorobenzene; 4-chlorobenzotrifluoride; 1-chloro-3,5-difluorobenzene; 4-chlorobenzotrifluoride; 1-chloro-3-(trifluoromethyl)benzene; 1-chloro-3-chlorobenzene; 4-chlorobenzamide; 1-chloro-4-methoxybenzene; 1-chloro-4-methoxybenzene; 1-chloro-3,5-dimethoxybenzene; 4-chlorobenzonitrile; methyl 4-chlorobenzonitrile; 1-(4-chlorophenyl)ethan-1-one; 3-chloropyrididine; 5-chloropyrimidine, and the like), and aryl iodide (e.g., iodobenzene; 4-iodobenzotrifluoride; 3-iodobenzotrifluoride; 1-iodo-3,5-difluorobenzene; 4-iodobenzotrifluoride; 1-iodo-3-(trifluoromethyl)benzene; 1-iodo-3-chlorobenzene; 4-iodobenzamide; 1-iodo-4-methylbenzene; 1-iodo-4-methoxybenzene; 1-iodo-3-methoxybenzene; 1-iodo-3,5-dimethoxybenzene; 4-iodobenzonitrile; methyl 4-iodobenzonitrile; 1-(4-bromophenyl)ethan-1-one; 3-iodopyridine; 5-iodopyrimidine; 2-iodotoluene, and the like).

(b) Amine

[0060] In another aspect of the disclosure, the reaction comprises an amine. In some embodiments, the amine may be a primary amine or secondary amine. In other embodiments, the amine may be a primary amine.

[0061] In accordance with the disclosure, the impact of the amine was investigated (FIG. 3B). Secondary (FIG. 3B, species 1-9), primary alkyl (FIG. 3B, species 10-13) and primary (hetero)arylamines (FIG. 3B, species 14-17) were all successfully coupled with an aryl halide (e.g., 4-bromobenzotrifluoride) to yield the corresponding C—N products.

[0062] By way of non-limiting example, for morpholine, in addition to aryl bromide (FIG. 3B, species 1a, 87%), 4-iodobenzotrifluoride (FIG. 3B, species 1b) was effectively coupled in 70% isolated yield in 3 hours. 4-chlorobenzotrifluoride (FIG. 3B, species 1c), in contrast, gave 18% yield after 15 hours of irradiation. C—N cross-coupling between morpholine and 4-bromobenzotrifluoride was further scaled to 6.4 mmol and isolated in 82% yield (1.21 grams) after 15 hours of irradiation. Piperidine (FIG. 3B, species 2, 81%) and pyridoline (FIG. 3B, species 7, 77%) were both coupled in high yield without added base. A variety of functional groups were tolerated under these reaction conditions. For example, piperidine derivatives containing methyl (FIG. 3B, species 3, 87%), cyano (FIG. 3B, species 4, 88%), hydroxyl (FIG. 3B, species 5, 84%), and ester (FIG. 3B, species 6, 69%) functional groups were efficiently coupled. Highlighting the tolerance to oxygen, species 3 was isolated in 86% yield when the solvent and reagents were used as received, without degassing. Significantly, hydroxyl groups are tolerated by this C—N coupling condition as a strong base (e.g., alkoxide) is not employed. The efficacious coupling of unprotected piperazine (FIG. 3B, species 8, 81%) is particularly notable as the aryl C—N coupled piperazine moiety is prevalent among therapeutic compounds 24 such as aripiprazole and flibanserin, although the Boc-protected piperazine (FIG. 3B, species 9) was shown to be more reactive, yielding the C—N product in 85%.

[0063] In accordance with certain aspects of the disclosure, primary alkyl amines were typically less reactive than secondary amines, generally resulting in lower yield while requiring longer irradiation times (e.g., 15 hours). Nonetheless, cyclohexylamine (FIG. 3B, species 10, 70%), propylamine (FIG. 3B, species 11, 41%), heptylamine (FIG. 3B, species 12, 57%), and phenethylamine (FIG. 3B, species 13, 33%) were successfully coupled to an aryl halide (e.g., 4-bromobenzotrifluoride) in moderate to good yield. It is noteworthy that phenethylamine and its analogues are naturally-occurring alkaloids that are commonly found in psychoactive drugs.25 Furfuryl amine (FIG. 3B, species 16, 28%) and aromatic amines such as aniline (FIG. 3B, species 14, 67%), 4-fluoroaniline (FIG. 3B, species 15, 46%), and 3-aminopyridine (FIG. 3B, species 17, 90%) were also effectively coupled. Since aromatic amines are less basic than primary or secondary amine amines, 1.5 equivalent of quinuclidine as the base was required to obtain appreciable yields.

[0064] Suitable primary amines include, without limit, propylamine, cyclohexylamine, phenethylamine, pyridine-3-amine, furan-2-ylmethanamine, aniline, 4-fluoroaniline, and pyridoline.

[0065] Suitable secondary amines include, without limit, piperidine, piperazine, tert-butyl piperazine-1-carboxylate, morpholine, 4-methyl-piperidine, piperidine-4-ol, piperidine-4-carbonitrile, methyl piperidine-4-carboxylate, cyclo-
hexanamine, 3-aminopyridine, propan-1-amine, hexan-1-amine, 2-phenylethan-1-amine, and indoline.

In some embodiments, the amine in the reaction mixture may generally be present in a molar excess to the aryl halide. In certain embodiments, the amine may be present from about 1.1 to about 5.5 equivalents, from about 1.1 to about 4.5, from about 1.1 to about 3.5, etc., to 1 equivalent of the aryl halide. In some embodiments, the amine in the reaction mixture may be about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 1.6, about 1.7, about 1.8, about 1.9, about 2, about 2.1, about 2.2, about 2.3, about 2.4, about 2.5, about 2.6, about 2.7, about 2.8, about 2.9, about 3, about 3.1, about 3.2, about 3.3, about 3.4, about 3.5, about 3.6, about 3.7, about 3.8, about 3.9, about 4.0 equivalents, etc., of the aryl halide. In an exemplary embodiment, the amine in the reaction mixture may be present from about 1.5 equivalents to about 3.5 equivalents to 1 equivalent of the aryl halide.

(c) Nickel (Ni) Salt Catalyst Solution

In general, the reaction is performed in the presence of a nickel salt catalyst solution. In some embodiments, the nickel salt catalyst solution may include a nickel salt and a solvent, e.g., a polar solvent, which the nickel salt is dissolved in. In some embodiments, the nickel may have an oxidation number of +2 (i.e., Ni(II)).

Any suitable nickel salt may be used in connection with the methods of the disclosure, preferably those with an oxidation number of +2 (i.e., Ni(II)). Example nickel salts include, without limit, a nickel bromide salt (e.g., NiBr₂, glycine, NiBr₂·3H₂O, and the like), a nickel chloride salt (e.g., NiCl₂·6H₂O, NiCl₂·glycine, and the like), a nickel fluoride salt, a nickel iodide salt, a nickel carbonate salt, a nickel perchlorate salt, a nickel sulfamate salt, a nickel sulfate salt, etc. In an exemplary embodiment, the nickel salt may be NiBr₂·3H₂O. By way of non-limiting example, suitable nickel salts include Ammonium nickel(II) sulfate hexahydrate, Nickel(II) acetate tetrahydrate, Nickel(II) bromide anhydrous, Nickel(II) bromide hydrate, Nickel carbonate basic hydrate, Nickel(II) carbonate hydroxide tetrahydrate, Nickel(II) chloride anhydrous, Nickel(II) chloride hydrate, Nickel(II) fluoride hydrate, Nickel(II) iodide anhydrous, Nickel(II) iodide, Nickel(II) nitrate hexahydrate, Nickel(II) perchlorate hexahydrate, Nickel(II) sulfamate tetrahydrate, Nickel(II) sulfate anhydrous, and Nickel(II) sulfate hexahydrate. In other embodiments, suitable nickel salts include NiBr₂·glycine, NiCl₂·6H₂O, NiCl₂·glycine, and NiBr₂·3H₂O.

As discussed herein, in some embodiments, the nickel salt may be dissolved in a solvent, particularly a polar solvent. In other embodiments, the reaction mixture may include a polar solvent, and the components of the reaction mixture may be dissolved in the polar solvent. Suitable polar solvents include, without limit, N,N-dimethylacetamide (DMAc), dimethyl sulfoxide (DMSO), methanol (MeOH), dimethylformamide (DMF), acetonitrile (MeCN), and the like. In an exemplary embodiment, the polar solvent may be N,N-dimethylacetamide.

In some embodiments, the amount of nickel salt in the reaction mixture may be from about 1 mol % to about 15 mol %. In other embodiments, the amount of nickel salt in the reaction mixture may be about 1 mol %, about 2 mol %, about 3 mol %, about 4 mol %, about 5 mol %, about 6 mol %, about 7 mol %, about 8 mol %, about 9 mol %, about 10 mol %, about 11 mol %, about 12 mol %, about 13 mol %, about 14 mol %, or about 15 mol %. In other embodiments, the nickel salt may be present in the reaction mixture in an amount ranging from about 0.01 equivalents to about 0.1 equivalents, about 0.01 equivalents to about 0.05 equivalents, about 0.05 equivalents, of the aryl halide.

(d) Base

In certain embodiments, the reaction may be carried out in the presence of an optional base. In certain embodiments, the base may be an amine containing base. Suitable bases include, without limit, quinuclidine, morpholine, N-methylmorpholine, N,N-diisopropylethylamine (DIPEA), 1,4-diazabicyclo[2.2.2]octane (DABCO), 4-dimethylaminopyridine (DMAP), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), N,N,N’,N,N’-pentamethyldiethylenetriamine (PMDTA), triethylamine (TEA), proton sponge, and the like. In an exemplary embodiment, the base may be quinuclidine.

In particular embodiments, the optional base may be selected from quinuclidine, morpholine, N-methylmorpholine, triethylamine, N,N-diisopropylethylamine (DIPEA), and DABCO (1,4-diazabicyclo[2.2.2]octane). In another embodiment, the optional base may be selected from quinuclidine, morpholine, N-methylmorpholine, triethylamine, and N,N-diisopropylethylamine (DIPEA). In another embodiment, the optional base may be selected from oxygen, morpholine, triethylamine, and N,N-diisopropylethylamine (DIPEA). In other embodiments, no base may be utilized, and instead a molar excess of amine may be used, as discussed further herein.

In accordance with aspects of the disclosure and described in the Examples below, the choice of base significantly impacts the yield of the reaction. In accordance with aspects of the disclosure, it has been unexpectedly found that quinuclidine outperforms other organic bases such as triethylamine, N,N-diisopropylethylamine and DABCO (1,4-diazabicyclo[2.2.2]octane), while the stronger base DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) almost completely halts the reaction (2% yield, Table 1, entry 8). Unexpectedly, 55% yield is obtained in the absence of a base (Table 1, entry 6), where excess morpholine acts to neutralize the HBr by-product. As such, in certain aspects of the disclosure, using a larger excess of morpholine (e.g., 3.5 equiv., Table 1, entry 7), the yield improves to 94% (87% isolated). In addition to water tolerance (through use of NiBr₂·3H₂O), the presence of oxygen also does not appreciably affect the yield (91%, Table 1, entry 9). Kinetically, this C−N cross-coupling reaction is reasonably fast, reaching 72% after one hour of irradiation (Table 1, entry 10).

In some embodiments, the base may be present in the reaction mixture in an amount ranging from about 0.5 to about 2.5 equivalents to 1 equivalent of the aryl halide. In some embodiments, the base in the reaction mixture may be about 1, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 1.6, about 1.7, about 1.8, about 1.9, about 2, about 2.1, about 2.2, about 2.3, about 2.4, or about 2.5 equivalents of the aryl halide. In an exemplary embodiment, the base in the reaction mixture may be present from about 1.5 equivalents to 1 equivalent of the aryl halide.

(e) Photoredox Catalyst

In general, the reaction may be performed in the presence of an optional photoredox catalyst (PC). Any
suitable photoredox catalyst may be used in connection with the methods of the disclosure, preferably an organic PC of higher triplet energy. Exemplary photoredox catalysts include, but are not limited to [Ru(bpy)$_3$]Cl$_2$ or an organic phenoxazine PC.

0076 As discussed herein, in some embodiments, the photoredox catalyst may be mixed with the nickel salt solution catalyst solution to form the reaction mixture.

0077 As discussed herein, in some embodiments, the photoredox catalyst may be dissolved in a solvent, particularly a polar solvent. In other embodiments, the reaction mixture may include a polar solvent, and the components of the reaction mixture may be dissolved in the polar solvent. Suitable polar solvents include, without limitation, N,N-dimethylacetamide (DMAc), dimethyl sulfoxide (DMSO), methanol (MeOH), dimethylformamide (DMF), acetonitrile (MeCN), and the like. In an exemplary embodiment, the polar solvent may be N,N-dimethylacetamide.

0078 In some embodiments, the amount of photoredox catalyst in the reaction mixture may be from about 0.1 mol % to about 1.5 mol %. In some embodiments, the amount of photoredox catalyst in the reaction mixture may be about 0.1 mol %, about 0.2 mol %, about 0.3 mol %, about 0.4 mol %, about 0.5 mol %, about 0.6 mol %, about 0.7 mol %, about 0.8 mol %, about 0.9 mol %, about 1.0 mol %, about 1.1 mol %, about 1.2 mol %, about 1.3 mol %, about 1.4 mol %, or about 1.5 mol %.

(f) Light

0079 In general, the aryl C—N coupling reaction of the disclosure reaction is performed in the presence of light. In some embodiments, the light may be visible light or UV light.

0080 In an embodiment, visible light may be from about 390 nm to about 700 nm. In other embodiments, visible light may be from about 390 nm to about 600 nm, about 390 nm to about 500 nm, or about 390 nm to about 400 nm. In an exemplary embodiment, the reaction may be performed in the presence of visible light at about 405 nm, 457 nm, 523 nm, etc.

0081 In an embodiment, UV light may be from about 10 nm to about 400 nm. In other embodiments, UV light may be from about 10 nm to about 400 nm, about 200 nm to about 400 nm, about 300 nm to about 400 nm, about 350 nm to about 400 nm, about 365 nm to about 400 nm, etc. In an exemplary embodiment, the reaction may be performed in the presence of UV light at about 365 nm.

0082 In other embodiments, the light may be from about 10 nm to about 1000 nm. In some embodiments, the light may be from about 100 nm to about 1000 nm, about 200 nm to about 1000 nm, about 300 nm to about 1000 nm, about 400 nm to about 1000 nm, about 500 nm to about 1000 nm, about 600 nm to about 1000 nm, about 700 nm to about 1000 nm, about 800 nm to about 1000 nm, about 900 nm to about 1000 nm, about 1000 nm to about 1000 nm, or about 1000 nm to about 400 nm.

(f) Reaction Conditions and Yield

0083 In some embodiments, the aryl C—N coupling reaction of the disclosure occurs for about 30 minutes to about 20 hours, about 1 hour to about 20 hours, about 1 hour to about 15 hours, about 1 hour to about 10 hours, about 1 hour to about 5 hours, about 1 hour to about 4 hours, about 1 hour to about 3 hours, etc. In other embodiments, the reaction occurs for about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, about 12 hours, about 13 hours, about 14 hours, about 15 hours, about 16 hours, about 17 hours, about 18 hours, about 19 hours, or about 20 hours. In yet other embodiments, the reaction occurs for at least about 1 hour, at least about 2 hours, at least about 3 hours, at least about 4 hours, at least about 5 hours, etc.

0084 In general, the aryl C—N coupling reaction of the disclosure may be performed at room temperature or at an elevated temperature. In some embodiments, the reaction may be performed at about 25°C, about 30°C, about 35°C, about 40°C, about 45°C, about 50°C, about 55°C, about 60°C, about 65°C, about 70°C, about 75°C, about 80°C, or about 85°C. In an exemplary embodiment, the reaction may be performed at about 25°C, etc.

0085 In general, the aryl C—N coupling reaction of the disclosure may be performed under an inert atmosphere. In some embodiments, the inert atmosphere may comprise nitrogen, helium, argon, krypton, xenon, and radon. In an exemplary embodiment, the inert atmosphere may comprise nitrogen.

0086 In certain embodiments, the aryl C—N coupling reaction of the disclosure may be performed under reaction conditions sufficient to result in about 30% yield, at least about 35% yield, at least about 40% yield, at least about 45% yield, about 50% yield, at least about 55% yield, at least about 60% yield, at least about 65% yield, at least about 70% yield, at least about 75% yield, at least about 80% yield, at least about 85% yield, at least about 90% yield, at least about 95% yield, at least about 97% yield, at least about 98% yield, etc.

0087 In certain embodiments, the aryl C—N coupling reaction of the disclosure may be performed under reaction conditions sufficient to form aryl carbon-nitrogen bond(s). As described herein, such reactions conditions include, e.g., holding the reaction mixture at between about room temperature and about 100°C, between room temperature and about 90°C, between about 25°C and about 100°C, between about 25°C and about 90°C, between about 25°C and about 80°C, etc., for between about 30 minutes and about 20 hours, about 1 hour and about 20 hours, about 1 hour and about 15 hours, about 1 hour and about 10 hours, about 1 hour and about 5 hours, etc., such that at least about 50% yield, at least about 55% yield, at least about 60% yield, at least about 65% yield, at least about 70% yield, at least about 75% yield, at least about 80% yield, at least about 85% yield, at least about 90% yield, at least about 93% yield, at least about 95% yield, etc., is obtained.

0088 The methods for forming aryl carbon-nitrogen bonds as described herein may be used to couple piperezine to aryl halides to produce precursors prevalent in many pharmaceutical active ingredients. By way of non-limiting example, the methods for forming aryl carbon-nitrogen bonds may be used to couple piperezine to 2,3-dichlorobromobenzene or 1,2-dichloro-3-iodobenzene to produce a C—N coupled precursor, which is used to produce
AMBLIFY; to couple 2,6-dichloroaniline and 2-bromophenylacetic acid or 2-iodophenylacetic acid to produce DICLFENAC.

(III) Photoreactor

[0089] This C–N coupling reaction utilizes a high radiant flux setup to achieve reduced reaction times. To this end, in another aspect of the disclosure, a photoreactor was developed (FIG. 4). However, it will be understood by those of skill in the art that the photoreactor of the disclosure is not limited to the C–N coupling reactions disclosed herein, and may be useful to perform any light-driven chemical reaction known in the art.

[0090] Now, with reference to FIG. 4, photoreactor 100 includes: (1) a reaction chamber 105; (2) a modular reaction vial holder 106 configured to hold one or more reaction vials located within the interior of the reaction chamber; (3) an LED Module 107 comprising one or more LEDs 102 that interfaces with the reaction chamber 105 to provide light at desired wavelength(s) to the interior of the reaction chamber, a heatsink 103 to extract heat from the one or more LEDs 102, and a first cooling source 104 to cool the heatsink 103; and (4) a second cooling source 101 to cool the reaction chamber.

[0091] The reaction chamber includes an interior wall and exterior wall so as to form an interior area. The modular reaction vial holder is located within the interior area of the reaction chamber. As described in further detail herein, the LED Module interfaces with the reaction chamber such that the one or more LEDs emit light into the interior area of the reaction chamber. For instance, in certain embodiments, there may be an opening perpendicular to the principal axis of the reaction chamber through which the LED emitter is oriented so that it irradiates the interior of the reaction chamber. Further, in certain embodiments, the interior wall of the reaction chamber may include a reflective surface coating, as described in further detail herein.

[0092] In certain embodiments, the one or more LEDs may be industrial light emitting diodes (LEDs) which provide high radiant flux at a desired wavelength, e.g., between 200 nm to 700 nm, specifically 365 nm or 405 nm for the C–N coupling reactions of the disclosure. In certain aspects of the disclosure, the LEDs produce enough heat that active cooling is needed both to protect the LED and to ensure that its emission profile remains constant throughout the reaction.

[0093] To facilitate this, in certain aspects of the disclosure, the LED Module may further include a metal core printed circuit board (MCPCB). In certain embodiments, the one or more LEDs may be mounted to the MCPCB, and the MCPCB may in turn be mounted to the heatsink. Again, with reference to FIG. 4, the one or more LEDs 102 may be mounted to a MCPCB to enable efficient heat transfer from the LEDs 102 to the heatsink 103. In accordance with the disclosure, any suitable heatsink may be used which is sufficient to absorb the emitted heat from the LEDs, e.g., an aluminum heatsink. This heatsink 103 is then actively cooled by a first cooling source 104, e.g., by a 60 mm computer fan. In addition, the reaction chamber may be separately cooled by a second cooling source 101, e.g., a 40 mm computer fan or water/liquid cooling jacket, to allow for consistent reaction conditions. However, any suitable method for cooling the LEDs and reaction chamber may be utilized without departing from the scope of the disclosure.

[0094] In certain embodiments, if desired, the reaction chamber 105 may include a reflective interior surface coating, e.g., formed from aluminum tape or similar reflective material, to maximize reflection of emitted light back to the reaction vial.

[0095] In certain embodiments, the photoreactor also includes a modular reaction vial holder 106 that ensures consistent vial placement and distance from the one or more LEDs 102, and allows for consistent irradiation and cooling of the reaction vial. In certain embodiments, the modular reaction vial holder 106 is removable and replaceable, with size and shape to accommodate the desired reaction vial size and volume. Further, the modular reaction vial holder 106 may be located within the reaction chamber 105 at any suitable location so as to achieve the desired reaction conditions.

[0096] By way of non-limiting example, in one embodiment, the vial may be sized to accommodate from about 0.1 mL to about 30 mL. In other embodiments, the vial may be sized to accommodate from about 0.2 mL (0.5 dram), 0.6 mL (1.5 dram), or 20 mL. In one embodiment, the vial may be from about 1 mm to about 20 mm from the LED light. In other embodiments, the vial may be about 1 mm, about 5 mm, about 10 mm, about 15 mm, or about 20 mm from the LED light.

[0097] The LED Module 107 comprising the one or more LEDs 102, the heatsink 103, and the first cooling source 104 may be configured to allow for easy and facile exchange of LEDs with differing emission wavelengths, as may be desired.

[0098] The photoreactor may generally be constructed from commercially available parts, with the exception of the reaction chamber and modular reaction vial holder. In accordance with aspects of the disclosure, the reaction chamber and modular reaction vial holder may be sized and shaped as desired, and printed using a 3D-printer, or formed using any suitable methodology known in the art.

[0099] For instance, the modular reaction vial holder, reaction chamber body, and fan adapter parts were designed in-house using Autodesk Inventor software and 3D-printing using stereolithography with a Form2 printer (FormLabs) or fused filament fabrication with a Creator Pro (Flashforge). Modular reaction vial position in the reaction chamber was optimized by 3D-printing vial holders with distances of 5 mm, 10 mm, and 15 mm from the LED emitter surface to the vial. The 5 mm position yielded higher 1H NMR conversion after 1 hour compared to other distances under standard reaction conditions on a 0.2 mmol scale (Table 2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from conditions above</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 mm irradiation distance</td>
<td>91%</td>
</tr>
<tr>
<td>2</td>
<td>10 mm irradiation distance</td>
<td>75%</td>
</tr>
<tr>
<td>3</td>
<td>15 mm irradiation distance</td>
<td>69%</td>
</tr>
</tbody>
</table>

[0100] As constructed, the reaction chamber is cylindrical in shape and oriented vertically, with a computer fan
screwed to the top that blows air downwards. However, other suitable sizes and configurations may be used, as recognized by those of skill in the art. As described herein, the interior wall of the reaction chamber may be coated with to provide a reflective finish to redirect light towards the center of the chamber. In certain embodiments, the reaction chamber may be configured to include an opening perpendicular to the principal axis of the reaction chamber through which the LED emitter is oriented so that it irradiates the center/interior of the chamber. The perpendicular opening may be sized and shaped so as to interface and mate with the LED emitter in a suitable manner, e.g., to minimize light loss to the surrounding environment.

[0101] In certain embodiments, the reaction vial holder may be 3-D printed so as to be modular with different versions sized to hold, e.g., 0.5 dram, 1.5 dram, or 20 mL scintillation vials. In certain embodiments, the modular reaction vial holder may be configured with an open design that maximizes airflow when attached to the reaction chamber. It may be designed to provide an optimized distance, e.g., of 5 mm, 10 mm, 15 mm, etc., from the vial edge to the LED emitter lens when the vial is held in place and the modular reaction vial holder is attached to the reaction chamber. The design may additionally be optimized to minimize blockage of incoming light from the LED. Alternatively, a version incorporating a heating/cooling jacket has also been developed that allows for direct heating or cooling of the reaction vial via a suitable coolant fluid, e.g., water, brine, ammonia, glycerol, ethylene glycol, etc., depending on the heat transfer required.

[0102] In certain embodiments, the LED Module including the LED-heatsink-fan assembly may be configured to be modular so that it can be easily switched between assemblies with different mounted LEDs (i.e., with different emitter wavelengths). LEDs are commercially available mounted to a MCPPB. This package may then mounted on one end of the heatsink (also commercially available) utilizing a thermally conducting paste (commercially available) and may be screwed in for security. A computer fan may be attached to the other end of the heatsink via a 3D-printed adapter.

[0103] In use, these components function to irradiate a vial with high-flux light while simultaneously cooling both the reaction chamber and the LED, thus enabling consistency and efficient temperature control. In addition, the design of the photoreactor of the disclosure allows for reaction vial volumes that range from 20 mL to less than 0.5 mL in scale. This enhanced flexibility provides for improved scope of use.

[0104] All reactions described in the examples herein were performed at the 5 mm irradiation distance.

Examples

[0105] The following examples are included to demonstrate various embodiments of the present disclosure. It should be appreciated by those of skill in the art that the techniques disclosed in the examples that follow represent techniques discovered by the inventors to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

[0106] Anhydrous DMAC solvent, aryl halides, and amines were purchased from Sigma-Aldrich (St. Louis, Mo.), TCI (Portland, Oreg.), or Alfa Aesar (Haverhill, Mass.). All commercially available solvents and reagents were degassed and used without further purifications. The photoreactor was custom designed and built. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator (New Castle, Del.) using a water bath. Flash column chromatography was performed using the COMBIBLASH R1+ Lumen instrument (Lincoln, Nebr.). Reactions were analyzed by TLC using TLC silica gel F254 250 μm precoated-plates from Merck (Kenilworth, N.J.). Developed chromatogram was visualized using a UV lamp and permanganate stain was used for UV-inactive compounds.

[0107] The 1H, 13C, and 19F NMR spectra were recorded on a Bruker Avance Neo (400, 101, and 376 MHz, respectively) instrument. Deuterated solvents were purchased from Cambridge Isotope Laboratories (Andover, Mass.) and used as received. All 1H NMR experiments are reported in 8 units, parts per million (ppm), and were measured relative to the signals for residual chloroform (7.26 ppm) or dimethylsulfoxide (2.50 ppm) in the deuterated solvents. Data for 1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, p=quintet, m=multiplet, dd=doublet of doublet, dt=doublet of triplets . . . . etc., br=broad), coupling constant (Hz) and integration. All 13C NMR spectra are reported in ppm relative to CDCl3 (77.16 ppm) or DMSO-δ6 (39.52 ppm). Mass spectrometry analysis was performed using an Agilent 6220 TOF LC/MS (“OTOF”) interfaced to an Agilent 1200 HPLC with electrospray (ESI), multi-mode (combined ESI and APCl), atmospheric pressure photoionization (APPI), and Direct Analysis in Real Time (DART) sources at Colorado State University.

[0108] The following abbreviations are used in the Examples: CPCM: conductor-like polarizable continuum model; DFT: density functional theory; DMSO: dimethyl sulfoxide; Eq or equiv: equivalent; 𝛀max: maximum absorption wavelength; and emax: molar absorptivity at 𝛀max.

Example 1. C—N Cross-Coupling Via Direct Photoexcitation of Nickel-Amine Complexes

[0109] General Procedure A:

[0110] Under nitrogen atmosphere in a glovebox, a stir bar, an aryl halide (0.40 mmol, 1.0 equivalent), and 1 mL of DMAC solution containing dissolved NiBr2·SH2O (0.02 mmol, 0.05 equiv., 5.5 mg) was added to a 0.5 dram glass vial. The glass vial was then capped using a screw cap equipped with a PTFE/silicone septum and sealed with a strip of PARAFILM. The capped vial was then brought out of the glovebox and liquid amine (degassed, 1.40 mmol, 3.5 equiv.) was added via a HAMILTON syringe. Solid amines were weighed and added inside the glovebox. The capped glass vial containing the reaction mixture was then placed in a 3D-printed vial holder and subjected to 365 nm LED irradiation with fan cooling to maintain the vial at room temperature. After the time specified in the reaction schemes, the reaction mixture was washed with water, extracted with EtOAc or DCM, and concentrated under vacuum. Purification of the crude product by flash chromatography on silica gel using the indicated solvent system afforded the desired product.
General Procedure B:

Under nitrogen atmosphere in a glovebox, a stir bar, an aryl halide (0.40 mmol, 1.0 equiv.), quinuclidine (0.60 mmol, 1.5 equiv., 66.7 mg), and 1 mL of DMAC solution containing dissolved NiBr₂₃H₂O (0.02 mmol, 0.05 equiv., 5.5 mg) was added to a 0.5 dram glass vial. The glass vial was then capped using a screw cap equipped with a PTFE/silicone septum and sealed with a strip of PARAFILM. The capped vial was then brought out of the glovebox and liquid amine (degassed, 0.60 mmol, 1.5 equiv.) was added via a HAMILTON syringe. Solid amine were weighed and added inside the glovebox. The capped glass vial containing the reaction mixture was then placed in a 3D-printed vial holder and subjected to 365 nm LED irradiation with fan cooling to maintain the vial at room temperature. After the time specified in the reaction schemes, the reaction mixture was washed with water, extracted with EtOAc or DCM and concentrated under vacuum. Purification of the crude product by flash chromatography on silica gel using the indicated solvent system afforded the desired product.

Model Substrates

4-bromobenzotrifluoride and morpholine were used as model substrates and employed General Procedure B to perform control experiments and reaction optimizations detailed below (Table 3, Table 4, Table 5, Table 6, Table 7, and Table 8). The conversion of the C—N coupled product (4-(4-(trifluoromethyl)phenyl)morpholine) was monitored as a function of time (e.g., 1 hour, 2 hours, and 3 hours) using ¹⁹F NMR (FIG. 5). Without being bound by theory, it was assumed that during the course of the reaction, the number of CF₃ groups in the reaction mixture is conserved, allowing the conversion of the C—N coupled product to be calculated (FIG. 5). This method was sufficiently accurate that ¹⁹F NMR conversion closely matches isolated yield. For example, C—N coupled product was isolated at 91% yield with ¹⁹F NMR conversion of 95%. To obtain ¹⁹F NMR conversion as a function of time, a 10 μL aliquot was withdrawn from the reaction mixture under oxygen-free conditions and the sample was diluted with 600 μL of deuterated chloroform before subjecting the sample to ¹⁹F NMR spectroscopy.

### TABLE 4

<table>
<thead>
<tr>
<th>Solvent</th>
<th>1 hr</th>
<th>2 hr</th>
<th>3 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMAC (365 nm)</td>
<td>72%</td>
<td>94%</td>
<td>95%</td>
</tr>
<tr>
<td>DMSO (365 nm)</td>
<td></td>
<td></td>
<td>95%</td>
</tr>
<tr>
<td>MeOH (365 nm)</td>
<td></td>
<td></td>
<td>60%</td>
</tr>
<tr>
<td>DMF (365 nm)</td>
<td></td>
<td></td>
<td>93%</td>
</tr>
<tr>
<td>MeCN (365 nm)</td>
<td></td>
<td></td>
<td>46%</td>
</tr>
</tbody>
</table>

*Isolated yield

### TABLE 5

<table>
<thead>
<tr>
<th>Nickel salts</th>
<th>1 hour</th>
<th>2 hour</th>
<th>3 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>NiBr₂glyme 5%</td>
<td>81%</td>
<td>96%</td>
<td>95%</td>
</tr>
<tr>
<td>NiCl₂·6H₂O 5%</td>
<td>76%</td>
<td>96%</td>
<td>95%</td>
</tr>
<tr>
<td>NiCl₂glyme 5%</td>
<td>68%</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>NiBr₂·3H₂O 5%</td>
<td>72%</td>
<td>94%</td>
<td>95%</td>
</tr>
<tr>
<td>NiBr₂·3H₂O 1%</td>
<td>82%</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>NiBr₂·3H₂O 2%</td>
<td>85%</td>
<td>96%</td>
<td>95%</td>
</tr>
<tr>
<td>NiBr₂·3H₂O 8%</td>
<td>74%</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>NiBr₂·3H₂O 10%</td>
<td>74%</td>
<td>95%</td>
<td>95%</td>
</tr>
</tbody>
</table>

*Isolated yield

### TABLE 6

<table>
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<tr>
<th>Base</th>
<th>1 hour</th>
<th>2 hour</th>
<th>3 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>quinuclidine 1.5 eq</td>
<td>79%</td>
<td>94%</td>
<td>94%</td>
</tr>
<tr>
<td>DABCO 1.5 eq</td>
<td>14%</td>
<td>26%</td>
<td>35%</td>
</tr>
<tr>
<td>DIPEA 1.5 eq</td>
<td>21%</td>
<td>48%</td>
<td>68%</td>
</tr>
<tr>
<td>morpholine 1.5 eq</td>
<td>20%</td>
<td>47%</td>
<td>64%</td>
</tr>
<tr>
<td>N-Me morpholine 1.5 eq</td>
<td>31%</td>
<td>46%</td>
<td>52%</td>
</tr>
<tr>
<td>DMAP 1.5 eq</td>
<td>0%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>TEA 1.5 eq</td>
<td>43%</td>
<td>70%</td>
<td>78%</td>
</tr>
<tr>
<td>DIBU 1.5 eq</td>
<td>0%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>PMDETA 1.5 eq</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Proton sponge 1.5 eq</td>
<td>2%</td>
<td>4%</td>
<td>7%</td>
</tr>
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</table>

*Isolated yield

### TABLE 7

<table>
<thead>
<tr>
<th>Base</th>
<th>1 hour</th>
<th>2 hour</th>
<th>3 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>morpholine 1.5 eq NiBr₂·3H₂O 5%</td>
<td>65%</td>
<td>85%</td>
<td>93%</td>
</tr>
<tr>
<td>morpholine 1.5 eq NiBr₂·3H₂O 2%</td>
<td>57%</td>
<td>80%</td>
<td>88%</td>
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<tr>
<td>morpholine 1.5 eq NiBr₂·3H₂O 1%</td>
<td>34%</td>
<td>63%</td>
<td>74%</td>
</tr>
<tr>
<td>morpholine 1.5 eq NiCl₂·6H₂O 5%</td>
<td>34%</td>
<td>65%</td>
<td>79%</td>
</tr>
<tr>
<td>morpholine 1.5 eq NiCl₂·6H₂O 2%</td>
<td>27%</td>
<td>58%</td>
<td>75%</td>
</tr>
<tr>
<td>morpholine 1.5 eq NiCl₂·6H₂O 1%</td>
<td>20%</td>
<td>47%</td>
<td>64%</td>
</tr>
<tr>
<td>DIPEA 1.5 eq NiBr₂·3H₂O 5%</td>
<td>45%</td>
<td>79%</td>
<td>85%</td>
</tr>
<tr>
<td>DIPEA 1.5 eq NiBr₂·3H₂O 2%</td>
<td>44%</td>
<td>76%</td>
<td>81%</td>
</tr>
<tr>
<td>DIPEA 1.5 eq NiBr₂·3H₂O 1%</td>
<td>23%</td>
<td>50%</td>
<td>68%</td>
</tr>
<tr>
<td>DIPEA 1.5 eq NiCl₂·6H₂O 5%</td>
<td>29%</td>
<td>69%</td>
<td>84%</td>
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</table>

*Isolated yield
TABLE 7-continued

<table>
<thead>
<tr>
<th>Base</th>
<th>Nickel</th>
<th>1 hour</th>
<th>2 hour</th>
<th>3 hour</th>
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<tr>
<td>DIPEA 1.5 eq</td>
<td>NiCl₂·6H₂O 2%</td>
<td>28%</td>
<td>65%</td>
<td>79%</td>
</tr>
<tr>
<td>DIPEA 1.5 eq</td>
<td>NiCl₂·6H₂O 1%</td>
<td>21%</td>
<td>48%</td>
<td>68%</td>
</tr>
<tr>
<td>TEA 1.5 eq</td>
<td>NiBr₂·3H₂O 5%</td>
<td>51%</td>
<td>77%</td>
<td>86%</td>
</tr>
<tr>
<td>TEA 1.5 eq</td>
<td>NiBr₂·3H₂O 2%</td>
<td>50%</td>
<td>78%</td>
<td>86%</td>
</tr>
<tr>
<td>TEA 1.5 eq</td>
<td>NiBr₂·3H₂O 1%</td>
<td>36%</td>
<td>65%</td>
<td>77%</td>
</tr>
<tr>
<td>TEA 1.5 eq</td>
<td>NiCl₂·6H₂O 5%</td>
<td>36%</td>
<td>68%</td>
<td>82%</td>
</tr>
<tr>
<td>TEA 1.5 eq</td>
<td>NiCl₂·6H₂O 2%</td>
<td>31%</td>
<td>64%</td>
<td>81%</td>
</tr>
<tr>
<td>TEA 1.5 eq</td>
<td>NiCl₂·6H₂O 1%</td>
<td>43%</td>
<td>70%</td>
<td>78%</td>
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</table>

TABLE 8

<table>
<thead>
<tr>
<th>Base</th>
<th>19 F-NMR Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>morpholine 0.0 eq</td>
<td>55%</td>
</tr>
<tr>
<td>morpholine 1.0 eq</td>
<td>52%</td>
</tr>
<tr>
<td>morpholine 1.5 eq</td>
<td>65%</td>
</tr>
<tr>
<td>morpholine 1.8 eq</td>
<td>63%</td>
</tr>
<tr>
<td>morpholine 2.0 eq</td>
<td>60%</td>
</tr>
<tr>
<td>TEA 1.5 eq</td>
<td>51%</td>
</tr>
<tr>
<td>TEA 1.8 eq</td>
<td>50%</td>
</tr>
</tbody>
</table>

TABLE 10

<table>
<thead>
<tr>
<th>Solution</th>
<th>λ&lt;sub&gt;max&lt;/sub&gt; (nm)</th>
<th>λ&lt;sub&gt;p&lt;/sub&gt; (nm)</th>
<th>R&lt;sub&gt;2&lt;/sub&gt; (s&lt;sup&gt;2&lt;/sup&gt;M&lt;sup&gt;-1&lt;/sup&gt;cm&lt;sup&gt;-1&lt;/sup&gt;)</th>
<th>R&lt;sub&gt;2&lt;/sub&gt; (s&lt;sup&gt;2&lt;/sup&gt;M&lt;sup&gt;-1&lt;/sup&gt;cm&lt;sup&gt;-1&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NiBr₂·3H₂O</td>
<td>657</td>
<td>473</td>
<td>169</td>
<td>30</td>
</tr>
<tr>
<td>NiBr₂·3H₂O + morpholine</td>
<td>427</td>
<td>736</td>
<td>126</td>
<td>36</td>
</tr>
<tr>
<td>NiBr₂·3H₂O + 4-BrBzCF₃</td>
<td>657</td>
<td>473</td>
<td>101</td>
<td>31</td>
</tr>
<tr>
<td>NiBr₂·3H₂O + morpholine + 4-BrBzCF₃</td>
<td>427</td>
<td>736</td>
<td>128</td>
<td>37</td>
</tr>
</tbody>
</table>

Computational Details

All calculations were performed using computational chemistry software package GAUSSIAN 09 ver. D01.

Geometries of all molecular structures were optimized at the uM06/6-31+G(d,p)/CPCM-DMAc level of theory followed by frequency calculations to obtain zero point energy (ZPE) corrections, thermal corrections, and entropic TS terms using ideal gas approximations. The obtained Gibbs free energy, G<sup>Δ</sup> (298K, 1 atm), by default has a standard reference state of 298.15K and 1 atm. However, a standard reference state of 298.15K and 1 mole/liter (G<sup>Δ</sup> (298K, 1 M)) is more relevant to our examined systems as the C—N cross-coupling reactions are carried out in the liquid phase in DMAc.

To obtain the Gibbs free energy with relevant standard state reference, G<sup>Δ</sup> (298K, 1 M)=G<sup>Δ</sup> (298K, 1 atm)+RT ln(R/(0.08206T)), where R is the gas constant and T is the temperature. ΔG<sup>Δ</sup> (298K, 1 M)=ΔG<sup>Δ</sup> (298K, 1 atm) when there is no mole change from the reactant to the product. However, for every net mole change ΔG<sup>Δ</sup> (298K, 1 M)=ΔG<sup>Δ</sup> (298K, 1 atm)+1.89 kcal/mol.

At the converged geometries, single point calculations at uM06/6-311+G(d,p)/CPCM-DMAc were performed; the various corrections and entropic TS terms from uM06/6-31+G(d,p) calculations were then applied to the energy obtained with uM06/6-311+G(d,p).

Characterizations

Synthesis of 4-(4-(trifluoromethyl)phenyl)morpholine (1a)

UV-Visible Spectroscopy

UV-Visible spectroscopy was performed for each reaction component and combination of reaction components using a Cary 5000 spectrophotometer (Agilent Technologies). Morpholine and 4-bromobenzotrifluoride (4-BrBzCF₃) are both colorless liquids without significant molar absorptivity at wavelengths greater than 300 nm (FIG. 6) at the concentrations present in the C—N coupling reaction mixture.

UV-Visible spectroscopy was also performed for NiBr₂·3H₂O alone and in combination with 4-BrBzCF₃ and morpholine. NiBr₂·3H₂O has a distinctive absorption profile which was not altered with addition of 4-BrBzCF₃. However, upon addition of morpholine, the λ<sub>max</sub> was blue-shifted from 657 nm to 427 nm (FIG. 7).

TABLE 10

Molar absorptivity for the most prominent peaks of each reaction combination. Data was extracted from spectra collected for 5 concentrations ranging from 0.02-0.008 M in NiBr₂·3H₂O.

[0114] During reaction optimization, it was determined that no reaction occurred in the absence of nickel salts or without irradiation at either room temperature or 800°C. (Table 3). 405 nm light gave slower conversion than 365 nm light (52% vs. 72% at 1 hour) but achieved similar conversion at 3 hours. Without an added quinuclidine, 55% conversion was obtained. DMF and DMSO gave similarly high conversion (>90%) to DMAc, while MeOH and MeCN gave considerably lower conversion (Table 4). Various nickel salts at different loadings have similar performance (Table 5). The effect of types of added organic bases were also investigated (Table 6 and Table 7). Quinuclidine gave the best performance while bases such as DMAP, DBU, and PMDETA almost completely shut off reactivity. Table 8 shows that excess morphology substrate can also function as a base. For example, when morpholine substrate was introduced at 3.5 equivalents, 94% of conversion was obtained with no added base.
General Procedure A was followed using 4-bromobenzotrifluoride as the aryl halide, and morpholine as the amine. The reaction was run at room temperature for 3 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-15% EtOAc/hexanes to give the product as a white solid (80.2 mg, 87%). NMR data matched previously reported spectra.\(^{35,36}\) \(^{1}H\) NMR (400 MHz, Chloroform-d) \(\delta\) 7.50 (d, \(J=8.4\) Hz, 2H), 6.92 (d, \(J=8.8\) Hz, 2H), 3.86 (t, \(J=4.8\) Hz, 4H), 3.24 (t, \(J=5.2\) Hz, 4H). \(^{13}C\) NMR (101 MHz, Chloroform-d) \(\delta\) 153.5, 126.6 (q, \(J_{C,F}=3.8\) Hz), 124.8 (q, \(J_{C,F}=271.7\) Hz), 121.1 (q, \(J_{C,F}=32.9\) Hz), 114.4, 66.8, 48.3. \(^{19}F\) NMR (376 MHz, Chloroform-d) \(\delta\) -61.4 (s, 3F). HRMS (DART-TOF): calculated for \(C_{13}H_{13}F_{3}NO\) ([M+H\(^{+}\)]\(^{+}\)) 232.0944, found 232.0943.

Synthesis of 1-(4-(trifluoromethyl)phenyl)piperidine (2)

General Procedure A was followed using 4-bromobenzotrifluoride as the aryl halide, and piperidine as the amine. The reaction was run at room temperature for 3 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-15% EtOAc/hexanes to give the product as a pale yellow oil (74.5 mg, 81%). NMR data matched previously reported spectra.\(^{35,36}\) \(^{1}H\) NMR (400 MHz, Chloroform-d) \(\delta\) 7.46 (d, \(J=8.7\) Hz, 2H), 6.92 (d, \(J=8.7\) Hz, 2H), 3.27 (t, \(J=5.2\) Hz, 4H), 1.77-1.58 (m, 6H). \(^{13}C\) NMR (101 MHz, Chloroform-d) \(\delta\) 154.0, 126.5 (q, \(J_{C,F}=3.7\) Hz), 124.9 (q, \(J_{C,F}=271.6\) Hz), 119.7 (q, \(J_{C,F}=32.7\) Hz), 114.7, 49.4, 25.6, 24.4. \(^{19}F\) NMR (376 MHz, Chloroform-d) \(\delta\) -61.2 (s, 3F). HRMS (DART-TOF): calculated for \(C_{13}H_{13}F_{3}NO\) ([M+H\(^{+}\)]\(^{+}\)) 255.1104, found 255.1093.

Synthesis of 1-(4-(trifluoromethyl)phenyl)piperidin-4-ol (5)

General Procedure A was followed using 4-bromobenzotrifluoride as the aryl halide, and 4-hydroxypiperidine as the amine. The reaction was run at room temperature for 3 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-40% EtOAc/hexanes to give the product as a white solid (82.4 mg, 84%). NMR data matched previously reported spectra.\(^{35,36}\) \(^{1}H\) NMR (400 MHz, Chloroform-d) \(\delta\) 7.46 (d, \(J=8.7\) Hz, 2H), 6.92 (d, \(J=8.8\) Hz, 2H), 3.89 (t, \(J=8.7\), 4.0 Hz, 2H), 3.74-3.56 (m, 2H), 3.03 (ddd, \(J=13.0, 9.7, 3.2\) Hz, 2H), 2.06-1.92 (m, 2H), 1.79 (s, 1H), 1.74-1.53 (m, 2H). \(^{13}C\) NMR (101 MHz, Chloroform-d) \(\delta\) 153.1, 126.5 (q, \(J_{C,F}=3.8\) Hz), 124.9 (q, \(J_{C,F}=271.5\) Hz), 120.1 (q, \(J_{C,F}=32.7\) Hz), 114.9, 67.7, 46.0, 33.8. \(^{19}F\) NMR (376 MHz, Chloroform-d) \(\delta\) -61.3 (s, 3F). HRMS (DART-TOF): calculated for \(C_{13}H_{13}F_{3}NO\) ([M+H\(^{+}\)]\(^{+}\)) 246.1104, found 246.1099.

Synthesis of Methyl 1-(4-(trifluoromethyl)phenyl)piperidine-4-carboxylate (6)

General Procedure A was followed using 4-bromobenzotrifluoride as the aryl halide, and 4-hydroxy piperidine as the amine. The reaction was run at room temperature for 3 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-40% EtOAc/hexanes to give the product as a white solid (82.4 mg, 84%). NMR data matched previously reported spectra.\(^{35,36}\) \(^{1}H\) NMR (400 MHz, Chloroform-d) \(\delta\) 7.46 (d, \(J=8.7\) Hz, 2H), 6.92 (d, \(J=8.8\) Hz, 2H), 3.89 (t, \(J=8.7\), 4.0 Hz, 2H), 3.74-3.56 (m, 2H), 3.03 (ddd, \(J=13.0, 9.7, 3.2\) Hz, 2H), 2.06-1.92 (m, 2H), 1.79 (s, 1H), 1.74-1.53 (m, 2H). NMR data matched previously reported spectra.\(^{35,36}\) \(^{1}H\) NMR (400 MHz, Chloroform-d) \(\delta\) 7.46 (d, \(J=8.7\) Hz, 2H), 6.92 (d, \(J=8.8\) Hz, 2H), 3.89 (t, \(J=8.7\), 4.0 Hz, 2H), 3.74-3.56 (m, 2H), 3.03 (ddd, \(J=13.0, 9.7, 3.2\) Hz, 2H), 2.06-1.92 (m, 2H), 1.79 (s, 1H), 1.74-1.53 (m, 2H). \(^{13}C\) NMR (101 MHz, Chloroform-d) \(\delta\) 153.1, 126.5 (q, \(J_{C,F}=3.8\) Hz), 124.9 (q, \(J_{C,F}=271.5\) Hz), 120.1 (q, \(J_{C,F}=32.7\) Hz), 114.9, 67.7, 46.0, 33.8. \(^{19}F\) NMR (376 MHz, Chloroform-d) \(\delta\) -61.3 (s, 3F). HRMS (DART-TOF): calculated for \(C_{13}H_{13}F_{3}NO\) ([M+H\(^{+}\)]\(^{+}\)) 246.1104, found 246.1099.

Synthesis of Methyl 1-(4-(trifluoromethyl)phenyl) piperidine-4-carboxylate (6)
[0132] General Procedure A was followed using 4-bromobenzotrifluoride as the aryl halide, and methyl 4-piperidinecarboxylate as the amine. The reaction was run at room temperature for 3 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-15% EtOAc/hexanes to give the product as a white solid (78.8 mg, 69%). 1H NMR (400 MHz, Chloroform-d) δ 7.46 (d, J=8.7 Hz, 2H), 6.92 (d, J=8.6 Hz, 2H), 3.80-3.68 (m, 5H), 2.90 (ddd, J=12.7, 11.3, 2.9 Hz, 2H), 2.51 (tt, J=11.0, 4.0 Hz, 2H), 1.52-1.77 (m, 3H). 13C NMR (101 MHz, Chloroform-d) δ 175.1, 153.4, 126.5 (q, JCF=3.8 Hz), 124.9 (q, JCF=271.7 Hz), 120.3 (q, JCF=32.8 Hz), 115.0, 51.9, 48.0, 40.9, 27.8. 19F NMR (376 MHz, Chloroform-d) δ -61.3 (s, 3F). HRMS (DART-TOF): calculated for C14H12F3NO2 ([M+H]+) 288.1206, found 288.1210.

Synthesis of Tert-Butyl 4-(4-(trifluoromethyl)phenyl)piperazine-1-carboxylate (9)

[0133]

[0134] General Procedure A was followed using 4-bromobenzotrifluoride as the aryl halide, and piperidine as the amine. The reaction was run at room temperature for 3 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-15% EtOAc/hexanes to give the product as a white solid (66.0 mg, 77%). NMR data matched previously reported spectra. 1H NMR (400 MHz, Chloroform-d) δ 7.44 (d, J=8.6 Hz, 2H), 6.55 (d, J=8.5 Hz, 2H), 3.36-3.27 (m, 4H), 2.10-1.97 (m, 4H). 13C NMR (101 MHz, Chloroform-d) δ 149.9, 126.5 (q, JCF=3.7 Hz), 125.5 (q, JCF=270.5 Hz), 116.8 (q, JCF=32.5 Hz), 116.0, 47.7, 25.6. 19F NMR (376 MHz, Chloroform-d) δ -60.6 (s, 3F). HRMS (DART-TOF): calculated for C16H16F3N2 ([M+H]+) 288.1206, found 288.1210.

Synthesis of N-cyclohexyl-4-(trifluoromethyl)aniline (10)

[0135]

[0136] General Procedure A was followed using 4-bromobenzotrifluoride as the aryl halide, and piperazine as the amine. DMSO was used as the solvent instead of DMAc. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-20% MeOH/DCM to give the product as a pale yellow solid (56.1 mg, 61%). NMR data matched previously reported spectra. 1H NMR (400 MHz, Chloroform-d) δ 7.47 (d, J=8.5 Hz, 2H), 6.91 (d, J=8.6 Hz, 2H), 3.23 (t, J=4.8 Hz, 4H), 3.02 (t, J=5.0 Hz, 4H), 1.81 (s, 3H). 13C NMR (101 MHz, Chloroform-d) δ 153.9, 126.5 (q, JCF=271.7 Hz), 120.6 (q, JCF=32.6 Hz), 114.6, 49.2, 46.0. 19F NMR (376 MHz, Chloroform-d) δ -61.4 (s, 3F). HRMS (DART-TOF): calculated for C16H11F3N2 ([M+H]+) 231.1104, found 231.1101.

Synthesis of Tert-Butyl 4-(4-(trifluoromethyl)phenyl)piperazine-1-carboxylate (9)

[0137]

[0138] General Procedure B was followed using 4-bromobenzotrifluoride as the aryl halide, and tert-butyl piperazine-1-carboxylate as the amine. The reaction was run at room temperature for 3 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-15% EtOAc/hexanes to give the product as a white solid (112.4 mg, 85%). NMR data matched previously reported spectra. 1H NMR (400 MHz, Chloroform-d) δ 7.49 (d, J=8.0 Hz, 2H), 6.92 (d, J=8.4 Hz, 2H), 3.58 (t, J=4.8 Hz, 4H), 3.23 (t, J=5.6 Hz, 4H), 1.49 (s, 9H). 13C NMR (101 MHz, Chloroform-d) δ 154.8, 153.3, 126.6 (q, JCF=3.7 Hz), 124.8 (q, JCF=271.7 Hz), 121.1 (q, JCF=32.8 Hz), 115.1, 80.2, 48.2, 28.5. 19F NMR (376 MHz, Chloroform-d) δ -61.4 (s, 3F). HRMS (DART-TOF): calculated for C16H16F3N2O2 ([M+H]+) 351.1628, found 351.1630.

Synthesis of N-cyclohexyl-4-(trifluoromethyl)aniline (10)

[0139]

[0140] General Procedure A was followed using 4-bromobenzotrifluoride as the aryl halide, and cyclohexylamine as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-15% EtOAc/hexanes to give the product as a pale yellow solid (68.1 mg, 70%). NMR data matched previously reported spectra. 1H NMR (400 MHz, Chloroform-d) δ 7.38 (d, J=8.5 Hz, 2H), 6.57 (d, J=8.5 Hz, 2H), 3.88 (d, J=7.8 Hz, 2H), 3.38-3.20 (m, 11H), 2.13-1.96 (m, 2H), 1.86-1.72 (m, 2H), 1.73-1.59 (m, 11H), 1.47-1.32 (m, 2H), 1.32-1.07 (m, 31H). 13C NMR (101 MHz, Chloroform-d) δ 149.9, 126.8 (q, JCF=3.8 Hz), 125.2 (q, JCF=271.1 Hz), 118.2 (q, JCF=32.7 Hz), 112.10, 51.5, 33.3, 25.9, 25.0. 19F NMR (376 MHz, Chloroform-d) δ -60.9 (s, 3F). HRMS (DART-TOF): calculated for C18H17F3N ([M+H]+) 244.1308, found 244.1293.
Synthesis of N-propyl-4-(trifluoromethyl)aniline (11)

General Procedure A was followed using 4-bromobenzotrifluoride as the aryl halide, and propylamine as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-15% EtOAc/hexanes to give the product as a pale yellow oil (33.1 mg, 41%). NMR data matched previously reported spectra.\textsuperscript{36} \textsuperscript{1}H NMR (400 MHz, Chloroform-d) δ 7.39 (d, J=8.5 Hz, 2H), 6.59 (d, J=8.5 Hz, 2H), 3.97 (s, 1H), 3.11 (q, J=5.2 Hz, 2H), 1.66 (t, J=7.2 Hz, 2H), 1.01 (t, J=7.4 Hz, 3H). \textsuperscript{13}C NMR (101 MHz, Chloroform-d) δ 151.0, 126.7 (q, J=271.2 Hz)), 118.6 (q, J=3.2 Hz), 111.8, 45.4, 22.75, 11.1. \textsuperscript{19}F NMR (376 MHz, Chloroform-d) δ -60.9 (s, 3F). HRMS (DART-TOF): calculated for CH\textsubscript{3}F\textsubscript{3}N ([M+H]\textsuperscript{+}) 204.0995, found 204.0989.

Synthesis of N-phenethyl-4-(trifluoromethyl)aniline (13)

[Diagram]}

General Procedure B was followed using 4-bromobenzotrifluoride as the aryl halide, and phenethylamine as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-15% EtOAc/hexanes to give the product as a yellow oil (34.9 mg, 33%). NMR data matched previously reported spectra.\textsuperscript{26} \textsuperscript{1}H NMR (400 MHz, Chloroform-d) δ 7.44 (d, J=8.5 Hz, 2H), 7.40-7.33 (m, 2H), 7.32-7.22 (m, 3H), 6.63 (d, J=8.5 Hz, 2H), 4.04 (s, 1H), 3.47 (q, J=6.6 Hz, 2H), 2.96 (t, J=6.9 Hz, 2H). \textsuperscript{13}C NMR (101 MHz, Chloroform-d) δ 150.5, 138.9, 128.89, 128.86, 126.78 (q, J=271.3 Hz), 126.77, 125.1 (q, J=271.3 Hz), 119.0 (q, J=271.3 Hz), 112.1, 44.6, 35.4. \textsuperscript{19}F NMR (376 MHz, Chloroform-d) δ -61.0 (s, 3F). HRMS (DART-TOF): calculated for C\textsubscript{13}H\textsubscript{13}F\textsubscript{3}N ([M+H]\textsuperserscript{+}) 266.1151, found 266.1154.

Synthesis of N-hexyl-4-(trifluoromethyl)aniline (12)

[Diagram]}

General Procedure A was followed using 4-bromobenzotrifluoride as the aryl halide, and hexylamine as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-15% EtOAc/hexanes to give the product as a pale yellow oil (55.9 mg, 57%). NMR data matched previously reported spectra.\textsuperscript{35,36} \textsuperscript{1}H NMR (400 MHz, Chloroform-d) δ 7.40 (d, J=8.5 Hz, 2H), 6.59 (d, J=8.5 Hz, 2H), 3.94 (s, 1H), 3.29-2.97 (m, 2H), 1.63 (p, J=7.1 Hz, 2H), 1.46-1.28 (m, 6H), 1.00-0.83 (m, 3H). \textsuperscript{13}C NMR (101 MHz, Chloroform-d) δ 151.0, 126.7 (q, J=271.2 Hz)), 118.5 (q, J=3.2 Hz), 111.8, 43.7, 31.7, 29.4, 26.9, 22.8, 14.2. \textsuperscript{19}F NMR (376 MHz, Chloroform-d) δ -60.9 (s, 3F). HRMS (DART-TOF): calculated for C\textsubscript{13}H\textsubscript{13}F\textsubscript{3}N ([M+H]\textsuperscript{+}) 246.1464, found 246.1462.

Synthesis of N-phenyl-4-(trifluoromethyl)aniline (14)

[Diagram]}

[0148] General Procedure B was followed using 4-bromobenzotrifluoride as the aryl halide, and aniline as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-15% EtOAc/hexanes to give the product as a pale yellow oil (63.8 mg, 67%). NMR data matched previously reported spectra.\textsuperscript{35,36} \textsuperscript{1}H NMR (400 MHz, Chloroform-d) δ 7.49 (d, J=8.5 Hz, 2H), 7.36 (t, J=8.4 Hz, 2H), 7.16 (d, J=7.2 Hz, 2H), 7.12-7.02 (m, 2H), 5.91 (s, 1H). \textsuperscript{13}C NMR (101 MHz, Chloroform-d) δ 146.9, 141.3, 129.7, 126.8 (q, J=271.8 Hz), 123.1, 121.8 (q, J=32.8 Hz), 120.2, 115.5. \textsuperscript{19}F NMR (376 MHz, Chloroform-d) δ -61.4 (s, 3F). HRMS (DART-TOF): calculated for C\textsubscript{13}H\textsubscript{13}F\textsubscript{3}N ([M+H]\textsuperscript{+}) 238.0838, found 238.0826.

Synthesis of 4-fluoro-N-(4-(trifluoromethyl)phenyl)aniline (15)

[Diagram]}

[0149] General Procedure B was followed using 4-bromobenzotrifluoride as the aryl halide, and 4-fluoroaniline as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-15% EtOAc/hexanes to give the product as a pale yellow oil (42.1 mg, 52%). NMR data matched previously reported spectra.\textsuperscript{35,36} \textsuperscript{1}H NMR (400 MHz, Chloroform-d) δ 7.43 (d, J=8.5 Hz, 2H), 7.41-7.20 (m, 2H), 7.16 (d, J=7.2 Hz, 2H), 6.82 (s, 1H). \textsuperscript{13}C NMR (101 MHz, Chloroform-d) δ 146.8, 129.7, 126.8 (q, J=271.8 Hz), 119.0 (q, J=32.8 Hz), 112.1, 115.5. \textsuperscript{19}F NMR (376 MHz, Chloroform-d) δ -60.9 (s, 3F). HRMS (DART-TOF): calculated for C\textsubscript{13}H\textsubscript{13}F\textsubscript{3}N ([M+H]\textsuperscript{+}) 246.1464, found 246.1462.
General Procedure B was followed using 4-bromobenzotrifluoride as the aryl halide, and 4-fluoroaniline as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-10% EtOAc/hexanes to give the product as a yellow oil (46.9 mg, 46%). 1H NMR (400 MHz, Chloroform-d) δ 7.46 (d, J=8.5 Hz, 2H), 7.18-7.08 (m, 2H), 7.08-6.99 (m, 2H), 6.93 (d, J=8.4 Hz, 2H), 5.79 (s, 1H). 13C NMR (101 MHz, Chloroform-d) δ 159.3 (d, J_C-F=246.3 Hz), 147.7, 137.1 (d, J_C-F=27.7 Hz), 126.5 (q, J_C-F=3.9 Hz), 124.8 (q, J_C-F=271.8 Hz), 123.2 (d, J_C-F=8.1 Hz), 121.5 (q, J_C-F=32.8 Hz), 116.4 (d, J_C-F=22.7 Hz), 114.7. 19F NMR (376 MHz, Chloroform-d) δ -61.4 (s, 3F), -119.2 (m, 1F). HRMS (DART-TOF): calculated for C12H10FN ([M+H]+) 239.0791, found 239.0792.

Synthesis of 4-(3-(trifluoromethyl)phenyl)morpholine (18)

General Procedure B was followed using 4-bromobenzotrifluoride as the aryl halide, and furfurylamine as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-20% EtOAc/hexanes to give the product as a pale yellow solid (27.3 mg, 28%). NMR data matched previously reported spectra. 1H NMR (400 MHz, Chloroform-d) δ 7.42 (d, J=8.5 Hz, 2H), 7.39-7.36 (m, 1H), 6.68 (d, J=8.5 Hz, 2H), 6.34 (d, J=3.3, 1H), 6.25 (d, J=3.2 Hz, 1H), 4.36 (s, 3H). 13C NMR (101 MHz, Chloroform-d) δ 151.9, 150.1, 142.3, 126.7 (q, J_C-F=3.8 Hz), 125.0 (q, J_C-F=271.4 Hz), 119.6 (q, J_C-F=32.6 Hz), 112.3, 110.6, 107.5, 41.0. 19F NMR (376 MHz, Chloroform-d) δ -61.1 (s, 3F). HRMS (DART-TOF): calculated for C12H13F3NO ([M+H]+) 226.0774, found 226.0773.

Synthesis of N-(furan-2-ylmethyl)-4-(trifluoromethyl)aniline (16)

General Procedure B was followed using 4-bromobenzotrifluoride as the aryl halide, and furylamine as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-15% EtOAc/hexanes to give the product as a pale yellow oil solid (52.7 mg, 57%). NMR data matched previously reported spectra. 1H NMR (400 MHz, Chloroform-d) δ 7.42-7.29 (m, 1H), 7.16-7.06 (m, 2H), 7.08-7.03 (m, 1H), 3.88 (t, J=4.8, 4H), 3.21 (t, J=4.8, 4H), 1.21 (t, J=4.8, 4H). 13C NMR (101 MHz, Chloroform-d) δ 151.5, 151.7 (q, J_C-F=31.8 Hz), 129.8, 124.4 (q, J_C-F=273.4 Hz), 118.6, 116.4 (q, J_C-F=3.8 Hz), 112.0 (q, J_C-F=3.9 Hz), 66.9. 19F NMR (376 MHz, Chloroform-d) δ -62.8 (s, 3F). HRMS (DART-TOF): calculated for C12H12F3NO ([M+H]+) 242.0787, found 242.0787.

Synthesis of 4-(3-(trifluoromethyl)phenyl)piperazine-1-carboxylate (19)

General Procedure A was followed using 3-bromobenzotrifluoride as the aryl halide, and morpholine as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-15% EtOAc/hexanes to give the product as a pale yellow oil solid (52.7 mg, 57%). NMR data matched previously reported spectra. 1H NMR (400 MHz, Chloroform-d) δ 7.42-7.29 (m, 1H), 7.16-7.06 (m, 2H), 7.08-7.03 (m, 1H), 3.88 (t, J=4.8, 4H), 3.21 (t, J=4.8, 4H). 1H NMR (400 MHz, Chloroform-d) δ 7.32 (d, J=8.4 Hz, 2H), 7.64-7.58 (m, 1H), 7.55 (d, J=8.4 Hz, 2H), 7.32 (dd, J=8.4, 4.7 Hz, 1H), 7.17 (d, J=8.4 Hz, 2H). 13C NMR (101 MHz, DMSO-d6) δ 147.2, 142.9, 141.5, 138.7, 127.1 (q, J_C-F=3.8 Hz), 125.5, 125.2 (q, J_C-F=271.8 Hz), 124.40, 119.8 (q, J_C-F=32.3 Hz), 115.5. 19F NMR (376 MHz, DMSO-d6) δ -59.7 (s, 3F). HRMS (DART-TOF): calculated for C12H11F3N2 ([M+H]+) 331.1629, found 331.1632.
Synthesis of 1-(3-(trifluoromethyl)phenyl)piperidine (20)

General Procedure A was followed using 3-bromobenzotrifluoride as the aryl halide, and piperidine as the amine. The reaction was run at room temperature for 3 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-10% EtOAc/hexanes to give the product as a pale yellow oil (33.0 mg, 36%). NMR data matched previously reported spectra.33 😡 H NMR (400 MHz, Chloroform-d) δ 7.32 (t, J = 8.0 Hz, 1H), 7.12 (s, 1H), 7.10-6.99 (m, 2H), 3.21 (t, J = 5.2, 4H), 1.76-1.67 (m, 4H), 1.66-1.57 (m, 2H). 13C NMR (101 MHz, Chloroform-d) δ 152.3, 131.4 (q, J_{CF}=31.6 Hz), 129.5, 124.6 (q, J_{CF}=273.5 Hz), 119.2, 115.3 (q, J_{CF}=3.9 Hz), 112.6 (q, J_{CF}=3.9 Hz), 50.3, 25.8, 24.3. 19F NMR (376 MHz, Chloroform-d) δ 62.7 (s, 3F). HRMS (DART-TOF): calculated for C_{12}H_{15}F_{3}N ([M+H]^+) 230.1151, found 230.1151.

Synthesis of N-(3,5-difluorophenyl)pyridin-3-amine (23)

General Procedure A was followed using 3-bromobenzotrifluoride as the aryl halide, and piperidine as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-100% EtOAc/hexanes to give the product as a white solid (74.4 mg, 90%). 😡 H NMR (400 MHz, DMSO-d_{6}) δ 8.81 (s, 1H), 8.39 (d, J = 2.7 Hz, 1H), 8.26-8.07 (m, 1H), 7.68-7.48 (m, 1H), 7.41-7.21 (m, 1H), 6.83-6.48 (m, 3H). 13C NMR (101 MHz, DMSO-d_{6}) δ 163.4 (dd, J = 243.8, J = 163.5 Hz), 146.2 (t, J = 13.5 Hz), 142.6, 141.1, 138.1, 125.1, 124.0, 98.5-98.0 (m, 94.5 (t, J = 26.7 Hz). 😡F NMR (376 MHz, DMSO-d_{6}) δ -109.5 (t, J = 9.5 Hz, 2F). HRMS (DART-TOF): calculated for C_{12}H_{15}F_{3}N ([M+H]^+) 230.1151, found 230.1151.

Synthesis of 4-(3,5-difluorophenyl)morpholine (21)

General Procedure A was followed using 1-bromo-3,5-difluorobenzene as the aryl halide, and morpholine as the amine. The reaction was run at room temperature for 3 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-15% EtOAc/hexanes to give the product as a white solid (56.3 mg, 71%). NMR data matched previously reported spectra.44 😡 H NMR (400 MHz, Chloroform-d) δ 6.42-6.23 (m, 3H), 3.83 (t, J = 4.8 Hz, 4H), 3.14 (t, J = 4.8 Hz, 4H). 13C NMR (101 MHz, Chloroform-d) δ 164.1 (dd, J = 245.4, J = 16.2 Hz), 153.4 (t, J = 12.2 Hz), 98.0-97.8 (m, 94.6 (t, J = 26.3 Hz), 66.7, 48.4. 13F NMR (376 MHz, Chloroform-d) δ -109.7-109.9 (m, 2F). HRMS (DART-TOF): calculated for C_{11}H_{13}F_{2}NO ([M+H]^+) 200.0881, found 200.0874.

Synthesis of Tert-Butyl 4-(3,5-difluorophenyl)piperazine-1-carboxylate (22)

General Procedure B was followed using 1-bromo-3,5-difluorobenzene as the aryl halide, and tert-butyl piperazine-1-carboxylate as the amine. The reaction was run at room temperature for 3 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-15% EtOAc/hexanes to provide the product as a white solid (73.4 mg, 62%). 😡 H NMR (400 MHz, Chloroform-d) δ 6.40-6.50 (m, 2H), 6.27 (t, J = 8.8, 2.2 Hz, 1H), 3.55 (t, J = 5.2, 4H), 3.14 (t, J = 5.2, 4H), 1.48 (s, 9H). 13C NMR (101 MHz, Chloroform-d) δ 164.1 (dd, J = 245.4, J = 15.8 Hz), 154.7, 153.2 (t, J = 12.3 Hz), 98.7-98.3 (m, 94.7 (t, J = 23.3 Hz), 80.3, 48.3, 28.5. 😡F NMR (376 MHz, Chloroform-d) δ -109.6-109.8 (m, 2F). HRMS (DART-TOF): calculated for C_{15}H_{13}F_{2}NO_{2} ([M+H]^+) 299.1556, found 299.1556.

Synthesis of N-(3,5-difluorophenyl)pyridin-3-amine (23)

General Procedure B was followed using 1-bromo-3,5-difluorobenzene as the aryl halide, and 3-aminopyridine as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-100% EtOAc/hexanes to provide the product as a white solid (74.4 mg, 90%). 😡 H NMR (400 MHz, DMSO-d_{6}) δ 8.81 (s, 1H), 8.39 (d, J = 2.7 Hz, 1H), 8.26-8.07 (m, 1H), 7.68-7.48 (m, 1H), 7.41-7.21 (m, 1H), 6.83-6.48 (m, 3H). 13C NMR (101 MHz, DMSO-d_{6}) δ 163.4 (dd, J = 243.8, J = 163.5 Hz), 146.2 (t, J = 13.5 Hz), 142.6, 141.1, 138.1, 125.1, 124.0, 98.5-98.0 (m, 94.5 (t, J = 26.7 Hz). 😡F NMR (376 MHz, DMSO-d_{6}) δ -109.5 (t, J = 9.5 Hz, 2F). HRMS (DART-TOF): calculated for C_{11}H_{13}F_{2}NO ([M+H]^+) 230.1151, found 230.0738.

Synthesis of 4-(4-fluorophenyl)morpholine (24)

General Procedure B was followed using 1-bromo-4-fluorobenzene as the aryl halide, and morpholine as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-15% EtOAc/hexanes to give the product as a colorless oil (27.3 mg, 38%). NMR data matched previously reported spectra.45 😡 H NMR (400 MHz, Chloroform-d) δ 7.04-6.92 (m, 2H), 6.92-6.82 (m, 2H), 3.87 (t, J = 4.8 Hz, 4H), 3.09 (t, J = 4.8 Hz, 4H). 13C NMR (101 MHz, Chloroform-d) δ 157.5 (d, J_{CF}=243.3 Hz), 148.1, 117.6 (d, J_{CF}=7.8 Hz), 115.8 (d, J_{CF}=22.2 Hz), 67.1, 50.5. 😡F NMR (376 MHz, Chloroform-d) δ -124.2-124.5 (m, 1F). HRMS (DART-TOF): calculated for C_{10}H_{12}FNO ([M+H]^+) 182.0976, found 182.0976.
Synthesis of 4-(3-chlorophenyl)morpholine (25)

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\begin{align*}
\text{[0169]} \\
\text{[0170] General Procedure A was followed using 1-bromo-3-chlorobenzene as the aryl halide, and morpholine as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-15% EtOAc/hexanes to give the product as a colorless oil (65.4 mg, 83%). NMR data matched previously reported spectra.}^{35,71} \text{[0171] H NMR (400 MHz, Chloroform-d) } \delta 7.18 (t, J=8.1 Hz, 1H), 6.89-6.81 (m, 2H), 6.80-6.74 (m, 1H), 3.85 (t, J=4.8 Hz, 4H), 3.15 (t, J=5.2 Hz, 4H). \text{[0172]} ^{13} \text{C NMR (101 MHz, Chloroform-d) } \delta 152.5, 135.2, 130.2, 119.8, 115.6, 113.7, 66.9, 49.0. \text{HRMS (ESI-TOF): calculated for C}_{10} \text{H}_{15} \text{CINO} ([M+H]^+) } 198.0680, \text{found } 198.0691.
\end{align*}
\]

Synthesis of 4-morpholinobenzamide (26)

\[
\begin{align*}
\text{[0173] General Procedure A was followed using 4-bromobenzamide as the aryl halide, and morpholine as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-10% MeOH/DCM to give the product as a white solid (22.5 mg, 27%). NMR data matched previously reported spectra.}^{35,71} \text{[0174] H NMR (400 MHz, DMSO-d$_6$) } \delta 7.88-7.64 (m, 3H), 7.09-6.85 (m, 3H), 3.74 (t, J=4.8 Hz, 4H), 3.21 (t, J=4.8 Hz, 4H). \text{[0175]} ^{13} \text{C NMR (101 MHz, DMSO-d$_6$) } \delta 167.5, 152.9, 128.8, 123.9, 113.3, 65.9, 47.4. \text{HRMS (ESI-TOF): calculated for C}_{11} \text{H}_{16} \text{NO}_2 ([M+H]^+) } 207.1128, \text{found } 207.1121.
\end{align*}
\]

Synthesis of 4-phenylmorpholine (27)

\[
\begin{align*}
\text{[0176] General Procedure A was followed using 4-bromoanisole as the aryl halide, and morpholine as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-15% EtOAc/hexanes to give the product as a white solid (34.8 mg, 53%). NMR data matched previously reported spectra.}^{35,71} \text{[0177] H NMR (400 MHz, Chloroform-d) } \delta 7.35-7.26 (m, 2H), 6.99-6.83 (m, 3H), 3.87 (t, J=4.8 Hz, 4H), 3.17 (t, J=4.8 Hz, 4H). \text{[0178]} ^{13} \text{C NMR (101 MHz, Chloroform-d) } \delta 151.4, 129.3, 120.2, 115.8, 67.1, 49.5. \text{HRMS (DART-TOF): calculated for C}_{10} \text{H}_{14} \text{NO} ([M+H]^+) } 164.1070, \text{found } 164.1075.
\end{align*}
\]

Synthesis of 4-(p-tolyl)morpholine (28)

\[
\begin{align*}
\text{[0179] General Procedure A was followed using 4-bromotoluene as the aryl halide, and morpholine as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-15% EtOAc/hexanes to give the product as a white solid (23.4 mg, 33%). NMR data matched previously reported spectra.}^{35,71} \text{[0180] H NMR (400 MHz, Chloroform-d) } \delta 7.14-7.05 (m, 2H), 6.88-6.80 (m, 2H), 3.87 (t, J=4.8 Hz, 4H), 3.11 (t, J=4.8 Hz, 4H), 2.28 (s, 3H). \text{[0181]} ^{13} \text{C NMR (101 MHz, Chloroform-d) } \delta 149.3, 129.8, 129.7, 116.2, 67.1, 50.1, 20.6. \text{HRMS (DART-TOF): calculated for C}_{11} \text{H}_{16} \text{NO} ([M+H]^+) } 178.1226, \text{found } 178.1225.
\end{align*}
\]

Synthesis of 4-(4-methoxyphenyl)morpholine (29)

\[
\begin{align*}
\text{[0182] General Procedure A was followed using 4-bromoanisole as the aryl halide, and morpholine as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-15% EtOAc/hexanes to give the product as a white solid (5.6 mg, 7%). NMR data matched previously reported spectra.}^{35,71} \text{[0183] H NMR (400 MHz, Chloroform-d) } \delta 6.94-6.81 (m, 4H), 3.86 (t, J=4.4 Hz, 4H), 3.77 (s, 3H), 3.06 (t, J=4.8 Hz, 4H). \text{[0184]} ^{13} \text{C NMR (101 MHz, Chloroform-d) } \delta 154.2, 145.8, 118.0, 114.7, 67.2, 55.7, 51.0. \text{HRMS (DART-TOF): calculated for C}_{11} \text{H}_{16} \text{NO}_2 ([M+H]^+) } 194.1176, \text{found } 194.1174.
\end{align*}
\]

Synthesis of 4-(3-methoxyphenyl)morpholine (30)
product as a colorless oil (45.8 mg, 59%). NMR data matched previously reported spectra.\(^1\) \(^1\)H NMR (400 MHz, Chloroform-d) δ 7.24-7.14 (m, 1H), 6.57-6.50 (m, 1H), 6.48-6.41 (m, 2H), 3.85 (t, J=4.8 Hz, 4H), 3.80 (t, J=3.16 Hz, 4H), 3.18 (t, J=4.8 Hz, 4H). \(^13\)C NMR (101 MHz, Chloroform-d) δ 160.8, 152.8, 123.0, 108.6, 104.9, 102.4, 67.0, 55.3, 49.4. HRMS (DART-TOF): calculated for C\(_{19}\)H\(_{19}\)NO\(_3\) ([M+H]\(^+\)) 294.1176, found 194.1181.

Synthesis of 4-((3,5-dimethoxyphenyl)morpholine (31)

[0181]

\[\text{General Procedure A was followed using 1-bromo-3,5-dimethoxybenzene as the aryl halide, and morpholine as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-30% EtOAc/hexanes to give the product as a white solid (47.4 mg, 53%). NMR data matched previously reported spectra.} \]

\[\text{\(^1\)H NMR (400 MHz, Chloroform-d) δ 6.08 (d, J=2.1 Hz, 2H), 6.04 (t, J=2.1 Hz, 1H), 3.84 (t, J=4.8 Hz, 4H), 3.78 (s, 6H), 3.14 (t, J=4.8 Hz, 4H). \(^13\)C NMR (101 MHz, Chloroform-d) δ 161.7, 153.4, 94.9, 92.0, 67.0, 55.4, 49.5. HRMS (DART-TOF): calculated for C\(_{19}\)H\(_{19}\)NO\(_3\) ([M+H]\(^+\)) 222.1125, found 222.1121.}

[0182]

Synthesis of 1-((4-morpholinophenyl)ethan-1-one (34)

\[\text{General Procedure A was followed using 4'-bromoacetophenone as the aryl halide, and morpholine as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-30% EtOAc/hexanes to give the product as a pale yellow solid (34.4 mg, 42%). NMR data matched previously reported spectra.} \]

\[\text{\(^1\)H NMR (400 MHz, Chloroform-d) δ 7.88 (d, J=8.8 Hz, 2H), 6.86 (d, J=8.8 Hz, 2H), 3.85 (t, J=4.8 Hz, 4H), 3.30 (t, J=5.2 Hz, 4H), 2.52 (s, 3H). \(^13\)C NMR (101 MHz, Chloroform-d) δ 196.6, 154.3, 130.5, 128.3, 113.4, 66.7, 47.7, 26.3. HRMS (DART-TOF): calculated for C\(_{19}\)H\(_{19}\)NO\(_3\) ([M+H]\(^+\)) 206.1176, found 206.1177.}

[0183]

Synthesis of 4-morpholinobenzonitrile (32)

[0184]

General Procedure A was followed using 4-bromobenzonitrile as the aryl halide, and morpholine as the amine. The reaction was run at room temperature for 3 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-30% EtOAc/hexanes to give the product as a white solid (64.5 mg, 86%). NMR data matched previously reported spectra.\(^1\) \(^1\)H NMR (400 MHz, Chloroform-d) δ 7.54-7.45 (m, 2H), 6.89-6.81 (m, 2H), 3.83 (t, J=5.2 Hz, 4H), 3.27 (t, J=5.2 Hz, 4H). \(^13\)C NMR (101 MHz, Chloroform-d) δ 153.6, 133.6, 120.0, 114.1, 101.0, 66.5, 47.4. HRMS (DART-TOF): calculated for C\(_{19}\)H\(_{19}\)NO\(_3\) ([M+H]\(^+\)) 189.1022, found 189.1011.

[0185]

Synthesis of Methyl 4-morpholinobenzoate (33)

[0186] General Procedure A was followed using methyl 4-bromobenzoate as the aryl halide, and morpholine as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-30% EtOAc/hexanes to give the product as a white solid (57.7 mg, 65%). NMR data matched previously reported spectra.\(^2\) \(^1\)H NMR (400 MHz, Chloroform-d) δ 7.95-7.91 (m, 2H), 6.89-6.81 (m, 2H), 3.88-3.80 (m, 7H), 3.27 (t, J=4.8 Hz, 4H). \(^13\)C NMR (101 MHz, Chloroform-d) δ 167.1, 154.3, 131.3, 120.4, 113.6, 66.7, 51.8, 47.8. HRMS (DART-TOF): calculated for C\(_{19}\)H\(_{19}\)NO\(_3\) ([M+H]\(^+\)) 222.1125, found 222.1121.

[0187]

Synthesis of 1-(4-morpholinophenyl)ethan-1-one (34)

[0188]

General Procedure A was followed using 4'-bromoacetophenone as the aryl halide, and morpholine as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-30% EtOAc/hexanes to give the product as a pale yellow solid (34.4 mg, 42%). NMR data matched previously reported spectra.\(^3\) \(^1\)H NMR (400 MHz, Chloroform-d) δ 7.88 (d, J=8.8 Hz, 2H), 6.86 (d, J=8.8 Hz, 2H), 3.85 (t, J=4.8 Hz, 4H), 3.30 (t, J=5.2 Hz, 4H), 2.52 (s, 3H). \(^13\)C NMR (101 MHz, Chloroform-d) δ 196.6, 154.3, 130.5, 128.3, 113.4, 66.7, 47.7, 26.3. HRMS (DART-TOF): calculated for C\(_{19}\)H\(_{19}\)NO\(_3\) ([M+H]\(^+\)) 206.1176, found 206.1177.

[0189]

Synthesis of 4-(pyridin-3-yl)morpholine (35)

[0190] General Procedure B was followed using 3-bromopyridine as the aryl halide, and morpholine as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-100% EtOAc/hexanes to give the product as a pale yellow oil (23.4 mg, 36%). NMR data matched previously reported spectra.\(^4\) \(^1\)H NMR (400 MHz, Chloroform-d) δ 8.30 (s, 1H), 8.12 (t, J=2.8 Hz, 1H), 7.18-7.14 (m, 2H), 3.86 (t, J=4.8 Hz, 4H), 3.18 (t, J=4.8 Hz, 4H). \(^13\)C NMR (101 MHz, Chloroform-d) δ 147.0, 141.3, 138.5, 123.6, 122.2, 66.8, 48.7. HRMS (DART-TOF): calculated for C\(_{9}\)H\(_{11}\)N\(_2\)O ([M+H]\(^+\)) 165.1022, found 165.1018.
Synthesis of 4-(pyrimidin-5-yl)morpholine (36)

[0191]

[0192] General Procedure B was followed using 5-bromopyrimidine as the aryl halide, and morpholine as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-80% EtOAc/hexanes to give the product as a pale yellow solid (113.4 mg, 88%). $^1$H NMR (400 MHz, Chloroform-d) δ 8.39 (d, J=2.8 Hz, 1H), 8.20 (d, J=4.4 Hz, 1H), 7.88-7.80 (m, 2H), 7.45-7.38 (m, 1H), 7.32-7.26 (m, 3H), 7.20-7.12 (m, 2H), 7.10-7.02 (m, 2H), 6.06 (s, 1H), 2.56 (s, 3H). $^{13}$C NMR (101 MHz, Chloroform-d) δ 197.3, 144.3, 143.7, 142.9, 141.0, 139.0, 134.9, 134.0, 130.7, 129.1, 128.2, 126.3, 124.5, 123.9, 121.9, 117.6, 26.6. HRMS (ESI-TOF): calculated for C$_{14}$H$_{12}$N$_2$O$_5$ ([M+H]$^+$) 321.1056, found 321.1063.

Synthesis of 1-(4-(3-bromophenyl)thio)phenyl ethan-1-one (37)

[0193]

[0194] A 50 mL storage flask was charged with a stir bar, flame dried under vacuum and back filled with nitrogen three times. The flask was then charged with Cs$_2$CO$_3$ (1.466 g, 4.5 mmol, 1.5 equiv.), 3-bromothiophen-2-carboxylic acid (0.851 g, 4.5 mmol, 1.5 equiv.) and 23 mL DMSO. The reaction mixture was evacuated and purged with inert gas (N$_2$) three times. The reaction mixture was then placed into an LED-lined beaker along with a tube for air cooling and stirred. After stirring for 12 hours, the reaction mixture was washed with water, extracted with EtOAc, and concentrated under vacuum. The product was isolated by flash chromatography (1:5 EtOAc/hexanes) as a white solid (0.516 g, 56%). $^1$H NMR (400 MHz, Chloroform-d) δ 7.89-7.76 (m, 2H), 7.58 (t, J=1.8 Hz, 1H), 7.53-7.43 (m, 1H), 7.40-7.32 (m, 1H), 7.31-7.20 (m, 3H), 2.56 (s, 3H). $^{13}$C NMR (101 MHz, Chloroform-d) δ 197.1, 143.3, 135.4, 135.4, 135.3, 131.6, 131.5, 131.0, 129.2, 128.8, 123.4, 26.6. HRMS (ESI-TOF): calculated for C$_{14}$H$_{12}$BrOS ([M+H]$^+$) 306.9787, found 306.9813.

Synthesis of 1-(4-(3-(pyridin-3-ylamino)phenyl)thio)phenyl ethan-1-one (38)

[0195]

[0196] General Procedure B was followed using 1-(4-((3-bromophenyl)thio)phenyl)ethan-1-one (37) as the aryl halide, and 3-aminopyridine as the amine. The reaction was run at room temperature for 15 hours. Purification was done by flash chromatography on silica gel, eluting with a gradient of 0-80% EtOAc/hexanes to give the product as a pale yellow solid (113.4 mg, 88%). $^1$H NMR (400 MHz, Chloroform-d) δ 8.39 (d, J=2.8 Hz, 1H), 8.20 (d, J=4.4 Hz, 1H), 7.88-7.80 (m, 2H), 7.45-7.38 (m, 1H), 7.32-7.26 (m, 3H), 7.20-7.12 (m, 2H), 7.10-7.02 (m, 2H), 6.06 (s, 1H), 2.56 (s, 3H). $^{13}$C NMR (101 MHz, Chloroform-d) δ 197.3, 144.3, 143.7, 142.9, 141.0, 139.0, 134.9, 134.0, 130.7, 129.1, 128.2, 126.3, 124.5, 123.9, 121.9, 117.6, 26.6. HRMS (ESI-TOF): calculated for C$_{14}$H$_{12}$N$_2$O$_5$ ([M+H]$^+$) 321.1056, found 321.1063.

Synthesis of 1-(2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (39, Fibanserin)

[0197]

[0198] Using tert-butyl 4-(3-(trifluoromethyl)phenyl)piperazine-1-carboxylate (19) as the precursor, compound 39 was synthesized using previously published procedures.$^{19}$ NMR data matched previously reported spectra.$^{53}$ $^1$H NMR (400 MHz, Chloroform-d) δ 9.99 (s, 1H), 7.32 (t, J=8.0 Hz, 1H), 7.15-6.97 (m, 7H), 4.07 (t, J=6.8 Hz, 2H), 3.21 (t, J=4.8 Hz, 4H), 2.79 (t, J=6.9 Hz, 2H), 2.72 (t, J=5.2 Hz, 4H). $^{13}$C NMR (101 MHz, Chloroform-d) δ 155.8, 151.5, 131.6 (q, J$_{C-C}$=31.9 Hz), 130.5, 129.6, 128.2, 124.5 (q, J$_{C-C}$=273.5 Hz), 121.7, 121.4, 118.8, 115.9 (q, J$_{C-C}$=4.0 Hz), 112.2 (q, J$_{C-C}$=3.9 Hz), 109.8, 108.1, 55.9, 53.2, 48.8, 38.7. $^{33}$F NMR (376 MHz, Chloroform-d) δ -62.8 (s, 3F). HRMS (ESI-TOF): calculated for C$_{20}$H$_{17}$F$_{2}$N$_{6}$O ([M+H]$^+$) 391.1740, found 391.1739.

Synthesis of 1-(2-(4-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)ethyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (40)

[0199]

[0200] Using tert-butyl 4-(4-(3-(trifluoromethyl)phenyl)piperazin-1-carboxylate (9) as the precursor, compound 40 was synthesized using previously published procedures.$^{49}$ $^1$H NMR (400 MHz, Chloroform-d) δ 10.02 (s, 1H), 7.45 (d,
The synthesis of 1-(2-(3,5-difluorophenyl)piperazin-1-yl)(ethyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (41) was achieved using tert-butyl 4-(3,5-difluorophenyl)piperazin-1-carboxylate (22) as the precursor. The compound 41 was synthesized using previously published procedures. 33 H NMR (400 MHz, Chloroform-d) δ 10.25 (s, 1H), 7.17-6.94 (m, 4H), 6.37-6.27 (m, 2H), 6.23 (t, J = 8.9, 2.2 Hz, 1H), 4.06 (t, J = 6.8 Hz, 2H), 3.16 (t, J = 4.8 Hz, 4H), 2.77 (t, J = 6.8 Hz, 2H), 2.69 (t, J = 5.2 Hz, 4H). 13C NMR (101 MHz, Chloroform-d) δ 164.1 (dd, J = 244.8, 16.1 Hz), 155.9, 153.2 (t, J = 12.3 Hz), 130.4, 128.2, 121.7, 121.4, 109.8, 100.8, 98.2-97.8 (m), 94.1 (t, J = 26.2 Hz), 55.8, 53.0, 48.2, 38.7. F NMR (376 MHz, Chloroform-d) δ –110.0–110.1 (m, 2F). HRMS (ESI-TOF): calculated for C_{20}H_{21}F_{7}N_{2}O (M+H\textsuperscript{+}) 359.1678, found 359.1690.

Example 2—Mechanistic Study

Using similar methods, 1-(2-(3,5-difluorophenyl)piperazin-1-yl)ethyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (41) was synthesized using tert-butyl 4-(3,5-difluorophenyl)piperazin-1-carboxylate (22) as the precursor. The compound 41 was synthesized using previously published procedures. 33 H NMR (400 MHz, Chloroform-d) δ 10.25 (s, 1H), 7.17-6.94 (m, 4H), 6.37-6.27 (m, 2H), 6.23 (t, J = 8.9, 2.2 Hz, 1H), 4.06 (t, J = 6.8 Hz, 2H), 3.16 (t, J = 4.8 Hz, 4H), 2.77 (t, J = 6.8 Hz, 2H), 2.69 (t, J = 5.2 Hz, 4H). 13C NMR (101 MHz, Chloroform-d) δ 164.1 (dd, J = 244.8, 16.1 Hz), 155.9, 153.2 (t, J = 12.3 Hz), 130.4, 128.2, 121.7, 121.4, 109.8, 100.8, 98.2-97.8 (m), 94.1 (t, J = 26.2 Hz), 55.8, 53.0, 48.2, 38.7. F NMR (376 MHz, Chloroform-d) δ –110.0–110.1 (m, 2F). HRMS (ESI-TOF): calculated for C_{20}H_{21}F_{7}N_{2}O (M+H\textsuperscript{+}) 359.1678, found 359.1690.

To further establish the utility of the C—N cross-coupling methodology of the disclosure, it was employed in multi-step syntheses (FIG. 12A and FIG. 12B). Recently, a visible light-driven aryl C—S cross-coupling methodology that proceeds under mild conditions to synthesize a wide range of aryl thiocarboxylic acid products through white LED irradiation of a solution containing (thiophen)aryl sulfoxide and Cs\textsubscript{2}CO\textsubscript{3} in DMSO at room temperature in the absence of catalysts was reported. 30 Using this method, aryl thiocarboxylic acid products were synthesized at 56% yield which was subsequently subjected to the C—N cross-coupling conditions described herein, coupling it with 3-aminopyridine, to yield 38 in 88% yield (FIG. 12A). This example highlights two industrially important processes, namely aryl C—S and C—N cross-couplings that can be driven by light irradiation under mild conditions to reach molecular complexity.

The piperazine functionality is abundant across pharmaceutical products (vide supra). 33 Using established methods, in four synthetic steps aryl coupled piperazine derivatives 19, 9, and 22 were converted to ibanserin (39) and two ibanserin derivatives (40 and 41, FIG. 40). It should be noted that 40 can also be accessed from 8, therefore eliminating both Boc protection and deprotection steps. These examples illuminate the prospect of efficient and sustainable access to medicinally relevant precursors using the C—N coupling methodology of the disclosure for the development and manufacturing of pharmaceutical products.

To gain insight into this mechanism, density functional theory (DFT) calculations were performed to compute the energetics of intermediates involved in the proposed lowest energy potential energy surface (FIG. 13A, FIG. 13B, and FIG. 13C). 32, 33 Specifically, to construct possible mechanistic pathways, the mechanism to produce 1a was investigated. A proposed mechanism commences with a nickel-amine complex NiBr\textsubscript{2}(morpholine)\textsubscript{3} (complex A, FIG. 13A) as the characteristic yellow color of NiBr\textsubscript{2}Cl\textsubscript{2}O (complex A’) solution in DMF (\textit{λ}_{\text{max}} = 657 nm) significantly blue-shifted to brownish yellow (\textit{λ}_{\text{max}} = 427 nm) upon morpholine addition to generate the key complex A. The UV-vis spectra of A remained identical upon addition of 4-bromobenzotri fluoride and thus only A is responsible for photon absorption to initiate C—N cross coupling. Computationally, the displacement of three water molecules by three morpholine molecules to generate A was determined to be exergonic by 22.1 kcal/mol. In addition, the ground state of A was computationally determined to be triplet, which was 14.0 kcal/mol more stable than the corresponding singlet. Corroborating DFT predictions, A was previously isolated with a measured magnetic moment of 2.95 BM, reaffirming the triplet ground state of A. 34

Without being bound by theory, it is proposed that the catalytic activity for aryl C—N bond formation begins with photon absorption by A (\textit{λ}_{\text{max}} = 427 nm, \textit{ε}_{\text{max}} = 126 M\textsuperscript{-1} cm\textsuperscript{-1}, FIG. 13B). Photoinduced electron transfer from electron-rich morpholine to the electron-poor Ni(II) metal center results in the reduced Ni(I) and oxidized morpholine radical cation (B), which can subsequently dissociate into the corresponding ion pairs (C). Thermodynamically, the free energy cost to produce C from A (\Delta G\textsubscript{f,c-e}) is endergonic by 57.0 kcal/mol, which is energetically supplied by photon absorption (427 nm or 670 kcal/mol). The proton of the morpholine radical cation is relatively acidic and the bromide anion of Ni(I) complex C is also comparatively labile such that excess morpholine in solution can act as a base to neutralize the hydroxyboron to form D (\Delta G\textsubscript{f,c-b}) = 13.2 kcal/mol).

The Ni(I) species and morpholine radical in D are both reactive intermediates that can react with either 4-bromobenzotri fluoride through either step DE or DF. In step DE, the morpholine radical adds to 4-bromobenzotri fluoride to form the desired product 1a through bromine atom displacement (E). The DFT-predicted free energy of activation (\Delta G\textsubscript{f,c-e}) for this step is 23.3 kcal/mol while the free energy of reaction is thermodynamically favored by 10.0 kcal/mol. The Ni(I) species and the bromine atom in E can then quench (\Delta G\textsubscript{f,c-b}) = 55.6 kcal/mol to form the closed-shell NiBr\textsubscript{2}(morpholine)\textsubscript{3} complex (G). G can then associate with the morpholine in solution (\Delta G\textsubscript{f,c-e} =1.1 kcal/mol) to re-enter the catalytic cycle as A. Alternatively, 4-bromobenzotri fluoride can oxidatively add to Ni(I) species in D to form a Ni(III) intermediate (F) (\Delta G\textsubscript{f,c-b} = 19.6 kcal/mol and \Delta G\textsubscript{f,c-b} = 12.2 kcal/mol). This Ni(III) and the morpholine radical can then react energetically (\Delta G\textsubscript{f,c-b} = 77.8 kcal/mol) to eliminate the C—N product 1a while forming the aforementioned G.
Example 3. C—N Cross-Coupling Using Photoredox Catalysts to Excite Nickel-Amine Complexes

General Procedures

[0208] N,N-dimethylacetamide (DMAc) solvent, 4-bromobenzotrifluoride, amines, Bu4NPf6, AgNO3, and ferrocene were purchased from Sigma-Aldrich. TCI or Alfa Aesar and used as received. For all spectral studies, DMAc HPLC grade—99.5% purity was used. Anhydrous toluene was purified and dried using an MB-SPS solvent purification system (MBraun). All commercially available solvents and reagents were degassed and used without further purifications except for morpholine and aniline. Morpholine and aniline were dried over CaH2 with stirring for 24 hours, followed by vacuum distillation, according to a published procedure. The dried and degassed amines were stored under N2 in a sealed Schlenk flask until use. For aniline, the flask was wrapped in aluminum foil to protect from light. All Ni salt catalyst solutions (e.g. NiBr2,3H2O, NiBr2, glyme, and anhydrous NiBr2) were purchased from Sigma-Aldrich or Alfa Aesar, stored in a N2 filled glove box upon receipt, and used without further purification. All substrates used in C—N cross coupling reactions were purchased from Sigma-Aldrich or Alfa Aesar and used as received, with the exception of morpholine which was purified as mentioned above.

[0209] The photoreactor used was designed and built in house as described herein. All LEDs used were purchased from LED Engin and full emission spectra, as well as peak wavelength shift vs. temperature data, are available online in the respective manufacturer datasheets (Table 11).

<table>
<thead>
<tr>
<th>LED Information</th>
<th>Luminous Flux Model # URL</th>
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<tbody>
<tr>
<td>Green</td>
<td>640 lm, 700 mA LZ4-00G108 [<a href="http://www.ledengin.com/files/products/LZ4/LZ4-00G108.pdf">http://www.ledengin.com/files/products/LZ4/LZ4-00G108.pdf</a>]</td>
</tr>
<tr>
<td>Red</td>
<td>160 lm, 700 mA LZ4-00R108 [<a href="http://www.ledengin.com/files/products/LZ4/LZ4-00R108.pdf">http://www.ledengin.com/files/products/LZ4/LZ4-00R108.pdf</a>]</td>
</tr>
<tr>
<td>Yellow</td>
<td>145 lm, 700 mA LZ4-00Y108 [<a href="http://www.ledengin.com/files/products/LZ4/LZ4-00Y108.pdf">http://www.ledengin.com/files/products/LZ4/LZ4-00Y108.pdf</a>]</td>
</tr>
<tr>
<td>Far Red</td>
<td>2.1 W, 700 mA LZ4-00R308 [<a href="http://www.ledengin.com/files/products/LZ4/LZ4-00R308.pdf">http://www.ledengin.com/files/products/LZ4/LZ4-00R308.pdf</a>]</td>
</tr>
</tbody>
</table>

[0210] The 1H, 13C, and 19F NMR spectra were recorded on a Bruker US400 instrument at (400, 101, or 376 MHz, respectively) in the Colorado State University Central Instrument Facility. Deuterated chloroform was purchased from Cambridge Isotope Laboratories (Andover, Mass.) and used as received. All 1H NMR experiments are reported in δ units, parts per million (ppm), and were measured relative to the signals for residual chloroform (7.26 ppm) or dimethylsulfoxide (2.50 ppm) in the deuterated solvents. Data for 1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, h=heptet, br=broad), coupling constant (Hz) and integration. All 13C NMR spectra are reported in ppm relative to CDCl3 (77.16 ppm) or DMSO-d6 (39.52 ppm). Reactions were analyzed by thin layer chromatography (TLC) using TLC silica gel P254 250 μm precoated-plates from Merck. Developed chromatograms were observed using a UV lamp with emission at 255 nm or 365 nm. Accurate mass measurements were obtained using an Agilent 6224 Time of Flight (TOF) mass spectrometer interfaced to a direct analysis in real time (DART) ionization source (IonSense DART-SVP).

General Procedure A:

[0211] C—N cross coupling reactions were performed according to the following procedure. Under a nitrogen atmosphere in a glovebox, a DMAc solution containing dissolved NiBr2·3H2O (0.323 mL, 0.02 mmol, 0.05 equiv., 5.5 mg) was added to a 0.5 dram glass vial charged with a stir bar. This vial was removed from the glove box. If present, 500 μL photocatalyst (0.0016 mmol, 0.004 equiv.) dissolved in DMAc was added under air. If not, 500 μL DMAc was added. Aryl halide (50 μL, 0.4 mmol, 1.0 equiv.) and amine (1.40 mmol, 3.5 equiv.) was added by micropipette. The glass vial then was capped using a screw cap equipped with a PTFE/silicone septum and sealed with a strip of electrical tape. The vial was then sparged through the septum with Ar for 15 minutes. After sparging, the puncture was sealed with electrical tape and the capped glass vial containing the reaction mixture was then placed in a 3D-printed vial holder and subjected to LED irradiation with fan cooling to maintain the vial at room temperature using the reactor setup described herein. After 22 hours, the reaction was stopped by turning off the reactor and a 15 μL aliquot was removed for 19F NMR.

General Procedure B

[0212] C—N cross coupling reactions were performed according to the following procedure. Under a nitrogen atmosphere in a glovebox, aryl halide (1.0 equiv., 4.0 mmol) was added to a 0.5 dram glass vial charged with a stir bar and, if applicable, solid amine (1.5 equiv, or 3.5 equiv.) and/or KBr (1 equiv., 0.4 mmol, 47.6 mg). A DMAc solution containing dissolved NiBr2·3H2O (0.500 mL, 0.02 mmol, 0.05 equiv., 5.5 mg) was then added to the vial via micropipette. For reactions containing quinuclidine, the Ni solution was first added to a vial containing weighed out quinuclidine (1.5 equiv., 0.6 mmol, 66.7 mg). Once fully dissolved, the solution containing Ni and quinuclidine was added to the 0.5 dram vial. A solution of photocatalyst (0.0008 mmol, 0.002 equiv.) dissolved in DMAc (0.500 mL) was added via micropipette. The glass vial was then capped using a screw cap equipped with a PTFE/silicone septum and sealed with Parafilm®. The vial was removed from the glovebox and amine (1.40 mmol, 3.5 equiv., degassed) was added by using a degassed Hamilton syringe. The capped glass vial containing the reaction mixture was then placed in a 3D-printed vial holder...
and subjected to LED irradiation with fan cooling to maintain the vial at room temperature using a reactor setup described herein. After 15 hours, the reaction was stopped by turning off the reactor and a 10 μL aliquot was removed for \(^{19}\)F NMR, if the product contains fluorine. The crude reaction mixture was then transferred to a 100 mL column for separation by flash chromatography. The photocatalyst used is indicated prior to each reported yield. PhenO-3,7-di[(1,1'-biphenyl)-4-yl]-10-(naphthalen-1-yl)-10H-phenoxazine, Ru-[Ru(bpy)_3]Cl_2, where bpy=2,2-bipyridine.

These procedures were utilized for reactions in FIGS. 14A-14B and Tables 12 and 13 below.

**TABLE 12**

<table>
<thead>
<tr>
<th>Amine</th>
<th>Time (hrs)</th>
<th>Lights</th>
<th>Solvent</th>
<th>PC</th>
<th>% Conv.</th>
<th>% DH</th>
</tr>
</thead>
<tbody>
<tr>
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<td>22</td>
<td>LED</td>
<td>DMAC</td>
<td>none</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>morpholine</td>
<td>22</td>
<td>LED</td>
<td>DMAC</td>
<td>none</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>morpholine</td>
<td>22</td>
<td>LED</td>
<td>DMAC</td>
<td>none</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>morpholine</td>
<td>22</td>
<td>LED</td>
<td>DMAC</td>
<td>none</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>morpholine</td>
<td>22</td>
<td>LED</td>
<td>DMAC</td>
<td>none</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>morpholine</td>
<td>22</td>
<td>LED</td>
<td>DMAC</td>
<td>none</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>morpholine</td>
<td>22</td>
<td>LED</td>
<td>DMAC</td>
<td>none</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>morpholine</td>
<td>22</td>
<td>LED</td>
<td>DMAC</td>
<td>none</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>morpholine</td>
<td>22</td>
<td>LED</td>
<td>DMAC</td>
<td>none</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>morpholine</td>
<td>22</td>
<td>LED</td>
<td>DMAC</td>
<td>none</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>morpholine</td>
<td>22</td>
<td>LED</td>
<td>DMAC</td>
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<td>0%</td>
<td>0%</td>
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</tbody>
</table>

**TABLE 13**

<table>
<thead>
<tr>
<th>Amine</th>
<th>Substrate</th>
<th>Additive</th>
<th>Base</th>
<th>PC</th>
<th>% DH</th>
<th>% Conv.</th>
<th>(^{19})F NMR</th>
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<td>none</td>
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<td>0%</td>
<td>43%</td>
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<tr>
<td>morpholine</td>
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<td>propylamine</td>
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<td>13%</td>
<td>63%</td>
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<td>1</td>
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<td>4-BrBzCF_3</td>
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<td>99%</td>
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<td>KBr, 1 eq</td>
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<td>&lt;1%</td>
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<td>1</td>
<td>&lt;1%</td>
<td>28%</td>
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</tbody>
</table>

**[0215]**

General procedure B was used with morpholine as the amine and 4-bromobenzotri fluoride as the aryl halide. The product was purified by flash chromatography on silica gel in a 100 mL column. The solvent system for product elution was 50% EtOAc/50% hexanes and a white solid (PhenO: 75 mg, 76%; Ru: 53 mg, 54%) was recovered. NMR spectra matched those previously reported.

**[0216]**

General procedure B was used with morpholine as the amine and 4-bromobenzotri fluoride as the aryl halide. The product was purified by flash chromatography on silica gel in a 100 mL column. The solvent system for product elution was 50% EtOAc/50% hexanes and a white solid (PhenO: 75 mg, 76%; Ru: 53 mg, 54%) was recovered. NMR spectra matched those previously reported.

**[0214]**

As illustrated in Tables 12 and 13 above, for reactions involving morpholine, KBr was determined to be generally ineffective. However, with propylamine and piperazine, use of KBr led to higher yields. Without intending to be bound by theory, this observed improvement in yield may be due to several factors, such as the inhibition of the competing dehalogenation reaction, inhibition of bromide displacement (leading to inhibition of the stepwise equilibria and blue-shifting of Ni-amine complex absorption), or inhibition of bromide dissociation from Ni. However, inhibition of dehalogenation may be less important as, for piperazine, the balance of products was not changed with/without KBr (but more starting material was consumed).

**Characterizations**

**Synthesis of 4-(trifluoromethyl)phenylmorpholine**

**[0217]**

**Synthesis of 1-(trifluoromethyl)phenylpiperidine-4-ol**

**[0218]**

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Synthesis of 4-fluoro-N-(4-(trifluoromethyl)phenyl)aniline

General procedure B was used with cyclohexylamine as the amine and 4-bromobenzotrifluoride as the aryl halide. Flash chromatography was performed on silica gel with 10% EtOAc/90% hexanes to give the product as a pale yellow solid (PhenO: 56 mg, 55%; Ru: 27 mg, 26%). NMR spectra matched those previously reported. $^1$H NMR (400 MHz, Chloroform-d) δ 7.37 (d, J=8.4 Hz, 2H), 6.57 (d, J=8.6 Hz, 2H), 3.88 (s, 1H), 3.37-3.20 (m, 1H), 2.14-1.95 (m, 2H), 1.85-1.71 (m, 2H), 1.72-1.61 (m, 1H), 1.46-1.31 (m, 2H), 1.30-1.10 (m, 3H). $^{13}$C NMR (101 MHz, Chloroform-d) δ 149.9, 126.8 (q, $\text{J}_{13C,\text{F}}$=3.8 Hz), 125.2 (q, $\text{J}_{13C,\text{F}}$=271.1 Hz), 118.2 (q, $\text{J}_{13C,\text{F}}$=32.7 Hz), 112.1, 51.5, 33.3, 25.9, 25.0. $^{19}$F NMR (376 MHz, Chloroform-d) δ -60.9 (s, 3F). HRMS (DART-TOF): calculated for C$_{13}$H$_{7}$F$_3$N ($[M+H]^+$) 244.1325, found 244.1325.

Synthesis of 4-fluoro-N-(4-(trifluoromethyl)phenyl)morpholine

General procedure B was followed with 4-fluoroaniline as the amine and 4-bromobenzotrifluoride as the aryl halide. Flash chromatography was performed on silica gel, eluting with 20% EtOAc/80% hexanes to give the product as a yellow solid (PhenO: 56 mg, 55%; Ru: 27 mg, 26%). NMR spectra matched those previously reported. $^1$H NMR (400 MHz, Chloroform-d) δ 7.45 (d, J=8.4 Hz, 2H), 7.18-7.09 (m, 2H), 7.09-6.98 (m, 2H), 6.93 (d, J=8.4 Hz, 2H), 5.79 (s, 1H). $^{13}$C NMR (101 MHz, Chloroform-d) δ 159.3 (d, $\text{J}_{13C,\text{F}}$=242.5 Hz), 147.7, 137.1 (d, $\text{J}_{13C,\text{F}}$=2.8 Hz), 126.9 (q, $\text{J}_{13C,\text{F}}$=3.8 Hz), 124.8 (q, $\text{J}_{13C,\text{F}}$=270.6 Hz), 123.2 (d, $\text{J}_{13C,\text{F}}$=8.0 Hz), 121.6 (q, $\text{J}_{13C,\text{F}}$=32.8 Hz), 116.4 (d, $\text{J}_{13C,\text{F}}$=22.6 Hz), 114.7. $^{19}$F NMR (376 MHz, Chloroform-d) δ -61.5 (s, 3F), -119.2 (hept, J=5.1, 5.1, 4.5, 4.5, 3.5, 3.2 Hz, 1F). HRMS (DART-TOF): calculated for C$_{13}$H$_{10}$F$_5$N ($[M+H]^+$) 256.0744, found 256.0698.

Synthesis of N-propyl-4-(trifluoromethyl)aniline

General procedure B was used with morpholine as the amine and 3-bromobenzotrifluoride as the aryl halide. Flash chromatography was performed on silica gel with 15% EtOAc/85% hexanes to give the product as a pale yellow oil (PhenO: 78 mg, 84%; Ru: 11 mg, 12%). NMR spectra matched those previously reported. $^1$H NMR (400 MHz, Chloroform-d) δ 7.44-7.31 (m, 1H), 7.17-7.00 (m, 3H), 3.87 (t, J=4.8, 4H), 3.20 (t, J=4.9, 4H). $^{13}$C NMR (101 MHz, Chloroform-d) δ 151.6, 131.7 (q, $\text{J}_{13C,\text{F}}$=31.9 Hz), 129.8, 124.9 (q, $\text{J}_{13C,\text{F}}$=374.5 Hz), 118.6, 116.4 (q, $\text{J}_{13C,\text{F}}$=3.9 Hz), 112.0 (q, $\text{J}_{13C,\text{F}}$=3.9 Hz), 66.9, 49.0. $^{19}$F NMR (376 MHz, Chloroform-d) δ -62.76 (s, 3F). HRMS (DART-TOF): calculated for C$_{14}$H$_{11}$F$_3$N ($[M+H]^+$) 232.0944, found 232.0960.

Synthesis of 4-(4-methoxyphenyl)morpholine

General procedure B was used with propylamine as the amine and 3-bromobenzotrifluoride as the aryl halide. Flash chromatography was performed on silica gel with 15% EtOAc/85% hexanes to give the product as a pale yellow oil (PhenO: 41 mg, 50%; Ru: <2 mg, trace). NMR spectra matched those previously reported. $^1$H NMR (400 MHz, Chloroform-d) δ 7.39 (d, J=8.3 Hz, 2H), 6.59 (d, J=8.4 Hz, 2H), 4.01 (s, 1H), 3.11 (t, J=7.1 Hz, 2H), 1.67 (dt, J=14.4 Hz, 7.3 Hz, 2H), 1.01 (t, J=7.4 Hz, 3H). $^{13}$C NMR (101 MHz, Chloroform-d) δ 151.0, 126.7 (q, $\text{J}_{13C,\text{F}}$=3.8 Hz), 125.2 (q, $\text{J}_{13C,\text{F}}$=271.2 Hz), 118.6 (q, $\text{J}_{13C,\text{F}}$=32.7 Hz), 111.8, 45.4, 22.6, 11.7. $^{19}$F NMR (376 MHz, Chloroform-d) δ -60.9 (s, 3F). HRMS (DART-TOF): calculated for C$_{10}$H$_{13}$F$_3$N ($[M+H]^+$) 204.0995, found 204.1009.
General procedure B was used with morpholine as the amine and 4-bromoisocyanate as the aryl halide. Flash chromatography was performed on silica gel, eluting with 20% EtOAc/80% hexanes to give the product as a white solid (PhenO: 24 mg, 33%; Ru: 10 mg, 13%). NMR spectra matched those previously reported. $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 7.00-6.79 (m, 4H), 3.86 (t, $J$=4.7 Hz, 4H), 3.77 (s, 3H), 3.06 (t, $J$=4.8 Hz, 4H). $^{13}$C NMR (101 MHz, Chloroform-d) $\delta$ 154.1, 145.8, 118.0, 114.7, 67.2, 55.7, 51.0, 29.9. HRMS (DART-TOF): calculated for C$_{11}$H$_{13}$NO$_2$ ([M+H]$^+$) 194.1176, found 194.1192.

Synthesis of 4-(pyridin-3-yl)morpholine

General Procedure B was used with 3-aminopyridine as the amine and 4-bromobenzotrifluoride as the aryl halide. Flash chromatography on silica gel with 50% EtOAc/50% hexanes to give the product as a pale yellow oil (PhenO: 38 mg, 58%; Ru: 6 mg, 9%). NMR spectra matched those previously reported. $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 8.30 (s, 1H), 8.12 (t, $J$=2.8 Hz, 1H), 7.16 (d, $J$=2.5 Hz, 2H), 3.86 (t, $J$=4.8 Hz, 4H), 3.17 (t, $J$=5.3 Hz, 4H). HRMS (DART-TOF): calculated for C$_{11}$H$_{13}$F$_2$N$_2$ ([M+H]^+) 239.0791, found 239.0803.

Synthesis of 1-(4-(trifluoromethyl)phenyl)piperazine

General Procedure B was used with piperazine as the amine and 4-bromobenzotrifluoride as the aryl halide. Flash chromatography on silica gel with 30% MeOH/85% DCM to give the product as a yellow solid (PhenO: 18 mg, 20%; Ru: 47 mg, 51%). NMR spectra matched those previously reported. $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 8.13 (d, $J$=8.5 Hz, 2H), 3.56 (t, $J$=3.8 Hz, 4H), 3.36 (t, $J$=5.2 Hz, 4H), 1.25 (s, 1H). $^{13}$C NMR (101 MHz, DMSO-d$_6$) $\delta$ 152.5, 126.3 (q, $J$=3.6 Hz), 124.8 (q, $J$=271.2 Hz), 118.9 (q, $J$=32.1 Hz), 114.8, 44.7, 42.7. $^{19}$F NMR (376 MHz, Chloroform-d) $\delta$ -61.8 (s, 3F). HRMS (DART-TOF): calculated for C$_{19}$H$_{17}$F$_2$N$_2$ ([M+H]^+) 231.1104, found 231.1117.

Synthesis of tert-Butyl 4-(3-(trifluoromethyl)phenyl)piperazine-1-carboxylate

General Procedure B was used with tert-butyl piperazine-1-carboxylate as the amine and 4-bromobenzotrifluoride as the aryl halide. Flash chromatography on silica gel with 15% EtOAc/85% hexanes to give the product as a white solid (PhenO: 114 mg, 86%; Ru: 19 mg, 14%). NMR spectra matched those previously reported.
reported. \(^1\)H NMR (400 MHz, Chloroform-d) \(\delta\) 7.49 (d, \(J=8.2\) Hz, 2H), 6.92 (d, \(J=8.7\) Hz, 2H), 3.59 (t, \(J=5.1\) Hz, 4H), 3.24 (t, \(J=5.2\) Hz, 4H), 1.49 (s, 9H). \(^{13}\)C NMR (101 MHz, DMSO-d6) \(\delta\) 154.8, 153.3, 126.6 (q, \(J=3.8\) Hz), 124.8 (q, \(J=271.6\) Hz), 121.2 (q, \(J=33.2\) Hz), 115.1, 80.3, 48.3, 28.6. \(^{31}\)F NMR (376 MHz, Chloroform-d) \(\delta\) –61.5 (s, 3F). HRMS (DART-TOF): calculated for C\(_{15}\)H\(_3\)F\(_3\)N\(^{[M+H]^+}\) 331.1628, found 331.1644.

**Synthesis of 1-(4-(trifluoromethyl)phenyl)indoline**

[0239] General procedure B was used with indoline as the amine and 4-bromobenzotrifluoride as the aryl halide. Flash chromatography was performed on silica gel with 10% EtOAc/90% hexanes to give the product as a white solid (PhenO: 72 mg, 68%; Ru: 77 mg, 73%). NMR spectra matched those previously reported. \(^1\)H NMR (400 MHz, Chloroform-d) \(\delta\) 7.57 (d, \(J=8.9\) Hz, 2H), 7.30-7.21 (m, 4H), 7.13 (t, \(J=7.9\) Hz, 1H), 6.84 (td, \(J=7.4, 1.0\) Hz, 1H), 4.00 (t, \(J=8.4\) Hz, 2H), 3.17 (t, \(J=8.4\) Hz, 2H). \(^{13}\)C NMR (101 MHz, Chloroform-d) \(\delta\) 146.9, 145.7, 131.9, 127.3 126.5 (q, \(J=3.8\) Hz), 125.5, 124.7 (q, \(J=270.5\) Hz), 121.8 (q, \(J=32.7\) Hz), 120.3, 116.2, 109.2, 52.0, 28.2. \(^{31}\)F NMR (376 MHz, Chloroform-d) \(\delta\) –61.5 (s, 3F). HRMS (DART-TOF): calculated for C\(_{15}\)H\(_3\)F\(_3\)N\(^{[M+H]^+}\) 264.0995, found 264.1011.

**Example 4. Mechanistic Study**

To further establish the utility of the C—N cross-coupling methodology of the disclosure, it was initially confirmed that [Ru(bpy)]\(_2\)Cl\(_2\) (PC 1) is an effective PC for C—N cross-coupling involving 4-bromobenzotrifluoride and morpholine. The reaction with PC 1 achieved 88% conversion as measured by \(^{31}\)F NMR after 22 hours irradiation with a green (e.g. \(\lambda_{max}=523\) nm) LED (FIG. 14A). Importantly, no product was observed either in the absence of light or PC under these conditions, indicating that the direct excitation of the Ni complex was not a significant pathway, and thus the observed reactivity can be substantially ascribed to the role of PC 1.

To further elucidate via nanosecond TA experiments. It was noted that the speciation of the Ni-amine complexes formed in situ is detailed herein. Laser irradiation at \(\lambda_{max}=552\) nm in N,N-dimethylacetamide (DMAc) solution containing PC 1 produced the long-lived (e.g. 874±40 ns in DMAc) metal-to-ligand charge-transfer (MLCT) triplet excited state characterized by an excited state absorption (ESA) feature at \(\lambda=370\) nm and a prominent ground state bleach (GBS) at \(\lambda=450\) nm (FIG. 14B). The MLCT excited state lifetime measured here is consistent with previous reported values ranging from 800-1000 ns in polar, aprotic solvents.

**[0243]** In a C—N cross-coupling reaction mixture consisting of the same molar ratio of components detailed in FIG. 14A, the excited state quenching of PC 1 using \(\lambda_{probe}=370\) nm was monitored, consistent with the green LED used in cross coupling reactions. It is noted that under these conditions, Ni-morpholine complexes are formed in situ (vide infra) and are active in quenching PC 1’s excited state. Importantly, consistent with an EnT pathway, signals corresponding to PC 1’s excited state return fully to the baseline at all wavelengths from \(\lambda=300-800\) nm (FIG. 14D), indicative of reformation of the ground state PC 1. In particular, kinetic traces of PC 1 at both \(\lambda_{probe}=370\) nm and \(\lambda_{probe}=450\) nm returned fully to baseline (FIG. 14D, inset) and thus neither oxidized nor reduced PC 1 indicative of an ET mechanism was observed.

**[0244]** For a C—N cross-coupling reaction mixture consisting of the same molar ratio of components detailed in FIG. 14A, the excited state quenching of PC 1 was quenched to different degrees. To explore this relationship, a Stern-Volmer quenching study was performed with ratios of Ni/PC 1 increasing from 10:1 to 50:1. Notably, use of morpholine gives \(k_q=(2.3±0.1)\times10^6 \text{ M}^{-1} \text{s}^{-1}\) at \(\lambda_{probe}=450\) nm and propylene oxide quenched with a significantly reduced rate constant of \(k_q=3.5±0.4)\times10^5 \text{ M}^{-1} \text{s}^{-1}\) (FIG. 14D), consistent with the lower cross-coupling performance of primary amines relative to secondary amines observed herein and previously under direct excitation with 365 nm irradiation.

**[0245]** Unlike typical organic substrates for which the contribution of Förster type EnT can be deduced to be minimal a priori account of lacking significant electronic coupling with the excited PC, Ni-amine complexes absorb significantly in the wavelength range of PC 1 phosphorescence (FIG. 14F). Further, the overlap area for absorption of Ni-morpholine and Ni-propylene oxide mixtures appears correlated with the rate of quenching, supporting the hypothesis of Förster type EnT. However, the components of the quenching mixture should be further elucidated in order to determine the identity and molar absorptivity of the EnT acceptor(s) in order to utilize Förster theory quantitatively in this hypothesis.

**[0246]** To address this challenge, single crystals were grown from concentrated Ni-amine mixtures, and analyzed by single crystal X-ray diffraction (XRD) to reveal propylene oxide, morpholine, and quinuclidine form previously unreported 6-, 5-, and 4-coordinate Ni(II) bromide complexes, respectively (FIG. 15A). Importantly, these complexes are likely the EnT acceptors, but it must be confirmed that the structures obtained in solid-state can serve as reasonable approximations of the geometry of complexes formed in situ in DMAC solution. To confirm that this assumption is reasonable, single crystals were examined through solid state UV-visible absorption spectroscopy (FIG. 15B). Qualitatively, similar absorption features are observed in solution as are found in the single crystals for all complexes, suggesting that structures obtained from XRD are not changed significantly upon DMAC solution. As such, the EnT quenchers in TA experiments can now be assigned to specific complexes, namely [NiBr\(_2\)](morpholine)
[0247] Notably, the structure obtained for [NiBr₂(morpholine)]₂ closely matches the density functional theory (DFT) optimized ground state geometry in DmAc solution (not shown), supporting this assignment as well as the accuracy of reported DFT calculations. Furthermore, the addition of four propylamine molecules to Ni(II) cannot be explained by the amine’s lack of a cyclic structure as cyclohexylamine and aniline also form 6-coordinate Ni(II) complexes, suggesting that primary monodentate amines generally form 6-coordinate NiBr₂ complexes. Ni-amine complexes of the type characterized herein are proposed to form across Ni catalysis in systems lacking exogenous ligand and employing amines in conjunction with NiBr₂, regardless of the NiBr₂ source (e.g. NiBr₂, glyme, NiBr₂,3H₂O, or anhydrous NiBr₂). The same complexes also form in the presence of all PCs used in C–N coupling reactions (Ir(III), Ru(II), and phenoxazine), indicating they may broadly serve as mechanistically relevant species in many dual catalytic Ni(II) cross coupling systems.

[0248] Förster ET is allowed based on the conservation of spin angular momenta from the triplet excited state of PC 1 as the donor to form a triplet excited state Ni-amine complex. In order to employ Förster theory in modeling this excited state reactivity, the molar absorptivity of each acceptor complex overlapping with PC 1 emission must be known. However, UV-vis absorption peaks are observed in the Ni-amine solution which remain to be assigned (e.g. the feature at 550 nm in the Ni-morpholine DmAc solution, Fig. 14C) that might be viable ET acceptors. In accordance with the disclosure, it was hypothesized that these features must originate from other Ni-amine complexes with fewer amine ligands, since a stepwise series of amine additions is required in the formation of the observed complexes from the NiBr₂,3H₂O precatayst. These binding equilibria were directly observed through UV-vis isothermal titrations in which mixtures were analyzed with increasing ratios of the amine ligand:Ni.

[0249] UV-vis of these mixtures shows the evolution and demise of species with increasing numbers of amine ligands in the Ni-morpholine mixture (Fig. 16A). Initially, it was noted that the DmAc solvent forms the salt [Ni(DmAc)₃][NiBr₂] prior to amine addition, and that multiple pathways exist for the first two amine additions. However, all pathways converge to form the tetrahedral [NiBr₂(morpholine)]₂ as the product of κ₁, which can be assigned to the signal with λₘₐₓ₁ ≈ 427 nm and λₘₐₓ₂ ≈ 740 nm. To precisely determine the ratio of these species in the Ni-morpholine quenching mixture, the titration data was fitted to four variants (flavors) of a 1:3 (metal:ligand or host:guest) binding model (data not shown). This analysis was performed using a Matlab code based on the analytical solution to the system of equations for the 1:3 equilibria, similar to that described in a NMR study on a 3:1 complexation of a bis-antimony receptor with halide anions. A global analysis using the UV-vis binding isotherms from λ ≈ 395-1200 nm was performed. Comparing how the various flavors of the 1:3 binding model fitted the data clearly showed that the “full” 1:3 model which assumes i) cooperativity and ii) that the 1:1, 1:2, and 1:3 stepwise complexes have distinct spectra, gave a significantly better fit to the data than the other binding model (flavors) considered.

[0250] The full model allowed the stepwise equilibrium binding constants to be extracted, as well as the molar absorptivity (Fig. 16B) of each species, giving K₁ = (5.8 ± 2.6)×10⁴ M⁻¹, K₂ = 1.2±2×10⁴ M⁻¹, and K₃ = 2.6±0.5 M⁻¹ with the corresponding free energies (after correcting for statistical factors) ΔG₁ = −2.0±0.3 kcal mol⁻¹, ΔG₂ = −1.3±0.1 kcal mol⁻¹, and ΔG₃ = −0.5±0.1 kcal mol⁻¹, respectively (Fig. 17C). The increasing ΔG values indicate negative binding cooperativity, or less favorable addition of morpholine to Ni with each successive association. Notably, ΔG₃ = −0.5 kcal mol⁻¹ is reasonably close to the value of ΔG₃ = −1.1 kcal mol⁻¹ calculated by DFT in our previous work.

[0251] Furthermore, it was calculated that under C–N coupling conditions (e.g. 70:1 amine:Ni molar ratio), the Ni-morpholine quenching mixture consists of 73% [NiBr₂(morpholine)]₀, 27% [NiBr₂(morpholine)]₁, and <0.3% other complexes. As shown in Fig. 14F, both [NiBr₂(morpholine)]₀ and [NiBr₂(morpholine)]₁ demonstrate absorptions that overlap significantly with PC 1’s emission. While [NiBr₂(morpholine)]₀ shows the largest overlap, it is present in lower concentration. Interestingly, [NiBr₂(morpholine)]₁ contains a morpholine bound in the apical position (Fig. 15A) with a significantly shortened Ni–N bond of 2.050(4) Å compared to the other morpholines (e.g. 2.090(4) and 2.101(4)); thus, this morpholine is the strongest donor and may facilitate the subsequent proposed mechanistic step, intramolecular ET to generate a Ni(I) center and a morpholine radical cation (See Fig. 18 for proposed mechanism). As such, both [NiBr₂(morpholine)]₀ and [NiBr₂(morpholine)]₁ show positive features for ET catalysis and we conclude that both are the ET acceptors.

[0252] With the acceptors and their respective molar absorptivities known, classical Förster theory is assessed, in which the theoretical energy transfer rate constant, kₑ, can be calculated as follows:

\[ \text{Eq. 1} \]

\[ k_{ET} = k_{D,A} \frac{R_0^6}{R^6} \]

\[ \text{Eq. 2} \]

\[ R_0^6 = 8.79 \times 10^{-20} \, \text{m}^6 \]

\[ \text{Eq. 3} \]

\[ J = \int_0^\infty F_D(\nu)v(\nu)J(\nu) \, d\nu \]

[0253] In these equations, R is the donor-acceptor distance, R₀ is the critical Förster distance defined in Eq. 2. kₑ is the radiative decay constant of the donor in absence of acceptor, K is the dipolar orientation factor, J is the refractive index of the solvent, \( \eta \) is the radiative decay constant of the donor, and J is the spectral overlap integral defined in Eq. 3 which involves FD, the area-normalized emission spectrum of the donor, and ϵ, the molar absorptivity of the acceptor as a function of frequency. In order to apply this equation to the reaction between excited state PC 1 and a Ni-amine complex, variables R and K needed to be eliminated, which are difficult to measure in solution with freely tumbling donors and acceptors.

[0254] Utilizing an approach similar to that first demonstrated in a study of a system involving intramolecular ET from a Re donor to a transition metal acceptor, an expression was derived to evaluate the ratio of quenching rate constants (e.g. \( k_{D,T,1}/k_{D,T,2} \)) as the donor, PC 1, was held constant but the acceptor was changed, from the Ni-morpholine quench-
ing mixture to the Ni-propylamine quenching mixture, according to the following equation:

\[
\frac{k_{\text{Ni,41}}}{k_{\text{Ni,42}}} = \frac{f_1}{f_2} \quad (\text{Eq. } 4)
\]

[0255] Using Equation 4, the ratio for PC 1 was calculated as \(\frac{k_{\text{Ni,41}}}{k_{\text{Ni,42}}} = 4.6\), which compares favorably with the experimental value of 6.5 obtained from the TA experiments described above. Thus, based on equations 1-3, it can be seen that selection of a PC with higher radiative rate constant \(k_{\text{r,1}}\) and higher overlap integral \(J\) will result in a higher \(\text{EnT}\) rate.

[0256] As such, in accordance with the disclosure, it was hypothesized that changing the donor PC from PC 1 to the organic phenoxazine PC 2 would impart improved performance in C—N cross coupling reactions given that PC 2 covers increased spectral range in its emission compared to PC 1, and has a radiative rate constant reported to be \(4 \times 10^3 \text{ s}^{-1}\), almost 2 orders of magnitude greater than that of PC 1 (e.g. \(7 \times 10^1 \text{ s}^{-1}\)). First, it was confirmed that PC 2 also reacts via \(\text{EnT}\) as opposed to \(\text{ET}\) through spectroscopic and electrochemical control experiments. To theoretically probe the hypothesis that PC 2 will increase the rate of \(\text{EnT}\), a second equation was derived to predict the ratio of quenching rate constants as the PC is changed but the Ni-morpholine mixture is kept constant as the acceptor:

\[
\frac{k_{\text{Ni,11}}}{k_{\text{Ni,12}}} = \frac{k_{\text{Ni,21}}}{k_{\text{Ni,22}}} \quad (\text{Eq. } 5)
\]

[0257] It was noted that the photophysics of PC 2 are more complicated than PC 1 in that both singlet and triplet excited states are populated. The triplet state is unlikely to react at a kinetically significant rate via a Förster type pathway given the extremely low phosphorescence radiative decay rates of organic PCs in solution, typically on the order of \(10^5-10^6 \text{ s}^{-1}\). Thus, the fluorescence spectrum and fluorescence radiative decay constant were used in conjunction with Eq. 5 to calculate the ratio of \(k_{\text{Ni,PC2}}/k_{\text{Ni,PC1}} = 20.4\), which is within a factor of 3 of the value of 12.7 determined experimentally from quenching studies. Agreement between these values suggests that the observed \(\text{EnT}\) occurs through primarily a Förster type pathway in the case of both PCs and with a much higher rate constant for PC 2 (2.9 \(\times\) 10^5 M^-1 s^-1), as compared to that for PC 1 (2.3 \(\times\) 10^5 M^-1 s^-1).

[0258] With these results in hand, the performance of PCs 1 and 2 in C—N cross coupling reactions were compared (FIG. 17). In order to directly compare the PCs, the same conditions were used for all reactions. In particular, blue 457 nm light irradiation was chosen since PC 2 cannot absorb green light. Further, an irradiation time of 15 hours was chosen to allow for direct comparison with previous work. Control reactions confirmed that no product is formed in the absence of PC under blue irradiation, and it was further noted that for PC 1 blue LED irradiation accesses the same absorption band as green irradiation, forming the same lowest MLCT excited state that was proposed for reactions via \(\text{EnT}\).

[0259] Under these conditions, the performance with PC 1 and morpholine is worsened (e.g. 43% conversion vs. 88% in FIG. 14A), and this can be attributed to a combination of factors, namely the lower catalyst loading and lower flux of the blue LED as compared with the green LED. Despite these conditions, PC 1 is effective for coupling of other secondary aliphatic amines with 4-bromobenzotrifluoride, highlighted by the use of unprotected piperazine (51%) and indoline (73%), nitrogen heterocycles that are among those most frequently used in medicinal chemistry.

[0260] On the other hand, PC 2 is more broadly effective, achieving higher yields than PC 1 with almost all substrates (FIG. 17). Notably, PC 2 is effective in coupling difficult aliphatic (e.g. propylamine, 50%) and aromatic primary amines such as 4-fluoroaniline (55%) and 3-aminopyridine (33%) with 4-bromobenzotrifluoride while PC 1 is ineffective, achieving only trace product formation. Notably, PC 2’s emission extends 100 nm further into the blue than PC 1, overlapping an absorption band of \([\text{NiBr}_2(\text{propylamine})_4]\) that PC 1 cannot access. Since the efficiency of \(\text{EnT}\) has been shown to depend on specific electronic transitions, in certain aspects, this blue-shifted band may facilitate \(\text{EnT}\) and likewise PC 2’s increased performance. Interestingly, use of 1 equivalent of KBr as an additive improved the performance of some amines such as propylamine and unprotected piperazine (14% and 26% increase, respectively).

[0261] With regards to the aryl halide coupling partner, PC 2 successfully promotes coupling of morpholine with aryl halides containing electronically-withdrawing groups (EWGs, e.g. 4-bromobenzotrifluoride, 92%) as well as electronically-donating groups (EDGs, e.g. 4-bromoanisole, 31%). Notably, a heterocyclic aryl bromide, 3-bromopyridine, could be coupled in good yield (58%). In addition, the difficult ortho-substituted aryl halide, 2-iodotoluene could be coupled with morpholine in moderate yield (27%), constituting the first example of C—N bond formation with this substrate pair in light-driven Ni catalysis.

[0262] Trends in reactivity for both PCs reflect secondary>primary>primary aromatic amines in terms of yield. Similarly, with regards to the aryl halide, those containing EWGs gave greater yields than those containing EDGs. Overall, the similarities in these trends across both PCs illustrate that a similar Ni-amine excited state intermediate forms and can be accessed either via \(\text{EnT}\) from a PC under visible light or via direct excitation under UV (e.g., 365 nm) irradiation.

[0263] The description above includes example systems, methods, techniques, and/or instruction sequences that embody techniques of the present disclosure. However, it is understood that the described disclosure may be practiced without these specific details.

REFERENCES


What is claimed is:

1. A dual catalytic method for forming an aryl carbon-nitrogen bond, the method comprising:
   contacting an aryl halide with an amine in the presence of a dual catalytic solution comprising a Ni(II) salt catalyst, a photocatalyst, and an optional base, thereby forming a reaction mixture; and exposing the reaction mixture to light under reaction conditions sufficient to form the aryl carbon-nitrogen bond.

2. The method of claim 1, wherein the reactions comprising hold the reaction mixture at between about room temperature and about 80°C for between about 1 hour and about 20 hours such that at least about 50% reaction yield is obtained.

3. The method of claim 2, wherein at least about 80% reaction yield is obtained.

4. The method of claim 1, wherein the aryl halide is selected from the group consisting of an aryl bromide, an aryl chloride, and an aryl iodide.

5. The method of claim 4, wherein the aryl halide is selected from the group consisting of bromobenzene; 4-bromobenzotrichloride; 3-bromobenzotrichloride; 1-bromo-3,5-dichlorobenzene; 1-bromo-3-(trifluoromethyl)benzene; 1-bromo-3-chlorobenzene; 4-bromobenzamide; 1-bromo-4-methylbenzene; 1-bromo-4-methoxybenzene; 1-bromo-3-methoxybenzene; 1-bromo-5-methoxybenzene; 4-bromobenzonitrile; methyl 4-bromobenzoate; 4-(4-bromophenyl)ethan-1-one; 3-bromopyridine; 5-bromopyrimidine; chloro benzene; 4-chlorobenzotrichloride; 3-chlorobenzotrichloride; 1-chloro-3,5-difluorobenzene; 4-chlorobenzonitrile; 1-chloro-3-(trifluoromethyl)benzene; 1-chloro-3-chlorobenzene; 4-chlorobenzamide; 1-chloro-4-methylbenzene; 1-chloro-4-methoxybenzene; 1-chloro-3-methoxybenzene; 1-chloro-3,5-dimethoxybenzene; 4-chlorobenzonitrile; methyl 4-chlorobenzoate; 1-(4-chlorophenyl)ethan-1-one; 3-chloropyridine; 5-chloropyrimidine; iodobenzene; 4-iodobenzotrichloride; 3-iodobenzotrichloride; 1-iodo-3,5-difluorobenzene; 4-iodobenzonitrile; 1-iodo-3-(trifluoromethyl) benzene; 1-iodo-3-chlorobenzene; 4-iodobenzamide; 1-iodo-4-methylbenzene; 1-iodo-4-methoxybenzene; 1-iodo-3-methoxybenzene; 4-iodobenzonitrile; methyl 4-iodobenzoate; 1-(4-bromophenyl)ethan-1-one; 3-iodopyridine; 5-iodopyrimidine; and 2-iodotoluene.

6. The method of claim 1, wherein the amine is a primary amine or a secondary amine.

7. The method of claim 6, wherein the amine is selected from the group consisting of propylamine, cyclohexylamine, phenethylamine, pyridine-3-amine, furan-2-ylmethylamine, aniline, 4-fluorobenzenamine, pyridoxamine, pyridine, piperidine, piperazine, tert-butyl piperazine-1-carboxylate, morpholine, 4-methylpiperidine, piperidine-4-ol, piperidine-4-carbonitrile, methyl piperidine-4-carboxylate, cyclohexanamine, 3-aminopyridine, propan-1-amine, hexan-1-amine, 2-phenylethyl-1-amine, and indoline.

8. The method of claim 1, wherein the amine is present in a molar excess of the aryl halide present in the reaction mixture.

9. The method of claim 8, wherein the amine is present in about 1.0 to about 5.5 molar excess of the aryl halide present in the reaction mixture.

10. The method of claim 1, wherein the Ni salt catalyst solution comprises a Ni(II) salt.

11. The method of claim 10, wherein the Ni salt catalyst solution comprises a Ni(II) salt selected from the group consisting of Ammonium nickel(II)

12. The method of claim 10, wherein the Ni(II) salt is selected from the group consisting of NiBr₂·glyme, NiCl₂·6H₂O, NiCl₂·glyme, and NiBr₂·3H₂O.

13. The method of claim 10, wherein the Ni(II) salt is NiBr₂·3H₂O.

14. The method of claim 1, wherein the dual catalyst solution further comprises a polar solvent, and the Ni(II) salt is dissolved in the polar solvent.

15. The method of claim 14, where the polar solvent is selected from the group consisting of N,N-dimethylacetamide, dimethyl sulfoxide, methanol, dimethylformamide, and acetonitrile.

16. The method of claim 15, wherein the polar solvent is N,N-dimethylacetamide.

17. The method of claim 1, wherein the photocatalyst is [Ru(bpy)$_3$]Cl₂ or an organic phenoxazine.

18. The method of claim 1, wherein the optional base is selected from the group consisting of quinuclidine, morpholine, N,N-disopropylethylamine, and triethylamine.

19. The method of claim 18, wherein the optional base is quinuclidine.

20. The method of claim 1, wherein the light is visible light or UV light.

21. The method of claim 19, wherein the light is at about 300 nm to about 1000 nm.

22. The method of claim 19, wherein the light is at about 365 nm, 457 nm, or 523 nm.

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