Photoinduced Nickel-Catalyzed Deaminative Cross-Electrophile Coupling

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Abstract: The construction of carbon-carbon bonds through cross-coupling between two electrophiles in the absence of excess metallic reducing agents is a desirable objective in chemistry. Here, we show that *N*-alkylpyridinium salts can be efficiently merged with aryl or alkyl halides in an intermolecular fashion, affording products in up to 90% yield at ambient temperature. These reactions harness the ability of *N*-alkylpyridinium salts to form electron donor–acceptor complexes with Hantzsch esters, enabling photoinduced single-electron transfer and fragmentation to afford alkyl radicals that are subsequently trapped by a Ni-based catalytic species to promote C(sp²)–C(sp³) and C(sp³)–C(sp³) bond formation. The operationally simple protocol is applicable to site-selective cross-coupling and tolerates diverse functional groups, including those that are sensitive towards metal reductants.

Transition metal-catalyzed C–C bond forming cross-coupling^[1] has revolutionized the way countless organic molecules are assembled, and is an indispensable tool in the modern synthetic chemist's arsenal.^[2] In particular, reductive cross-electrophile coupling has witnessed rapid development over the last two decades.^[3] These transformations obviate the need to pre-synthesize organometallic reagents, allowing the direct union of two relatively more stable electrophilic organohalides,^[4] pseudohalides^[5] or redox-active substrates^[6] to deliver the product.

Owing to the ubiquity, low cost and ease of accessibility associated with aliphatic primary amines, recent advances have taken advantage of these feedstock chemicals to prepare air- and moisture-stable Katritzky pyridinium salts^[7] as alkylating precursors in reductive coupling^[8] (Scheme 1A). However, examples of these deaminative processes are limited and often involve elevated temperatures^[8a–d], and superstoichiometric amounts of an expensive organic reagent (such as tetrakis(dimethylamino)ethylene)^[9], diboryl compound/base^[10] or a metal (such as Mn, Zn)^[8a–d] are required as terminal reducing agents. Consequently, problems such as reaction reproducibility that may arise from inconsistencies in the quality of commercially available metallic reductants^[4a,4c,11], as well as environmental^[12] and toxicity^[13] issues during metal waste disposal, especially when the reactions are performed at large scale are inevitable. Adding to these challenges is the incompatibility of certain reactive functional groups to metal reductive conditions (see below for further discussion). It merits mention that methods for deaminative alkylation^[8b,14] are scarce, and the majority of these C(sp³)–C(sp³) bond-forming processes rely on olefins as alkyl group precursors.

A. Catalytic reductive cross-electrophile coupling with *N*-alkylpyridinium salts

B. Catalyst-free photoinduced deaminative functionalizations via EDA complexes

C. This work: Photoinduced Ni-catalyzed deaminative arylation and alkylation

Scheme 1. Strategies for deaminative functionalizations with *N*-alkylpyridinium salts.

In addition to metal-catalyzed cross-coupling^[7d,14b,15] and photocatalyzed C–C bond formation^[14d–e,16], the redox-active nature of *N*-alkylpyridinium salts was recently exploited in efficient photoexcitation of electron-donor–acceptor (EDA) complexes generated from the pyridinium salt with bis-(catecholato)diboron (B₂cat₂)^[17], Hantzsch ester^[18] or triethylamine^[18] to deliver C–X (X = B, C, S) bonds under catalyst-free conditions (Scheme 1B). Inspired by these preceding observations, we speculated if we could leverage the photoactive EDA complex I formed between an *N*-alkylpyridinium salt 1 and a relatively inexpensive electron donor 3, which under visible light irradiation would furnish an unactivated alkyl radical species that could be captured in a nickel catalytic cycle (involving the reaction of organohalide 2) to deliver the final adduct 4 (Scheme 1C). Through this new catalytic platform, stoichiometric metals or expensive reducing agents are avoided, enabling facile entry to a broader spectrum of multifunctional products that are otherwise inaccessible using

previously established reductive regimes. Furthermore, the orthogonal activation of **1** and **2** means that difficult alkyl-alkyl cross-coupling reactions that are often susceptible to competitive homocoupling^[4b,19] side pathways can be achieved under mild base-free conditions at ambient temperature without an exorbitantly large excess of either reactant, thereby reducing waste generation. Herein, we describe the successful implementation of a photoinduced deaminative strategy to facilitate C(sp²)-C(sp³) and C(sp³)-C(sp³) cross-electrophile coupling with readily available organohalides.

Scheme 2. Reaction conditions identified for photoinduced Ni-catalyzed deaminative arylation and alkylation. Yields are for isolated and purified products.

A survey of various Ni-based salts, ligands, electron donors and solvents was carried out to merge pyridinium salt **1a** with aryl bromide **2a** under blue light irradiation at ambient temperature (see Supporting Information (SI) for details). In the event, we found that the desired deaminative arylation product **4a** was obtained in 85% isolated yield within 16 hours, using 10 mol % of NiBr₂·diglyme and 11 mol % of bipyridine **L1** in the presence of Hantzsch ester **3a** as reductant and DMA as solvent (Scheme 2A). Replacing the Ni complex, ligand or solvent with other alternatives led to lower yields, and no product was detected in the absence of the catalyst, **3a** or light (see SI for details).

Reaction conditions were separately evaluated for the more challenging union of pyridinium salt **1b** with alkyl iodide **2b** (see SI for details), and 20 mol % of the Ni-based complex derived from

NiBr₂·diglyme and **L2** was revealed to be optimal to furnish **4b** in 76% isolated yield (83% GC yield; Scheme 2B). Decreasing the catalyst loading to 10 mol % resulted in diminished efficiency (62% GC yield). Remarkably, performing the alkylation using a 1:1 ratio of **1b** and **2b** delivered **4b** with a respectable GC yield of 55% (see SI for details). This compares favorably with other reductive cross-electrophile protocols that employ superstoichiometric quantities of one cross-partner (2–3 equiv.) to suppress adventitious homocoupling^[8c], or entail strongly basic^[7d, 14b] and cryogenic conditions.^[5h] It is worth noting that the analogous alkylation with bromoalkane **2b'** in the presence of tetrabutylammonium iodide (TBAI) as additive could also generate **4b** in 47% yield.

With the established conditions in hand, we first examined the scope of deaminative arylation using a diverse array of pyridinium salts **1** (secondary and primary alkyl, cyclic and acyclic) as well as bromoarenes **2** (Scheme 3). In general, various electronically modified aryl bromides served as effective substrates in cross-coupling, affording products in up to 90% yield. These include molecules containing a nitrile (**4c**), an alcohol (**4z**), an aldehyde (**4d**), a ketone (**4e**, **4j**), an ester (**4i**, **4k**, **4o**, **4s**), an amide (**4h**, **4q**, **4v–4z**), a sulfone (**4f**) and a sulfoamide (**4g**, **4ac–4ad**). Synthesis of Lewis basic heterocycle **4r** as well as products derived from multifunctional bioactive compounds (**4l–4n**, **4aa–4ab**, **4ae–4af**) further underscores the exceptional functional group compatibility of the photoinduced catalytic reaction system.

Reactions with functionalized aliphatic iodides were subsequently investigated (Scheme 4). Deaminative alkylation was found to proceed efficiently to deliver **4ag–4at** in up to 73% yield. Commonly occurring functional groups such as a phthalimide (**4ag**, **4ai–4aj**, **4ap–4aq**), an amino ester (**4al**), an ether (**4ar**) as well as an electron-deficient enoate (**4ah**, **4as**) are tolerated. Chemoselective cross-coupling with the iodoalkane motif enables access to **4ak**, which bears a reactive aryl bromide handle that could be subjected to further transformations. Similar to the processes in Scheme 3, deaminative alkylation with substrates appended to complex molecules could be effected to generate the corresponding products **4am–4ao**. Of particular note, the formation of **4at** demonstrates a key advantage of the present photoinduced catalytic manifold, since alkyl-substituted aldehydes are found to be sensitive towards excess metallic reductants^[8b,8d] (see SI for details).

Secondary alkyl pyridinium salts

Primary alkyl pyridinium salts

Scheme 3. The scope of deaminative arylation. Yields are for isolated and purified products. [a] **4n** was obtained in 1:1 diastereomeric ratio. [b] The reaction was conducted with 20 mol% Ni complex, 25 mol% **L1** and 2 equiv. pyridinium salt. [c] The reactions were conducted with 12 mol% 4,4'-di-*t*-Bu-bpy, 1.5 equiv. pyridinium salt and 3 equiv. Et₃N.

Scheme 4. The scope of deaminative alkylation. Yields are for isolated and purified products. [a] The reaction was conducted with 20 mol% Ni complex and 25 mol% **L2**.

Formation of photoactive EDA complexes between *N*-alkylpyridinium salts **1** and **3a** have already been documented in previous studies.^[18] Further control experiments were performed to provide evidence for the formation of radical intermediates (from **1**) in our system (Scheme 5A).

Scheme 5. Mechanistic studies.

When excess TEMPO was added to the standard reaction mixture, cross-electrophile coupling was suppressed and the TEMPO-trapped product **5** was detected by GC analysis. On the other hand, deaminative arylation of enantiomerically enriched **1d** (prepared from commercially available (*R*)-2-amino-1-butanol) with **2a** led to complete erosion of stereochemistry in the final product **4au** (isolated in 58% yield as a racemic mixture), suggesting the formation of a radical species through a putative single-electron transfer (SET) pathway from **1d**.^[7d,8c]

To probe the supposed intermediacy of organonickel species, a separately-synthesized bipyridine-Ni(II) complex **Ni-1** (derived from oxidative addition of the corresponding Ni(0) complex with **2a**) was reacted with **1c** under the established photoinduced cross-coupling conditions, and **4o** was produced in 58% yield (Scheme 5B). As expected, <2% conv. to **4o** was observed in the absence of the electron donor **3a**. Furthermore, deaminative arylation of **1c** with **2a** was found to proceed smoothly in the presence of catalytic amounts of **Ni-1** and **L1**. These results substantiate the occurrence of an oxidative insertion process involving the organohalide **2** prior to alkylation with the pyridinium salt **1**.

Based on our studies as well as past observations, we propose a tentative reaction mechanism as shown in Scheme 6. An EDA complex **I**^[18] is likely formed between *N*-alkylpyridinium salt **1** and Hantzsch ester **3a**, which then undergoes photoexcitation and SET to give dihydropyridine radical **II** and **III**. Subsequent deaminative fragmentation of **III** yields triphenylpyridine **IV** and alkyl radical **V**, which presumably enters a Ni catalytic cycle by associating with Ni(II) complex **ii**, the oxidative insertion adduct derived from Ni(0) species **i** and organohalide **2** (either by direct oxidative addition or halogen atom abstraction/radical recombination^[3a]). The resulting alkylnickel species **iii** is poised to undergo reductive elimination to furnish **iv** with concomitant release of the desired product **4**. To turn over

the cycle, we surmised that **iv** is reduced back to **i** in the presence of **II** and **IV**, affording protonated pyridine by-products **VI** and **VII**. Overall, the chemoselective activation of **1** and **2** enables the photoinduced catalytic cross-coupling to occur under mild ambient conditions. Further investigations to shed light on the exact nature of the in situ-generated organonickel species are ongoing and will be disclosed in due course.

Scheme 6. Proposed mechanism for photoinduced Ni-catalyzed deaminative cross-coupling.

To showcase the value of our reaction system, dibromide **2c** was subjected to sequences of photoinduced deaminative cross-coupling using *N*-alkylpyridinium salts **1b** and **1e** (Scheme 7A). In the event, the alkyl bromide motif within **2c** selectively underwent alkylation with **1e** to give **6** in 55% yield. Following another alkylation with **1b**, **7** was obtained in 70% yield. In a second set of transformations, **2c** was selectively alkylated at the bromoarene site using **1e** to furnish **8** in 62% yield, which was further converted to **9** in 46% yield. Thus, access to both regioisomers **7** and **9** could be readily achieved without the need for tedious protection/deprotection strategies.

In stark contrast, treatment of **2c** to previously reported reductive deaminative conditions (with Mn or Zn)^[8b,8d] only led to complex product mixtures (Scheme 7B). These results highlight the unique capability of our photoinduced catalytic regime to effectively discriminate the multiple reactive sites of a substrate, which is crucial for attaining site-selective cross-coupling.^[20]

In conclusion, we have developed a new catalytic manifold for deaminative arylation and alkylation that operates under mild reaction conditions. Central to this approach is the facile generation of aliphatic radicals from photoexcitation of pyridinium salt EDA complexes, and their subsequent engagement with an appropriate organonickel species to promote carbon-carbon bond formation. The present method demonstrates excellent functional group tolerance and offers a reliable avenue for site-selective installation of carbogenic motifs through orthogonal halide activation. Further extension of the strategy to other related transformations is ongoing.

A. Site-selective alkylation by orthogonal halide activation

B. Chemoselectivity complications with previous deaminative alkylation conditions using metal reductants

Scheme 7. Site- and chemoselective incorporation of aliphatic groups by photoinduced catalytic cross-coupling.

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Keywords: Nickel • Photochemistry • Electron donor–acceptor complex • Cross-coupling • Pyridinium salt

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1. General information

All commercial reagents were used without additional purification, unless otherwise stated. Anhydrous solvents were purchased from commercial sources and transferred under an argon atmosphere. NMR spectra were recorded on Bruker 400 MHz and Bruker DPX 500 MHz spectrometer. Chemical shifts are reported in ppm from tetramethyl silane with the solvent resonance resonance from incomplete deuterium incorporation as the internal standard (CDCl_3 , 77.0 ppm). Integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on Bruker 400 MHz and Bruker DPX 500 MHz spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethyl silane with the solvent resonance as the internal standard (CDCl_3 , 77.00 ppm). High-resolution mass spectrometric data were obtained using Agilent 7200 QTOF and Bruker MicroTOF II. GC/MS analysis was performed on Shimadzu GC14B2020 gas chromatography coupled to a Shimadzu QP2010 mass selective detector. Column conditions reported in the experimental section below. Values for regioisomer ratio of products were determined by GC (GC QP2030) and ^1H NMR analysis.

Solvents

Solvents (acetonitrile, CH_2Cl_2 , diethyl ether, tetrahydrofuran) were purified under a positive pressure of dry nitrogen gas by a modified Innovative Technologies purification system. *N,N*-Dimethylacetamide (anhydrous), *N,N*-dimethylformamide (anhydrous), dimethyl sulfoxide (anhydrous), dimethoxyethane (anhydrous), and dioxane (anhydrous) were used as received. All purification procedures of products were carried out with reagent grade solvents.

Materials

Unless otherwise noted, commercial reagents were purchased from Aldrich, Alfa Aesar, or other commercial suppliers and were used as received. Anhydrous NiCl_2DME and anhydrous $\text{NiBr}_2(\text{diglyme})$ were purchased from Sigma Aldrich.

2. Optimization of the reaction conditions

General procedure for optimization of cross-coupling of pyridinium salts with aryl bromides

To an oven-dried 5 mL vial equipped with a magnetic stir bar was added aryl bromide (0.1 mmol), pyridinium salts (0.13 mmol), HE (0.2 mmol), and Ligand (0.11 mmol). The vial was transferred to a dried glovebox. $\text{NiBr}_2(\text{diglyme})$ (0.01 mmol) was added to the vial, and the mixture was then dissolved in 1.0 mL solvent. The vial was tightly sealed and removed from the glovebox. The reaction was allowed to stir under 40 W blue LED irradiation for 16 h with fans to maintain the temperature below 30 °C (the vial was placed about 3 mm from the LEDs, experimental setup). After that, the reaction was diluted with 6 mL EtOAc, and washed with saturated NaCl (2×3 mL), the organic was separated and concentrated under reduced pressure. The residue was subjected to flash silica gel column chromatography to afford the pure product.

Table S1 Optimization of cross-coupling of secondary pyridinium salts with aryl bromides

Entry	Deviation standard conditions	Yield (%) ^b
1	none	85
2	L2 instead of L1	81
3	L3 instead of L1	68
4	$\text{NiCl}_2 \cdot \text{DME}$ instead of $\text{NiBr}_2 \cdot \text{diglyme}$	77
5	DMF as solvent	20
6	DMSO as solvent	0
7	MeCN as solvent	trace
8	THF as solvent	12
9	TMEDA instead of 3a	0
10	No Ni, L1, 3a or light	0
11	0.5 mL DMA was used	78

L1 R= OMe
L3 R= ^tBu
L4 R= H

^aReaction Conditions: **2a** (0.1 mmol), **1a** (0.13 mmol), Ni cat. (10 mol%), **L1** (11 mol%), **3a** (0.2 mmol), in solvent (1.0 mL) at RT under 40 W blue LED irradiation for 16 h. Isolated yield.

Table S2 Optimization of cross-coupling of primary pyridinium salts with aryl bromides

^a

entry	L	additive	Yield (%) ^b
1	L1	none	0
2	L2	none	0
3	L3	none	0
4	L4	none	0
5	L5	none	0
6	L6	none	0
7	L3	TEA	51 ^c
8	L3	DABCO	6
9	L3	ⁱ Pr ₂ NEt	21
10	L3	K ₂ CO ₃	4
11	L3	K ₃ PO ₄	10

^aReaction Conditions: aryl bromide (0.1 mmol), py salt (0.15 mmol), Ni cat. (10 mol%), Ligand (12 mol%), **3a** (0.2 mmol), and additive (3.0 mmol) in DMA (0.8 mL) at RT under 40 W blue LED irradiation for 24 h. Determined by GC analysis with dodecane as an internal standard. Isolated yield.

General procedure for optimization of cross-coupling of pyridinium salts with alkyl iodides

To an oven-dried 5 mL vial equipped with a magnetic stir bar was added alkyl iodide (0.1 mmol), pyridinium salts (0.15 mmol), HE (0.3 mmol), Ligand (0.025 mmol). The vial was transferred to a N₂-filled glovebox. NiBr₂(diglyme) (0.02 mmol) was added to the vial, and the mixture was then dissolved in DMA (0.8 mL). The vial was tightly sealed and removed from the glovebox. The reaction was allowed to stir under 40 W blue LED irradiation for 16 h with fans to maintain the temperature below 30 °C (the vial was placed about 3 mm from the LEDs, see experimental setup). After that, the reaction was diluted with 1 mL EtOAc, and *n*-tridecane (12 mg) as an internal standard was added.

Table S3 Optimization of cross-coupling of pyridinium salts with alkyl iodides

Entry	Deviation standard conditions	Yield (%) ^b
1	none	83% (76%) ^c
2	L5 instead of L2	5%
3	L1, L3 or L4 instead of L2	trace
5	10 mol% Ni and 12.5 mol% L2	62%
6	15 mol% Ni and 18.5 mol% L2	71%
7	DMF as solvent	6%
8	NMP as solvent	trace
9	Alkyl bromide was used	ND
10	Alkyl bromide and NaI were used	trace
11	0.6 mL DMA was used	77%
12	1.0 eq py salt was used	55%
13	1.8 eq py salt was used	85%

^aReaction Conditions: alkyl iodide (0.1 mmol), py salt (0.15 mmol), Ni cat. (20 mol%), Ligand (25 mol%), **3a** (0.3 mmol), in DMA (0.8 mL) at RT under 40 W blue LED irradiation. ^bDetermined by GC analysis with *n*-tridecane as an internal standard. ^cIsolated yield.

Table S4 Optimization of Electron donors with aryl bromide

Entry	Deviation standard conditions	Yield (%) ^b
1	<i>none</i>	86
2	mNADH instead of 3a	51
3	Et ₃ N instead of 3a	49

^a Reaction Conditions: **aryl bromide** (0.1 mmol), **py salt** (0.13 mmol), **NiBr₂·diglyme** (10 mol%), **L1** (11 mol%), **3a** (0.2 mmol), in **DMA** (1.0 mL) at RT under 40 W blue LED irradiation for 16 h. ^b Isolated yield.

Table S5 Optimization of Electron donors with alkyl iodide

Entry	Deviation standard conditions	Yield (%) ^b
1	<i>none</i>	71
2	mNADH instead of 3a	45
3	Et ₃ N instead of 3a	trace

^a Reaction Conditions: **alkyl iodide** (0.1 mmol), **py salt** (0.15 mmol), **NiBr₂·diglyme** (20 mol%), **L2** (25 mol%), **3a** (0.3 mmol), in **DMA** (0.8 mL) at RT under 40 W blue LED irradiation for 24 h. ^b Isolated yield.

3. Preparation of starting materials

General Procedure 1 (GP1): Conversion of amines to pyridinium salts

According to the procedure described by Watson et al., a primary amine (1.2 eq.) was added to a suspension of 2,4,6-triphenylpyrylium tetrafluoroborate (1.0 eq.) and EtOH (1.0 M) in a long Schlenk tube. The mixture was stirred and heated at reflux in an oil bath at 85°C to 90°C for 4 h. The mixture was then allowed to cool to room temperature. If product precipitation occurred after cooling to room temperature, the solid was filtered, washed with EtOH (3 × 5 mL) and then (3 × 25 mL), and dried under high vacuum. If product precipitation did not occur during reflux, the solution was diluted with Et (2–3 × volume of EtOH used) and vigorously stirred for 1 h to induce trituration. The resulting solid pyridinium salt was filtered and washed with (3 × 25 mL). If the pyridinium salt failed to precipitate at this point, it was subjected to flash column chromatography, eluting with acetone/DCM.

$\text{ssudv}_{1,2,3,4}$

4. Synthesis and characterization of products

General Procedure 2 (GP2): Cross-coupling of pyridinium salts with aryl bromides

To an oven-dried 5 mL vial equipped with a magnetic stir bar was added aryl bromide (0.1 mmol), pyridinium salts (0.13 mmol), HE (0.2 mmol), and 4,4'-dimethoxy-2,2'-bipyridine (0.011 mmol). The vial was transferred to a N₂-filled glovebox. NiB(diglyme) (0.01 mmol) was added to the vial, and mixture was then dissolved in 1.0 mL DMA. The vial was tightly sealed and removed from the glovebox. The reaction was allowed to stir under 40 W blue LED irradiation for 16 h with fans to maintain the temperature below 30 °C (the vial was placed about 3 mm from the LEDs, see experimental setup). After setup, the reaction was diluted with 6 mL EtOAc, and washed with sat. aq. NaCl (2×3 mL), the organic was separated and concentrated under reduced pressure. The residue was subjected to flash silica gel column chromatography to afford the pure product.

General Procedure 3 (GP3): Cross-coupling of pyridinium salts with alkyl iodides

To an oven-dried 5 mL vial equipped with a magnetic stir bar was added alkyl iodide (0.1 mmol), pyridinium salts (0.15 mmol), HE (0.3 mmol), and di(2,4,6-trimethylpyridin-1-yl)pyridine (0.025 mmol). The vial was transferred to a fume hood. Ni(dppf) (0.02 mmol) was added to the vial, and the mixture was then dissolved in 0.8 mL DMA. The vial was tightly sealed and removed from the fume hood. The reaction was allowed to stir under 40 W blue LED irradiation for 24 h with fans to maintain the temperature at 30 °C (the vial was placed about 3 mm from the LEDs, see experimental setup). After setup, the reaction was diluted with 6 mL EtOAc, and washed with saturated NaCl (2 × 3 mL), the organic was separated and concentrated under reduced pressure. The residue was subjected to flash silica gel column chromatography to afford the pure product.

Photochemical Reaction Setup

A. before reaction. **B.** Pyridinium salt with aryl bromide after irradiation for 16 h. **C.** Pyridinium salt with alkyl iodide after irradiation for 24 h. **DEF.** experiment setup.

4.1 Characterization of products

tert-Butyl 4-(4-(methoxycarbonyl)phenyl)piperidine-1-carboxylate (**4a**)⁵:

Following the GP2, the title compound was prepared from methyl 4-iodobenzoate (21.5 mg) and Py S1 (75.1 mg). Purification using flash silica gel column chromatography (eluent: 15:1 hexane:EtOAc) gave the pure product as a colorless oil (27.1 mg, 85% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.26 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 4.25 (s, 2H), 3.89 (s, 3H), 2.80 (s, 2H), 2.70 (t, 1.1, 3.4 Hz, 1H), 1.82 (d, 12.8 Hz, 2H), 1.62 (qd, *J* = 12.7, 4.2 Hz, 2H), 1.47 (s, 9H). ¹³C NMR (126 MHz, CDCl₃): δ 171.9, 128.3, 126.8, 79.5, 52.0, 44.2, 42.8, 32.8, 28.4 ppm.

***tert*-Butyl 4-(4-cyanophenyl)piperidine-1-carboxylate (4c)⁵:**

Following the **GP2**, the title compound was prepared from bromobenzonitrile (18.1 mg) and Py S1 (75.1 mg). Purification using flash silica gel column chromatography (eluent: 15:1 hexane:EtOAc) gave the pure product as a colorless oil (10.3 mg, 69% yield).

¹H NMR (500 MHz, CDCl₃) J = 8.3 Hz, (d, 2H), 7.30 (d, 8.2 Hz, 2H), 4.25 (s, 2H), 2.79 (s, 2H), 2.70 (t, 12.2, 3.5 Hz, 1H), 1.80 (d, 13.0 Hz, 2H), 1.64-1.55 (m, 2H), 1.47 (s, 9H). **¹³C NMR** (126 MHz, CDCl₃) 43.9, 42.9, 32.7, 28.4 ppm.

***tert*-Butyl 4-(4-formylphenyl)piperidine-1-carboxylate (4d)⁵:**

Following the **GP2**, the title compound was prepared from bromobenzaldehyde (18.4 mg) and Py S1 (75.1 mg). Purification using flash silica gel column chromatography (eluent: 15:1 hexane:EtOAc) gave the pure product as a colorless oil (8.2 mg, 42% yield).

¹H NMR (500 MHz, CDCl₃) J = 8.2 Hz, (d, 2H), 7.36 (d, 8.1 Hz, 2H), 4.26 (s, 2H), 2.81 (s, 2H), 2.74 (t, 12.1, 3.5 Hz, 1H), 1.83 (d, 12.8 Hz, 2H), 1.68-1.61 (m, 2H), 1.48 (s, 9H). **¹³C NMR** (126 MHz, CDCl₃) 79.6, 44.1, 43.0, 32.8, 28.5 ppm.

***tert*-Butyl 4-(4-acetylphenyl)piperidine-1-carboxylate (4e)⁵:**

Following the **GP2**, the title compound was prepared from 4-bromophenyl)ethan-1-one (20.0 mg) and Py S1 (75.1 mg). Purification using flash silica gel column chromatography (eluent: 15:1 hexane:EtOAc) gave the pure product as a colorless oil (21.2 mg, 70% yield).

¹H NMR (500 MHz, CDCl₃) J = 8.3 Hz, (d, 2H), 7.28 (d, 8.3 Hz, 2H), 4.25 (s, 2H), 2.80 (s, 2H), 2.70 (t, 12.0, 3.5 Hz, 1H), 2.57 (s, 3H), 1.89 (m, 2H), 1.67-1.58 (m, 2H), 1.47 (s, 9H). **¹³C NMR** (126 MHz, CDCl₃) 154.8, 151.3, 135.5, 128.7, 127.0, 79.5, 44.2, 42.8, 32.8, 28.4, 26.5 ppm.

***tert*-Butyl 4-(4-(methylsulfonyl)phenyl)piperidine-1-carboxylate (4f)⁵:**

Following the **GP2**, the title compound was prepared from 4-(methylsulfonyl)benzene (235 mg) and Py S1 (75.1 mg). Purification using flash silica gel column chromatography (eluent: 5:1 hexane:EtOAc) gave the pure product as a colorless oil (25.8 mg, 76% yield).

¹H NMR (500 MHz, CDCl₃) J = 8.4 Hz, (d, 2H), 7.39 (d, 8.3 Hz, 2H), 4.26 (s, 2H), 3.03 (s, 3H), 2.80 (s, 2H), 2.78 (m, 1H), 1.82 (d, 13.0 Hz, 2H), 1.64-1.58 (m, 2H), 1.47 (s, 9H). **¹³C NMR** (126 MHz, CDCl₃) 44.0, 42.7, 32.8, 28.4 ppm.

***tert*-Butyl 4-(4-(morpholinosulfonyl)phenyl)piperidine-1-carboxylate (4g)⁶:**

Following the **GP2**, the title compound was prepared from 4-(4-bromophenyl) sulfonylmorpholine (31 mg) and Py S1 (75.1 mg). Purification using flash silica gel column chromatography (eluent: 5:1 hexane:EtOAc) gave the pure product as a colorless oil (36.9 mg, 90% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.36 (d, 8.3 Hz, 2H), 4.26 (s, 2H), 3.74–3.72 (m, 4H), 2.92–2.97 (m, 4H), 2.80 (s, 2H), 2.73 (t, 12.2, 3.5 Hz, 1H), 1.82 (d, 12.8 Hz, 2H), 1.62 (d, 12.7, 4.2 Hz, 2H), 1.47 (s, 9H). **¹³C NMR** (126 MHz, CDCl₃): δ 154.7, 151.3, 133.0, 128.2, 127.5, 126.0, 45.9, 44.1, 42.7, 32.8, 28.4 ppm.

tert-Butyl 4-(4-(dibenzylcarbamoyl)phenyl)piperidine-1-carboxylate (4h)⁷:

Following the **GP2**, the title compound was prepared from 4-(4-bromophenyl) dibenzylcarbamate (38.0 mg) and Py S1 (75.1 mg). Purification using flash silica gel column chromatography (eluent: 15:1 hexane:EtOAc) gave the pure product as a colorless oil (32.0 mg, 66% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.37–7.34 (m, 4H), 7.37–7.28 (m, 4H), 7.20 (d, 8.2 Hz, 2H), 7.15 (d, 5.4 Hz, 2H), 4.69 (s, 2H), 4.42 (s, 2H), 4.23 (s, 2H), 2.78 (s, 2H), 2.64 (t, 12.1, 3.4 Hz, 1H), 1.79 (d, 12.1 Hz, 2H), 1.63–1.60 (m, 2H), 1.47 (s, 9H). **¹³C NMR** (126 MHz, CDCl₃): δ 128.6, 128.4, 127.6, 127.5, 127.0, 126.9, 79.5, 51.6, 46.8, 44.3, 42.5, 32.9, 28.4 ppm.

tert-Butyl 4-(3-(methoxycarbonyl)phenyl)piperidine-1-carboxylate (4i)⁶:

Following the **GP2**, the title compound was prepared from methyl 3-bromobenzoate (21.5 mg) and Py S1 (75.1 mg). Purification using flash silica gel column chromatography (eluent: 15:1 hexane:EtOAc) gave the pure product as a colorless oil (25.2 mg, 79% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.88 (m, 2H), 7.43–7.35 (m, 2H), 4.26 (s, 2H), 3.91 (s, 3H), 2.80 (s, 2H), 2.70 (t, 12.1, 3.5 Hz, 1H), 1.83 (d, 12.9 Hz, 2H), 1.69–1.63 (m, 2H), 1.48 (s, 9H). **¹³C NMR** (126 MHz, CDCl₃): δ 128.0, 127.6, 79.5, 52.1, 44.3, 42.5, 33.0, 28.5 ppm.

tert-Butyl 4-(1-oxo-2,3-dihydro-1H-inden-5-yl)piperidine-1-carboxylate (4j):

Following the **GP2**, the title compound was prepared from 5-bromo-2,3-dihydro-1H-inden-1-one (21.1 mg) and Py S1 (75.1 mg). Purification using flash silica gel column chromatography (eluent: 15:1 hexane:EtOAc) gave the pure product as a colorless oil (26.2 mg, 83% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.9 (s, 1H), 7.29 (s, 1H), 7.20 (d, 7.9 Hz, 1H), 4.25 (s, 2H), 3.13–3.09 (m, 2H), 2.80 (s, 2H), 2.72 (t, 12.1, 3.4 Hz, 1H), 2.62–2.65 (m, 2H), 1.82 (d, 12.9 Hz, 2H), 1.68–1.60 (m, 2H), 1.47 (s, 9H). **¹³C NMR** (126 MHz, CDCl₃): δ 125.7 ppm.

25.7 ppm.

HRMS (ESI): Calcd. 338.1727 for C₂₅H₂₅NNaO₃⁺ (M+Na)⁺, found 338.1729.

tert-Butyl 4-(6-(methoxycarbonyl)naphthalen-2-yl)piperidine-1-carboxylate (4k):

Following the **GP2**, the title compound was prepared from methyl 6-bromo-2-naphthoate (26.5 mg) and Py S1 (75.1 mg). Purification using flash silica gel column chromatography (eluent: 15:1 hexane:EtOAc) gave the pure product as a colorless oil (28.5 mg, 76% yield).

¹H NMR (500 MHz, CDCl₃): δ 8.12 (m, 2H), 7.89 (d, *J* = 8.6, 1.7 Hz, 1H), 7.82 (d, *J* = 8.6 Hz, 1H), 7.66 (s, 1H), 7.41 (d, *J* = 8.5, 1.7 Hz, 1H), 4.29 (s, 2H), 3.97 (s, 3H), 2.86–2.80 (m, 3H), 1.91 (d, *J* = 12.8 Hz, 2H), 1.73 (dd, *J* = 24.9, 12.4, 3.8 Hz, 2H), 1.50 (s, 9H).

¹³C NMR (126 MHz, CDCl₃): δ 127.8, 126.9, 126.6, 124.7, 79.5, 52.2, 44.3, 42.9, 33.0, 28.5 ppm.

HRMS (ESI): Calcd. 392.1832 for C₂₀H₂₄NNaO₄⁺ (M+Na)⁺, found 392.1829.

tert-butyl 4-(4-((2-((4R,6R)-6-(2-(tert-butoxy)-2-oxoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)carbamoyl)phenyl)piperidine-1-carboxylate (4l):

Following the **GP2**, the title compound was prepared from tert-butyl 2(6-(2-(4-bromobenzamido)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (46 mg) and Py S1 (75.1 mg). Purification using flash silica gel column chromatography (eluent: 5:1 hexane:EtOAc) gave the pure product as a colorless oil (28.4 mg, 52% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.24 (d, *J* = 8.2 Hz, 2H), 7.08–7.06 (m, 1H), 4.31–4.25 (m, 3H), 4.14–4.07 (m, 1H), 3.72 (dd, *J* = 12.6, 11.0, 6.2 Hz, 1H), 3.41 (qd, *J* = 8.4, 4.2 Hz, 1H), 2.79 (s, 2H), 2.68 (t, *J* = 12.1, 3.4 Hz, 1H), 2.43 (dd, *J* = 15.2, 7.1 Hz, 1H), 2.30 (dd, *J* = 15.2, 6.0 Hz, 1H), 1.86–1.79 (m, 2H), 1.75–1.54 (m, 4H), 1.47 (s, 12H), 1.44 (s, 9H), 1.42 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 132.8, 127.0, 126.9, 98.8, 80.7, 79.5, 69.4, 64.6, 42.6, 42.5, 37.9, 36.0, 34.7, 32.9, 30.2, 29.7, 28.4, 28.1, 19.8 ppm.

HRMS (ESI): Calcd. 583.3354 for C₃₁H₄₈N₂NaO₇⁺ (M+Na)⁺, found 583.3348.

tert-Butyl 4-(4-((((8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)oxy)carbonyl)phenyl)piperidine-1-carboxylate (4m):

Following the **GP2**, the title compound was prepared from (8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl 4-bromobenzoate (455 mg) and Py S1 (75.1 mg). Purification using flash silica gel column chromatography (eluent: 1:1 hexane:EtOAc) gave the pure product as a colorless oil (40.2 mg, 72% yield).

¹H NMR (500 MHz, CDCl₃): δ 8.12 (m, 2H), 7.34–7.31 (dd, *J* = 8.3, 4.5 Hz, 3H), 6.96 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.93 (d, *J* = 2.5 Hz, 1H), 4.27 (s, 2H), 2.93 (dd, *J* = 12.7, 4.9 Hz, 2H), 2.82 (s, 1H), 2.74 (t, *J* = 12.1, 3.4 Hz, 1H), 2.50 (dd, *J* = 19.0, 8.6 Hz, 1H), 2.42–2.40 (m, 1H), 2.31 (td, *J* = 10.8, 4.0 Hz, 1H), 2.18–2.11 (m, 1H), 2.08–1.95 (m, 3H), 1.85 (d, *J* = 12.8 Hz, 2H), 1.70–1.57 (m, 4H), 1.56–1.44 (m, 4H), 1.49 (s, 9H), 0.91 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 132.8, 127.0, 126.9, 98.8, 80.7, 79.5, 69.4, 64.6, 42.6, 42.5, 37.9, 36.0, 34.7, 32.9, 30.2, 29.7, 28.4, 28.1, 19.8 ppm.

MHz, CDCl₃ δ 7.3, 130.4, 127.7, 127.0, 126.4, 121.6, 118.8, 79.5, 50.4, 47.9, 44.1, 44.0, 42.8, 38.0, 35.8, 32.8, 31.5, 29.4, 28.4, 26.3, 21.5, 13.8 ppm.

HRMS (ESI): Calcd. 580.3033 for [M+Na]⁺, found 580.3029.

tert-Butyl 4-(4-((((3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran-2-yl)oxy)carbonyl)phenyl)piperidine-1-carboxylate (4n):

Following the **GP2**, the title compound was prepared from **4b** (3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran-2-yl 4-bromobenzoate (73 mg) and Py S1 (75.1 mg). Purification using flash silica gel column chromatography (eluent: 5:1 hexane:EtOAc) gave the pure product as a colorless oil (76% yield, 1:1).

¹H NMR (500 MHz, CDCl₃) δ 7.37-7.24 (m, 20H), 7.16 (d, *J* = 8.3 Hz, 2H), 7.2, 2.1 Hz, 2H), 6.60 (d, *J* = 3.5 Hz, 1H), 4.99 (d, *J* = 10.9 Hz, 1H), 4.88 (d, *J* = 6.7 Hz, 1H), 4.86 (d, *J* = 7.1 Hz, 1H), 4.75 (d, *J* = 11.6 Hz, 1H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.62 (d, *J* = 12.1 Hz, 1H), 4.54 (d, *J* = 10.5 Hz, 1H), 4.48 (d, *J* = 12.1 Hz, 1H), 4.27 (s, 2H), 4.06 (t, *J* = 3 Hz, 1H), 3.99-3.96 (m, 1H), 3.84-3.77 (m, 3H), 3.65 (d, *J* = 10.9 Hz, 1H), 2.82 (t, *J* = 11.1 Hz, 1H), 2.73 (t, *J* = 12.0 Hz, 3.3 Hz, 1H), 1.83 (d, *J* = 12.7 Hz, 2H), 1.67-1.62 (m, 2H), 1.49 (s, 9H). **¹³C NMR** (126 MHz, CDCl₃) δ 128.5, 128.4, 128.1, 128.1, 128.0, 127.9, 127.7, 127.6, 127.0, 90.5, 81.8, 79.6, 79.0, 77.0, 75.7, 75.5, 73.6, 73.1, 73.0, 68.1, 44.0, 42.8, 32.8, 28.5 ppm.

HRMS (ESI): Calcd. 850.3926 for [M+Na]⁺, found 850.3916.

¹H NMR (500 MHz, CDCl₃) δ 7.37-7.25 (m, 15H), 7.21 (s, 5H), 7.17-7.15 (m, 2H), 5.88 (d, *J* = 7.8 Hz, 1H), 4.91 (d, *J* = 11.0 Hz, 1H), 4.85 (d, *J* = 3.7 Hz, 1H), 4.84-4.82 (m, 1H), 4.82 (d, *J* = 11.1 Hz, 1H), 4.77 (d, *J* = 11.1 Hz, 1H), 4.61 (d, *J* = 12.1 Hz, 1H), 4.56 (d, *J* = 10.8 Hz, 1H), 4.48 (d, *J* = 12.1 Hz, 1H), 4.27 (s, 2H), 3.84-3.73 (m, 5H), 3.67-3.65 (m, 1H), 2.82 (t, *J* = 10.6 Hz, 2H), 2.72 (t, *J* = 12.1 Hz, 3.4 Hz, 1H), 1.84 (d, *J* = 12.3 Hz, 2H), 1.68-1.63 (m, 2H), 1.49 (s, 9H). **¹³C NMR** (126 MHz, CDCl₃) δ 151.8, 138.4, 138.0, 137.9, 137.8, 130.4, 128.4, 128.3, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.4, 126.9, 94.6, 84.9, 80.9, 79.6, 77.3, 75.7, 75.6, 75.0, 73.5, 64.4, 42.8, 32.8, 29.7, 28.5 ppm.

Methyl 4-cyclohexylbenzoate (4o)⁵:

Following the **GP2**, the title compound was prepared from methyl benzoate (21.5 mg) and Py S2 (62 mg). Purification using flash silica gel column chromatography (eluent: 30:1 hexane:EtOAc) gave the pure product as a colorless oil (5.4 mg, 75% yield).

¹H NMR (500 MHz, CDCl₃) J = 8.3 Hz, (d, 2H); 7.29 (d, 8.2 Hz, 2H), 3.92 (s, 3H), 2.57 (ddd, J = 11.5, 7.3, 3.1 Hz, 1H), 1.906 (m, 4H), 1.801.77 (m, 1H), 1.491.37 (m, 4H), 1.33 1.25 (m, 1H). **¹³C NMR** (126 MHz, CDCl₃) δ 2, 153.4, 127.127.7, 126.8, 50, 44.7, 34.1, 26.7, 26.0 ppm.

1-Cyclohexyl-4-methoxybenzene (**4p**):

Following the **GP2**, the title compound was prepared from 4-methoxybromobenzene (19 mg) and Py S2 (95 mg, 2.0 eq) using 20 mol% Ni and 25 mol% L. Purification using flash silica gel column chromatography (eluent: 30:1 hexane:EtOAc) gave the pure product as a colorless oil (5 mg, 34% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.06 (m, 2H), 6.96.77 (m, 2H), 3.79 (s, 3H), 2.50 2.38 (m, 1H), 1.84 (t, 5.6, 2.5 Hz, 4H), 1.7768 (m, 1H), 1.451.34 (m, 4H), 1.29 1.24 (m, 1H). **¹³C NMR** (101 MHz, CDCl₃) δ 26.9, 26.0 ppm.

HRMS (EI) for: C₁₁H₁₈O [M]⁺: calcd 190.1352 found 190.1357.

(4-Cyclohexylphenyl)(pyrrolidin-1-yl)methanone (**4q**):

Following the **GP2**, the title compound was prepared from 4-bromophenyl(methyl)pyrrolidin-1-yl)methanone (25.5 mg) and Py S2 (62 mg). Purification using flash silica gel column chromatography (eluent: 2:1 hexane:EtOAc) gave the pure product as a colorless oil (18.8 mg, 73% yield).

¹H NMR (500 MHz, CDCl₃) J = 8.1 Hz, (d, 2H); 7.21 (d, 8.1 Hz, 2H), 3.62 (s, 2H), 3.45 (s, 2H), 2.52.48 (m, 1H), 1.931.83 (m, 8H), 1.74 (t, 12.6 Hz, 1H), 1.44.33 (m, 4H), 1.28 1.23 (m, 1H). **¹³C NMR** (126 MHz, CDCl₃) δ 126.6, 49.6, 46.2, 44.4, 34.2, 26.8, 26.24.26 ppm.

HRMS (EI): Calcd. 256.1696 for C₁₄H₂₂NO⁺ [M-H]⁺, found 256.1700.

4-Cyclohexylpicolinonitrile (**4r**):

Following the **GP2**, the title compound was prepared from 4-picolonitrile (18.3 mg) and Py S2 (62 mg). Purification using flash silica gel column chromatography (eluent: 5:1 hexane:EtOAc) gave the pure product as a colorless oil (13.8 mg, 74% yield).

¹H NMR (500 MHz, CDCl₃) J = 5.1 Hz, (t, 2H); 7.54 (d, 1.7 Hz, 1H), 7.34 (d, 5.2, 1.7 Hz, 1H), 2.56 (t, 9.9, 6.4 Hz, 1H), 1.89 (d, 7.2, 4.6 Hz, 4H), 1.8274 (m, 1H), 1.46 1.34 (m, 4H), 1.29.23 (m, 1H). **¹³C NMR** (101 MHz, CDCl₃) δ 150.9, 133.9, 127.3, 125.6, 117.5, 43.5, 33.3, 26.3, 25.6.

HRMS (EI) for: C₁₁H₁₄N₂ [M]⁺: calcd 186.1151 found 186.1158.

tert-Butyl 3-(4-(methoxycarbonyl)phenyl)pyrrolidine-1-carboxylate (4s)⁵:

Following the **GP2**, the title compound was prepared from methyl 4-iodobenzoate (21.5 mg) and Py S4 (72 mg). Purification using flash silica gel column chromatography (eluent: 10:1 hexane:EtOAc) gave the pure product as a colorless oil (15.6 mg, 51% yield). rotator isomer (1:1)

¹H NMR (500 MHz, CDCl₃) δ: 7.30 (d, 8.2 Hz, 2H), 3.90 (s, 3H), 3.87–3.76 (m, 1H), 3.63–3.54 (m, 1H), 3.43–3.27 (m, 3H), 2.22–2.26 (m, 1H), 1.99 (dt, *J* = 19.3, 9.6 Hz, 1H), 1.47 (s, 9H). **¹³C NMR** (126 MHz, CDCl₃) δ: 146.8, 129.9, 128.5, 127.1, 79.4, 52.2, 52.1, 51.5, 45.8, 45.5, 44.2, 43.3, 33.2, 32.3, 28.5 ppm.

1-(4-Phenylbutan-2-yl)-4-(trifluoromethyl)benzene (4t)⁸:

Following the **GP2**, the title compound was prepared from bromo-4-(trifluoromethyl)benzene (22.5 mg) and Py S3 (69 mg). Purification using flash silica gel column chromatography (eluent: 10:1 hexane:EtOAc) gave the pure product as a colorless oil (24.5 mg, 88% yield).

¹H NMR (500 MHz, CDCl₃) δ: 7.32 (d, 8.1 Hz, 2H), 7.29 (d, 10.4, 4.6 Hz, 2H), 7.19 (t, 7.4 Hz, 1H), 7.14 (d, 7.1 Hz, 2H), 2.82–2.77 (m, 1H), 2.58–2.48 (m, 2H), 2.00–1.90 (m, 2H), 1.30 (d, 7.0 Hz, 3H). **¹⁹F NMR** (471 MHz, CDCl₃) δ: 62.24 (s). **¹³C NMR** (126 MHz, CDCl₃) δ: 144.3 (d, *J* = 7.3, 3.6 Hz), 124.4 (d, *J* = 271.9 Hz), 39.7, 39.4, 33.8, 22.2 ppm.

2-Chloro-1-fluoro-4-(4-phenylbutan-2-yl)benzene (4u):

Following the **GP2**, the title compound was prepared from 4-bromo-2-chloro-1-fluorobenzene (210 mg) and Py S3 (69 mg). Purification using flash silica gel column chromatography (eluent: 10:1 hexane:EtOAc) gave the pure product as a colorless oil (18.9 mg, 72% yield).

¹H NMR (500 MHz, CDCl₃) δ: 7.26 (m, 2H), 7.22 (d, 7.1, 2.0 Hz, 1H), 7.19 (t, 7.3 Hz, 1H), 7.13 (d, 7.0 Hz, 2H), 7.09–7.03 (m, 1H), 2.73–2.66 (m, 1H), 2.52–2.47 (m, 2H), 1.91–1.86 (m, 2H), 1.26 (d, 7.0 Hz, 3H). **¹⁹F NMR** (471 MHz, CDCl₃) δ: -119.78 (s). **¹³C NMR** (126 MHz, CDCl₃) δ: 144.3 (d, *J* = 246.3 Hz), 142.0, 129.0, 128.3, 128.3, 126.6 (d, 6.8 Hz), 125.8, 116.4 (d, 20.7 Hz), 39.8, 38.7, 33.7, 22.4 ppm. **HRMS** (EI): Calcd. 262.0919 for C₁₆H₁₅ClF [M]⁺, found 262.0916.

Morpholino(4-(4-phenylbutan-2-yl)phenyl)methanone (4v):

Following the **GP2**, the title compound was prepared from (4-bromophenyl) (morpholino)methanone (27 mg) and Py S3 (69 mg). Purification using flash silica gel column chromatography (eluent: hexane:EtOAc) gave the pure product as a colorless oil (27.8mg, 86% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.27 (d, J = 8.1 Hz, 2H), 7.24 (m, 4H), 7.17 (t, J = 7.4 Hz, 1H), 7.12 (d, J = 7.1 Hz, 2H), 3.73 (m, 8H), 2.72 (m, 1H), 2.52 (m, 2H), 1.97–1.86 (m, 2H), 1.27 (t, J = 6.9 Hz, 3H). **¹³C NMR** (126 MHz, CDCl₃): δ 142.1, 132.9, 128.3, 127.3, 127.2, 125.7, 66.9, 48.3, 42.6, 39.7, 39.4, 33.8, 22.3 ppm. **HRMS** (EI): Calcd. 322.1802 for C₁₈H₂₄NO₂⁺ [M-H]⁺, found 322.1806.

(4-(Heptan-2-yl)phenyl)(morpholino)methanone (4w):

Following the **GP2**, the title compound was prepared from (4-bromophenyl) (morpholino)methanone (27 mg) and Py S10 (74 mg). Purification using flash silica gel column chromatography (eluent: hexane:EtOAc) gave the pure product as a colorless oil (23.7mg, 82% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.20 (d, J = 8.1 Hz, 2H), 3.69 (m, 8H), 2.69 (t, J = 7.0 Hz, 1H), 1.56 (m, 2H), 1.26 (m, 9H), 0.83 (t, J = 6.8 Hz, 3H). **¹³C NMR** (126 MHz, CDCl₃): δ 39.8, 38.2, 31.8, 27.2, 22.5, 22.1, 14.0 ppm.

HRMS (EI): Calcd. 288.1958 for C₁₆H₂₆NO₂⁺ [M-H]⁺, found 288.1952.

(4-(3-Methylbutan-2-yl)phenyl)(morpholino)methanone (4x):

Following the **GP2**, the title compound was prepared from (4-bromophenyl) (morpholino)methanone (27 mg) and Py S5 (61 mg). Purification using flash silica gel column chromatography (eluent: hexane:EtOAc) gave the pure product as a colorless oil (19.6mg, 75% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.18 (d, J = 8.1 Hz, 2H), 3.69 (m, 8H), 2.44 (t, J = 7.1 Hz, 1H), 1.79 (m, 1H), 1.22 (t, J = 7.0 Hz, 3H), 0.92 (d, J = 6.7 Hz, 3H), 0.74 (t, J = 6.7 Hz, 3H). **¹³C NMR** (126 MHz, CDCl₃): δ 127.8, 127.0, 66.9, 48.2, 46.7, 42.6, 34.3, 21.1, 20.1, 18.6 ppm.

HRMS (EI): Calcd. 260.1645 for C₁₆H₂₂NO₂⁺ [M-H]⁺, found 260.1644.

(4-(1-Cyclohexylethyl)phenyl)(morpholino)methanone (4y):

Following the **GP2**, the title compound was prepared from (4-bromophenyl)(morpholino)methanone (27 mg) and Py S6 (66 mg). Purification using flash silica gel column chromatography (eluent: hexane:EtOAc) gave the pure product as a colorless oil (23.5mg, 78% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.16 (d, 8.1 Hz, 2H), 3.63-3.52 (m, 8H), 2.46 (d, 7.2 Hz, 1H), 1.85 (d, 12.7 Hz, 1H), 1.72 (d, 10.4, 2.9 Hz, 1H), 1.61-1.59 (m, 2H), 1.42-1.35 (m, 2H), 1.21 (d, 7.0 Hz, 3H), 1.23-1.16 (m, 1H), 1.13-1.03 (m, 2H), 0.92 (dd, 24.2, 12.5, 3.5 Hz, 1H), 0.83 (m, 1H). **¹³C NMR** (126 MHz, CDCl₃): δ 26.4, 26.4, 18.6 ppm.

HRMS (EI): Calcd. 300.1958 for C₁₆H₂₄NO₂⁺ [M-H]⁺, found 300.1962.

(4-(1-Hydroxybutan-2-yl)phenyl)(morpholino)methanone (**4z**):

Following the GP2, the title compound was prepared from (4-bromophenyl)(morpholino)methanone (27 mg) and Py S8 (61 mg). Purification using flash silica gel column chromatography (eluent: hexane:EtOAc) gave the pure product as a colorless oil (10.5mg, 40% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.25 (d, 8.4 Hz, 2H), 3.73-3.49 (m, 10H), 2.72 (dd, 9.3, 7.7, 5.6 Hz, 1H), 1.82-1.73 (m, 1H), 1.62-1.53 (m, 2H), 0.83 (t, 7.4 Hz, 3H). **¹³C NMR** (126 MHz, CDCl₃): δ 66.9, 50.3, 48.2, 42.6, 24.9, 11.9 ppm.

HRMS (ESI): Calcd. 286.1414 for C₁₇H₂₁NNaO₃⁺ (M+Na)⁺, found 286.1419.

(4-(1-(2,6-Dimethylphenoxy)propan-2-yl)phenyl)(morpholino)methanone (**4aa**):

Following the **GP2**, the title compound was prepared from (4-bromophenyl)(morpholino)methanone (27 mg) and Py S11 (72 mg). Purification using flash silica gel column chromatography (eluent: hexane:EtOAc) gave the pure product as a colorless oil (21.6mg, 61% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.16 (d, 8.1 Hz, 2H), 6.88 (d, 8.1, 6.8 Hz, 1H), 3.85-3.79 (m, 2H), 3.73-3.48 (m, 8H), 3.33-3.25 (m, 1H), 2.14 (s, 6H), 1.46 (d, 7.0 Hz, 3H). **¹³C NMR** (126 MHz, CDCl₃): δ 127.3, 123.8, 66.9, 48.3, 42.6, 18.0, 16.1 ppm.

HRMS (EI): Calcd. 353.1985 for C₂₂H₂₇NO₃⁺ [M]⁺, found 353.1988.

2-(4-(Morpholine-4-carbonyl)phenyl)butyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate (4ab):

Following the **GP2**, the title compound was prepared from 4-bromophenyl(morpholino)methanone (27 mg) and Py S13 (105 mg) using 12-BuPy as ligand and 3.0 equiv TEA as additive, Purification using flash silica gel column chromatography (eluent: hexane:EtOAc) gave the pure product as a colorless oil (33.8mg, 56% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.1 Hz, 2H), 6.89 (d, *J* = 2.5 Hz, 1H), 6.85 (d, *J* = 9.0 Hz, 1H), 6.65 (dd, *J* = 9.0, 2.5 Hz, 1H), 4.22 (m, 2H), 3.80 (s, 3H), 3.78 (m, 8H), 3.57 (s, 2H), 2.77 (dq, *J* = 9.3, 6.4 Hz, 1H), 2.26 (s, 3H), 1.67 (dd, *J* = 14.5, 10.1, 6.6 Hz, 1H), 1.57 (m, 1H), 0.75 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 139.2, 135.8, 133.8, 133.6, 132.1, 129.1, 128.5, 128.0, 127.3, 127.0, 68.3, 66.8, 55.7, 48.2, 46.5, 42.6, 30.3, 25.1, 13.2, 11.7 ppm.

HRMS (ESI): Calcd. 625.2076 for [C₂₈H₂₅ClN₂O₆ + (M+Na)⁺, found 625.2073.

4-((4-phenethylphenyl)sulfonyl)morpholine (4ac):

Following the **GP2**, the title compound was prepared from 4-bromophenylsulfonyl morpholine (30.6 mg) and Py S14 (75 mg, 1.5 equiv) using 12-BuPy as ligand and 3.0 equiv TEA as additive, Purification using flash silica gel column chromatography (eluent: 3:1 hexane:EtOAc) gave the pure product as a colorless oil (16.9mg, 51% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.62 (m, 2H), 7.37 (m, 4H), 7.28 (m, 1H), 7.19 (m, 2H), 3.86 (m, 4H), 3.12 (m, 8H).

¹³C NMR (101 MHz, CDCl₃): δ 165.9, 159.1, 158.9, 158.7, 158.5, 158.3, 158.1, 157.9, 157.7, 157.5, 157.3, 157.1, 156.9, 156.7, 156.5, 156.3, 156.1, 155.9, 155.7, 155.5, 155.3, 155.1, 154.9, 154.7, 154.5, 154.3, 154.1, 153.9, 153.7, 153.5, 153.3, 153.1, 152.9, 152.7, 152.5, 152.3, 152.1, 151.9, 151.7, 151.5, 151.3, 151.1, 150.9, 150.7, 150.5, 150.3, 150.1, 149.9, 149.7, 149.5, 149.3, 149.1, 148.9, 148.7, 148.5, 148.3, 148.1, 147.9, 147.7, 147.5, 147.3, 147.1, 146.9, 146.7, 146.5, 146.3, 146.1, 145.9, 145.7, 145.5, 145.3, 145.1, 144.9, 144.7, 144.5, 144.3, 144.1, 143.9, 143.7, 143.5, 143.3, 143.1, 142.9, 142.7, 142.5, 142.3, 142.1, 141.9, 141.7, 141.5, 141.3, 141.1, 140.9, 140.7, 140.5, 140.3, 140.1, 139.9, 139.7, 139.5, 139.3, 139.1, 138.9, 138.7, 138.5, 138.3, 138.1, 137.9, 137.7, 137.5, 137.3, 137.1, 136.9, 136.7, 136.5, 136.3, 136.1, 135.9, 135.7, 135.5, 135.3, 135.1, 134.9, 134.7, 134.5, 134.3, 134.1, 133.9, 133.7, 133.5, 133.3, 133.1, 132.9, 132.7, 132.5, 132.3, 132.1, 131.9, 131.7, 131.5, 131.3, 131.1, 130.9, 130.7, 130.5, 130.3, 130.1, 129.9, 129.7, 129.5, 129.3, 129.1, 128.9, 128.7, 128.5, 128.3, 128.1, 127.9, 127.7, 127.5, 127.3, 127.1, 126.9, 126.7, 126.5, 126.3, 126.1, 125.9, 125.7, 125.5, 125.3, 125.1, 124.9, 124.7, 124.5, 124.3, 124.1, 123.9, 123.7, 123.5, 123.3, 123.1, 122.9, 122.7, 122.5, 122.3, 122.1, 121.9, 121.7, 121.5, 121.3, 121.1, 120.9, 120.7, 120.5, 120.3, 120.1, 119.9, 119.7, 119.5, 119.3, 119.1, 118.9, 118.7, 118.5, 118.3, 118.1, 117.9, 117.7, 117.5, 117.3, 117.1, 116.9, 116.7, 116.5, 116.3, 116.1, 115.9, 115.7, 115.5, 115.3, 115.1, 114.9, 114.7, 114.5, 114.3, 114.1, 113.9, 113.7, 113.5, 113.3, 113.1, 112.9, 112.7, 112.5, 112.3, 112.1, 111.9, 111.7, 111.5, 111.3, 111.1, 110.9, 110.7, 110.5, 110.3, 110.1, 109.9, 109.7, 109.5, 109.3, 109.1, 108.9, 108.7, 108.5, 108.3, 108.1, 107.9, 107.7, 107.5, 107.3, 107.1, 106.9, 106.7, 106.5, 106.3, 106.1, 105.9, 105.7, 105.5, 105.3, 105.1, 104.9, 104.7, 104.5, 104.3, 104.1, 103.9, 103.7, 103.5, 103.3, 103.1, 102.9, 102.7, 102.5, 102.3, 102.1, 101.9, 101.7, 101.5, 101.3, 101.1, 100.9, 100.7, 100.5, 100.3, 100.1, 99.9, 99.7, 99.5, 99.3, 99.1, 98.9, 98.7, 98.5, 98.3, 98.1, 97.9, 97.7, 97.5, 97.3, 97.1, 96.9, 96.7, 96.5, 96.3, 96.1, 95.9, 95.7, 95.5, 95.3, 95.1, 94.9, 94.7, 94.5, 94.3, 94.1, 93.9, 93.7, 93.5, 93.3, 93.1, 92.9, 92.7, 92.5, 92.3, 92.1, 91.9, 91.7, 91.5, 91.3, 91.1, 90.9, 90.7, 90.5, 90.3, 90.1, 89.9, 89.7, 89.5, 89.3, 89.1, 88.9, 88.7, 88.5, 88.3, 88.1, 87.9, 87.7, 87.5, 87.3, 87.1, 86.9, 86.7, 86.5, 86.3, 86.1, 85.9, 85.7, 85.5, 85.3, 85.1, 84.9, 84.7, 84.5, 84.3, 84.1, 83.9, 83.7, 83.5, 83.3, 83.1, 82.9, 82.7, 82.5, 82.3, 82.1, 81.9, 81.7, 81.5, 81.3, 81.1, 80.9, 80.7, 80.5, 80.3, 80.1, 79.9, 79.7, 79.5, 79.3, 79.1, 78.9, 78.7, 78.5, 78.3, 78.1, 77.9, 77.7, 77.5, 77.3, 77.1, 76.9, 76.7, 76.5, 76.3, 76.1, 75.9, 75.7, 75.5, 75.3, 75.1, 74.9, 74.7, 74.5, 74.3, 74.1, 73.9, 73.7, 73.5, 73.3, 73.1, 72.9, 72.7, 72.5, 72.3, 72.1, 71.9, 71.7, 71.5, 71.3, 71.1, 70.9, 70.7, 70.5, 70.3, 70.1, 69.9, 69.7, 69.5, 69.3, 69.1, 68.9, 68.7, 68.5, 68.3, 68.1, 67.9, 67.7, 67.5, 67.3, 67.1, 66.9, 66.7, 66.5, 66.3, 66.1, 65.9, 65.7, 65.5, 65.3, 65.1, 64.9, 64.7, 64.5, 64.3, 64.1, 63.9, 63.7, 63.5, 63.3, 63.1, 62.9, 62.7, 62.5, 62.3, 62.1, 61.9, 61.7, 61.5, 61.3, 61.1, 60.9, 60.7, 60.5, 60.3, 60.1, 59.9, 59.7, 59.5, 59.3, 59.1, 58.9, 58.7, 58.5, 58.3, 58.1, 57.9, 57.7, 57.5, 57.3, 57.1, 56.9, 56.7, 56.5, 56.3, 56.1, 55.9, 55.7, 55.5, 55.3, 55.1, 54.9, 54.7, 54.5, 54.3, 54.1, 53.9, 53.7, 53.5, 53.3, 53.1, 52.9, 52.7, 52.5, 52.3, 52.1, 51.9, 51.7, 51.5, 51.3, 51.1, 50.9, 50.7, 50.5, 50.3, 50.1, 49.9, 49.7, 49.5, 49.3, 49.1, 48.9, 48.7, 48.5, 48.3, 48.1, 47.9, 47.7, 47.5, 47.3, 47.1, 46.9, 46.7, 46.5, 46.3, 46.1, 45.9, 45.7, 45.5, 45.3, 45.1, 44.9, 44.7, 44.5, 44.3, 44.1, 43.9, 43.7, 43.5, 43.3, 43.1, 42.9, 42.7, 42.5, 42.3, 42.1, 41.9, 41.7, 41.5, 41.3, 41.1, 40.9, 40.7, 40.5, 40.3, 40.1, 39.9, 39.7, 39.5, 39.3, 39.1, 38.9, 38.7, 38.5, 38.3, 38.1, 37.9, 37.7, 37.5, 37.3, 37.1, 36.9, 36.7, 36.5, 36.3, 36.1, 35.9, 35.7, 35.5, 35.3, 35.1, 34.9, 34.7, 34.5, 34.3, 34.1, 33.9, 33.7, 33.5, 33.3, 33.1, 32.9, 32.7, 32.5, 32.3, 32.1, 31.9, 31.7, 31.5, 31.3, 31.1, 30.9, 30.7, 30.5, 30.3, 30.1, 29.9, 29.7, 29.5, 29.3, 29.1, 28.9, 28.7, 28.5, 28.3, 28.1, 27.9, 27.7, 27.5, 27.3, 27.1, 26.9, 26.7, 26.5, 26.3, 26.1, 25.9, 25.7, 25.5, 25.3, 25.1, 24.9, 24.7, 24.5, 24.3, 24.1, 23.9, 23.7, 23.5, 23.3, 23.1, 22.9, 22.7, 22.5, 22.3, 22.1, 21.9, 21.7, 21.5, 21.3, 21.1, 20.9, 20.7, 20.5, 20.3, 20.1, 19.9, 19.7, 19.5, 19.3, 19.1, 18.9, 18.7, 18.5, 18.3, 18.1, 17.9, 17.7, 17.5, 17.3, 17.1, 16.9, 16.7, 16.5, 16.3, 16.1, 15.9, 15.7, 15.5, 15.3, 15.1, 14.9, 14.7, 14.5, 14.3, 14.1, 13.9, 13.7, 13.5, 13.3, 13.1, 12.9, 12.7, 12.5, 12.3, 12.1, 11.9, 11.7, 11.5, 11.3, 11.1, 10.9, 10.7, 10.5, 10.3, 10.1, 9.9, 9.7, 9.5, 9.3, 9.1, 8.9, 8.7, 8.5, 8.3, 8.1, 7.9, 7.7, 7.5, 7.3, 7.1, 6.9, 6.7, 6.5, 6.3, 6.1, 5.9, 5.7, 5.5, 5.3, 5.1, 4.9, 4.7, 4.5, 4.3, 4.1, 3.9, 3.7, 3.5, 3.3, 3.1, 2.9, 2.7, 2.5, 2.3, 2.1, 1.9, 1.7, 1.5, 1.3, 1.1, 0.9, 0.7, 0.5, 0.3, 0.1, 0.0.

HRMS (EI) for: C₁₈H₂₁NO₃S [M]: calcd 331.1237, found 331.1235.

4-((4-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)phenyl)sulfonyl)morpholine (4ad):

Following the **GP2**, the title compound was prepared from 4-bromophenylsulfonyl morpholine (30.6 mg) and Py S17 (81 mg, 1.5 equiv) using 12-BuPy as ligand and 3.0 equiv TEA as additive, Purification using flash silica gel column chromatography (eluent: 3:1 hexane:EtOAc) gave the pure product as a white solid (18.0mg, 50% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.30 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 7.9 Hz, 1H), 6.62 (d, *J* = 1.7 Hz, 1H), 6.55 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.93 (s, 2H), 3.89 (m,

4H), 3.07 2.91 (m, 6H), 2.90 2.80 (m, 2H). **¹³C NMR** (101 MHz, CDCl₃) 145.9, 134.4, 132.6, 129.2, 127.9, 121.2, 108.8, 108.2, 100.9, 66.1, 46.0 ppm. **HRMS** (EI) for: C₁₉H₂₁NO₅S [M]⁺: calcd 375.1135 found 375.1133.

tert-butyl 2-(((4R,6R)-2,2-dimethyl-6-(4-(morpholine-4-carbonyl)phenethyl)-1,3-dioxan-4-yl)acetate (4ae):

Following the **GP2**, the title compound was prepared from bromo(4-phenyl) (morpholino)methanone (27 mg) and Py S15 (98 mg, 1.5 equiv) using 12 mol% t-Bu-bpy as ligand and 3.0 equiv TEA as additive, Purification using flash silica gel column chromatography (eluent: 1 hexane:EtOAc) gave the pure product as a colorless oil (127 mg, 58% yield).

¹H NMR (500 MHz, CDCl₃) 7.14 (m, 2H), 4.19 (dd, J = 11.5, 6.6, 2.5 Hz, 1H), 3.87 3.72 (m, 9H), 2.82 2.60 (m, 2H), 2.41 (dd, J = 15.1, 6.9 Hz, 1H), 2.27 (dt, J = 15.1, 4.8 Hz, 1H), 1.85 (m, 1H), 1.72 1.61 (m, 1H), 1.51 (dt, J = 12.8, 2.5 Hz, 1H), 1.42 (s, 9H), 1.40 (s, 3H), 1.37 (s, 3H), 1.16 (d, J = 16.2 Hz, 1H). **¹³C NMR** (126 MHz, CDCl₃) 170.6, 170.3, 144.2, 132.7, 128.7, 127.3, 98.7, 80.6, 67.5, 66.9, 66.2, 42.7, 37.6, 36.5, 30.9, 30.1, 28.1, 19.8.

HRMS (ESI) for: C₂₅H₃₇NO₆Na [M+Na]⁺: calcd 470.2513 found 470.2509

(4-(((1S,2R,5S)-6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)methyl)phenyl) (morpholino)methanone (4af):

Following the **GP2**, the title compound was prepared from bromo(4-phenyl) (morpholino)methanone (27 mg) and Py S16 (80 mg, 1.5 equiv) using 12 mol% di-bpy as ligand and 3.0 equiv TEA as additive, Purification using flash silica gel column chromatography (eluent: 1 hexane:EtOAc) gave the pure product as a colorless oil (137 mg, 42% yield).

¹H NMR (500 MHz, CDCl₃) 9.30 (s, 8H), 2.72 2.63 (m, 2H), 2.30 (ddt, J = 12.3, 8.3, 4.1 Hz, 2H), 1.89 1.78 (m, 2H), 1.88 1.79 (m, 3H), 1.57 1.47 (m, 1H), 1.19 (s, 3H), 1.13 (s, 3H), 0.84 (d, J = 9.6 Hz, 1H).

¹³C NMR (126 MHz, CDCl₃) 38.7, 33.7, 29.7, 28.2, 26.4, 23.5 ppm.

HRMS (EI) for: C₂₁H₂₉NO₂ [M]⁺: calcd 327.2193 found 327.2204

2-(5-Methyl-7-phenylheptyl)isoindoline-1,3-dione (4b):

Following the **GP3**, the title compound was prepared from 2-(4-iodobutyl)isoindoline 1,3-dione (33 mg) and Py S3 (79 mg). Purification using flash silica gel column chromatography (eluent 15:1 hexane:EtOAc) gave the pure product as a colorless oil (254 mg, 7% yield).

¹H NMR (500 MHz, CDCl₃): $J = 5.4, 3.0$ Hz, 2H), 7.73 (d, $J = 5.4, 3.0$ Hz, 2H), 7.30–7.27 (m, 2H), 7.27–7.17 (m, 3H), 3.70 (t, $J = 7.3$ Hz, 2H), 2.66 (dd, $J = 15.5, 10.6, 5.1$ Hz, 1H), 2.57 (dd, $J = 13.7, 9.9, 6.1$ Hz, 1H), 1.72–1.60 (m, 3H), 1.47–1.21 (m, 6H), 0.94 (d, $J = 6.3$ Hz, 3H).

¹³C NMR (126 MHz, CDCl₃): 128.2, 125.5, 123.1, 38.8, 38.0, 36.4, 33.4, 32.3, 28.9, 24.2, 19.5 ppm.

HRMS (EI): Calcd. 335.1880 for C₂₅H₂₅NO₂⁺ [M]⁺, found 335.1879.

tert-Butyl 4-(4-(1,3-dioxoisindolin-2-yl)butyl)piperidine-1-carboxylate (4ag)⁹:

Following the **GP3**, the title compound was prepared from 2-(4-iodobutyl)isoindoline 1,3-dione (33 mg) and Py S1 (87 mg). Purification using flash silica gel column chromatography (eluent 4:1 hexane:EtOAc) gave the pure product as a colorless oil (178 mg, 46% yield).

¹H NMR (500 MHz, CDCl₃): $J = 5.4, 3.0$ Hz, 2H), 7.71 (d, $J = 5.4, 3.0$ Hz, 2H), 4.04 (d, $J = 11.0$ Hz, 2H), 3.67 (t, $J = 7.2$ Hz, 2H), 2.64 (t, $J = 12.3$ Hz, 2H), 1.69–1.63 (m, 4H), 1.44 (s, 9H), 1.33–1.32 (m, 3H), 1.30–1.25 (m, 2H), 1.05 (dd, $J = 16.3, 12.6, 4.3$ Hz, 2H).

¹³C NMR (126 MHz, CDCl₃): 35.9, 32.1, 28.8, 28.5, 23.9 ppm.

tert-Butyl 4-(4-((2-oxo-2H-chromen-7-yl)oxy)butyl)piperidine-1-carboxylate (4ah):

Following the **GP3**, the title compound was prepared from 7-(4-iodobutoxy)2H-chromen-2-one (33.4 mg) and Py S1 (87 mg). Purification using flash silica gel column chromatography (eluent 4:1 hexane:EtOAc) gave the pure product as a colorless oil (189 mg, 47% yield).

¹H NMR (500 MHz, CDCl₃): $J = 9.4$ Hz, 1H), 7.35 (d, $J = 8.6$ Hz, 1H), 6.82 (d, $J = 8.6, 2.4$ Hz, 1H), 6.78 (d, $J = 2.4$ Hz, 1H), 6.23 (d, $J = 9.5$ Hz, 1H), 4.06 (s, 2H), 4.00 (t, 4 Hz, 2H), 2.66 (s, 2H), 1.82–1.77 (m, 2H), 1.65 (t, $J = 12.7$ Hz, 2H), 1.52–1.47 (m, 2H), 1.44 (s, 9H), 1.41–1.37 (m, 1H), 1.32–1.27 (m, 2H), 1.08 (dd, $J = 16.4, 12.6, 4.3$ Hz, 2H).

¹³C NMR (126 MHz, CDCl₃): 101.3, 79.2, 68.5, 44.0, 36.2, 35.9, 32.1, 29.1, 28.4, 23.0 ppm.

HRMS (ESI): Calcd. 424.2093 for C₂₈H₃₄NO₅⁺ (M+Na)⁺, found 424.2094.

2-(4-Cyclopentylbutyl)isoindoline-1,3-dione (4ai):

Following the **GP3**, the title compound was prepared from 2-(4-iodobutyl)isoindoline 1,3-dione (33 mg) and Py S7 (70 mg). Purification using flash silica gel column chromatography (eluent: 15:1 hexane:EtOAc) gave the pure product as a colorless oil (14.4mg, 53% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.70 (d, J = 5.4, 3.0 Hz, 2H), 7.41 (d, J = 5.4, 3.0 Hz, 2H), 3.68–3.65 (m, 2H), 1.73–1.69 (m, 3H), 1.68–1.65 (m, 2H), 1.60–1.53 (m, 2H), 1.52–1.44 (m, 2H), 1.37–1.30 (m, 4H), 1.06–1.02 (m, 2H). **¹³C NMR** (126 MHz, CDCl₃): δ 133.8, 132.2, 123.1, 40.0, 38.1, 35.6, 32.6, 28.8, 26.0, 25.1 ppm.

HRMS (EI): Calcd. 271.1567 for C₁₁H₁₅NO₂⁺ [M]⁺, found 271.1562.

2-(4-Cycloheptylbutyl)isoindoline-1,3-dione (4aj):

Following the **GP3**, the title compound was prepared from 2-(4-iodobutyl)isoindoline 1,3-dione (33 mg) and Py S9 (74 mg). Purification using flash silica gel column chromatography (eluent: 15:1 hexane:EtOAc) gave the pure product as a colorless oil (21.9mg, 73% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.70 (d, J = 5.4, 3.0 Hz, 2H), 7.41 (d, J = 5.5, 3.0 Hz, 2H), 3.68–3.65 (m, 2H), 1.67–1.51 (m, 9H), 1.47–1.42 (m, 2H), 1.41–1.27 (m, 2H), 1.34–1.29 (m, 2H), 1.25–1.20 (m, 2H), 1.16–1.09 (m, 2H). **¹³C NMR** (126 MHz, CDCl₃): δ 133.8, 132.2, 123.1, 39.1, 38.1, 37.7, 34.5, 32.6, 28.8, 26.4, 24.7 ppm.

HRMS (EI): Calcd. 299.1880 for C₁₅H₂₅NO₂⁺ [M]⁺, found 299.1871.

(4-(4-Bromophenoxy)butyl)cycloheptane (4ak):

Following the **GP3**, the title compound was prepared from 4-bromo-4-(4-iodobutoxy) benzene (355 mg) and Py S9 (74 mg). Purification using flash silica gel column chromatography (eluent: 10:1 hexane:EtOAc) gave the pure product as a colorless oil (23.4mg, 72% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.70 (d, J = 9.0 Hz, 2H), 6.77 (d, J = 9.0 Hz, 2H), 3.91 (t, J = 6.5 Hz, 2H), 1.77–1.71 (m, 2H), 1.70–1.61 (m, 6H), 1.51–1.37 (m, 7H), 1.29–1.24 (m, 2H), 1.16 (dtd, J = 12.0, 9.5, 2.5 Hz, 2H). **¹³C NMR** (126 MHz, CDCl₃): δ 68.3, 39.2, 37.9, 34.6, 29.5, 28.5, 23.8 ppm.

HRMS (EI): Calcd. 324.1083 for C₁₅H₂₅BrO⁺ [M]⁺, found 324.1075.

3-Cycloheptylpropyl benzoylprolinate (4al):

Following the **GP3**, the title compound was prepared from 3-benzoylpropyl benzoylprolinate (38.7mg) and Py S9 (74 mg). Purification using flash silica gel column chromatography (eluent: 5:1 hexane:EtOAc) gave the pure product as a colorless oil (24.7mg, 69% yield).

¹H NMR (500 MHz, CDCl₃): 7.54 (m, 2H), 7.43-7.36 (m, 4.5H), 4.66 (dd, 8.4, 5.1 Hz, 2H), 4.32 (t, 6.4 Hz, 0.3H), 4.18-4.09 (m, 2H), 3.93-3.93 (m, 0.3H), 3.91-3.86 (m, 0.3H), 3.79 (t, 6.9 Hz, 0.6H), 3.63 (dt, 10.5, 7.0 Hz, 1H), 3.53-3.49 (m, 1H), 2.35-2.28 (m, 1H), 2.24-2.17 (m, 0.3H), 2.05-1.97 (m, 3H), 1.90-1.82 (m, 1.3H), 1.69-1.52 (m, 10H), 1.48-1.35 (m, 8H), 1.29-1.25 (m, 3H), 1.18-1.12 (m, 3H). **¹³C NMR** (126 MHz, CDCl₃): 127.2, 126.5, 65.7, 65.6, 61.5, 59.2, 44.9, 38.8, 38.8, 34.4, 34.4, 34.1, 33.9, 31.5, 29.4, 28.4, 26.5, 26.4, 26.3, 25.3, 22.6 ppm. **HRMS** (EI): Calcd. 357.2298 for [C₂₁H₂₇NO₃]⁺ [M]⁺, found 357.2297.

3-Cycloheptylpropyl 2-(11-oxo-6,11-dihydrodibenzo[b,e]oxepin-2-yl)acetate (4am):

Following the **GP3**, the title compound was prepared from 3-cycloheptylpropyl 2-(11-oxo-6,11-dihydrodibenzo[b,e]oxepin-2-yl)acetate (43.6 mg) and Py S9 (74 mg). Purification using flash silica gel column chromatography (eluent: hexane:EtOAc) gave the pure product as a colorless oil (20.7 mg, 51% yield).

¹H NMR (500 MHz, CDCl₃): 7.89 (d, 7.7, 1.1 Hz, 1H), 7.55 (td, *J* = 7.5, 1.3 Hz, 1H), 7.47 (td, 7.6, 1.2 Hz, 1H), 7.43 (dd, 8.4, 2.4 Hz, 1H), 7.36 (dd, *J* = 7.0, 0.5 Hz, 1H), 7.02 (d, 8.4 Hz, 1H), 5.18 (s, 2H), 4.07 (t, 6.8 Hz, 2H), 3.63 (s, 2H), 1.63-1.53 (m, 7H), 1.46-1.36 (m, 6H), 1.21 (dd, 12.1, 8.9, 6.2 Hz, 2H), 1.13 (dd, 16.5, 9.9, 4.9 Hz, 2H). **¹³C NMR** (126 MHz, CDCl₃): 135.5, 132.7, 132.4, 129.5, 129.2, 128.0, 127.8, 125.1, 121.0, 73.6, 65.4, 40.3, 38.8, 34.1, 28.4, 26.4, 26.4 ppm. **HRMS** (EI): Calcd. 406.2144 for [C₂₆H₃₀O₄]⁺ [M]⁺, found 406.2136.

3-Cycloheptylpropyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate (4an):

Following the **GP3**, the title compound was prepared from 3-cycloheptylpropyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate (52.6 mg) and Py S9 (74 mg). Purification using flash silica gel column chromatography (eluent: 15:1 hexane:EtOAc) gave the pure product as a colorless oil (25.8 mg, 52% yield).

¹H NMR (500 MHz, CDCl₃): 7.65 (m, 2H), 7.47-7.46 (m, 2H), 6.97 (d, 2.5 Hz, 1H), 6.87 (d, 9.0 Hz, 1H), 6.66 (d, 9.0, 2.5 Hz, 1H), 4.07 (t, 6.7 Hz, 2H), 3.83 (s, 3H), 3.65 (s, 2H), 2.39 (s, 3H), 1.53 (m, 9H), 1.49-1.41 (m, 2H), 1.40-1.34 (m, 2H), 1.21-1.16 (m, 2H), 1.13-1.07 (m, 2H). **¹³C NMR** (126 MHz, CDCl₃): 139.2, 135.8, 133.9, 131.1, 130.8, 130.7, 129.1, 114.9, 112.8, 111.6, 101.3, 65.5, 55.6, 38.8, 34.4, 34.1, 30.4, 28.4, 26.5, 26.4, 13.3 ppm. **HRMS** (ESI): Calcd. 518.2069 for [C₂₉H₃₄ClN₂O₄]⁺ (M+Na)⁺, found 518.2060.

2-(6-(2,6-Dimethylphenoxy)-5-methylhexyl)isoindoline-1,3-dione (4ao):

Following the **GP3**, the title compound was prepared from 2-(4-iodobutyl)isoindoline 1,3-dione (33 mg) and Py S11 (84 mg). Purification using flash silica gel column chromatography (eluent: 15:1 hexane:EtOAc) gave the pure product as a colorless oil (12.1 mg, 33% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.70 (d, *J* = 5.4, 3.0 Hz, 2H), 7.70 (d, *J* = 5.5, 3.0 Hz, 2H), 6.98 (d, *J* = 7.5 Hz, 2H), 6.96 (d, *J* = 7.3 Hz, 2H), 3.71 (t, *J* = 7.3 Hz, 2H), 3.58 (t, *J* = 8.8, 5.8 Hz, 1H), 3.52 (dd, *J* = 8.8, 6.4 Hz, 1H), 2.24 (s, 6H), 1.94 (t, *J* = 9, 6.4 Hz, 1H), 1.78 (m, 1H), 1.67 (m, 1H), 1.61 (m, 1H), 1.54 (m, 1H), 1.46 (m, 1H), 1.43 (m, 1H), 1.37 (m, 1H), 1.34 (m, 1H), 1.27 (m, 1H), 1.07 (d, *J* = 6.7 Hz, 3H). **¹³C NMR** (126 MHz, CDCl₃): δ 128.8, 123.6, 123.1, 77.0, 38.0, 34.2, 33.0, 28.9, 24.4, 17.0, 16.2 ppm.

HRMS (EI): Calcd. 365.1985 for C₂₇H₃₇NO₃⁺ [M]⁺, found 365.1982.

2-(5-Methyldecyl)isoindoline-1,3-dione (4ap):

Following the **GP3**, the title compound was prepared from 2-(4-iodobutyl)isoindoline 1,3-dione (33 mg) and Py S10 (74 mg). Purification using flash silica gel column chromatography (eluent: 15:1 hexane:EtOAc) gave the pure product as a colorless oil (18.7 mg, 62% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.70 (d, *J* = 5.3, 3.2 Hz, 2H), 7.70 (d, *J* = 5.4, 3.1 Hz, 2H), 3.67 (t, *J* = 7.4 Hz, 2H), 1.67 (m, 2H), 1.61 (m, 2H), 1.37 (m, 11H), 1.15 (m, 2H), 0.86 (t, *J* = 7.1 Hz, 3H), 0.82 (t, *J* = 6.4 Hz, 3H). **¹³C NMR** (126 MHz, CDCl₃): δ 123.1, 38.1, 36.9, 36.5, 32.6, 32.2, 28.9, 26.7, 24.3, 22.7, 19.6, 14.1 ppm.

HRMS (EI): Calcd. 301.2036 for C₂₇H₃₇NO₂⁺ [M]⁺, found 301.2040.

2-(5,6-Dimethylheptyl)isoindoline-1,3-dione (4aq):

Following the **GP3**, the title compound was prepared from 2-(4-iodobutyl)isoindoline 1,3-dione (33 mg) and Py S5 (70 mg). Purification using flash silica gel column chromatography (eluent: 15:1 hexane:EtOAc) gave the pure product as a colorless oil (13.7 mg, 50% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.70 (d, *J* = 5.4, 3.0 Hz, 2H), 7.70 (d, *J* = 5.4, 3.0 Hz, 2H), 3.67 (t, *J* = 7.4 Hz, 2H), 1.69 (m, 2H), 1.63 (m, 2H), 1.56 (m, 1H), 1.48 (m, 1H), 1.37 (m, 5H), 1.15 (m, 1H), 0.83 (t, *J* = 6.8 Hz, 3H), 0.78 (t, *J* = 4.3 Hz, 3H), 0.77 (t, *J* = 4.2 Hz, 3H). **¹³C NMR** (126 MHz, CDCl₃): δ 18.0, 15.3 ppm.

HRMS (EI): Calcd. 273.1723 for C₂₃H₃₃NO₂⁺ [M]⁺, found 273.1724.

(6-(Benzyloxy)-3-methylhexyl)benzene (4ar):

Following the **GP3**, the title compound was prepared from (3-methyl-7-phenyloxy)propan-1-ol (27.6 mg) and Py S3 (79 mg). Purification using flash silica gel column chromatography (eluent: 10:1 hexane:EtOAc) gave the pure product as a colorless oil (20.1 mg, 71% yield).

¹H NMR (500 MHz, CDCl₃): 7.34 (m, 4H), 7.30–7.26 (m, 3H), 7.19–7.16 (m, 3H), 4.51 (s, 2H), 4.36 (t, *J* = 6.7 Hz, 2H), 2.65 (ddd, *J* = 15.4, 10.5, 5.1 Hz, 1H), 2.57 (ddd, *J* = 13.7, 9.8, 6.1 Hz, 1H), 1.70–1.60 (m, 3H), 1.51–1.40 (m, 3H), 1.29–1.20 (m, 1H), 0.95 (d, *J* = 6.3 Hz, 3H). **¹³C NMR** (126 MHz, CDCl₃): 127.6, 127.5, 127.2, 127.1, 125.5, 72.9, 70.8, 38.8, 33.4, 33.2, 32.3, 27.2, 19.5 ppm.

HRMS (EI): Calcd. 282.1978 for C₁₆H₂₀O⁺ [M]⁺, found 282.1986.

7-((5-Methyl-7-phenylheptyl)oxy)-2H-chromen-2-one (4as):

Following the **GP3**, the title compound was prepared from methyl 7-(4-iodobutoxy)-2H-chromen-2-one (4.4 mg) and Py S3 (79 mg). Purification using flash silica gel column chromatography (eluent: 5:1 hexane:EtOAc) gave the pure product as a colorless oil (2.1 mg, 63% yield).

¹H NMR (500 MHz, CDCl₃): 7.35 (d, *J* = 9.5 Hz, 1H), 7.29–7.26 (m, 2H), 7.19–7.16 (m, 3H), 6.83 (d, *J* = 8.6, 2.4 Hz, 1H), 6.80–6.77 (d, *J* = 2.3 Hz, 1H), 6.24 (d, *J* = 9.5 Hz, 1H), 4.01 (t, *J* = 6.5 Hz, 2H), 2.66 (ddd, *J* = 13.6, 10.5, 5.2 Hz, 1H), 2.57 (ddd, *J* = 13.7, 10.0, 6.1 Hz, 1H), 1.82–1.76 (m, 2H), 1.68–1.62 (m, 1H), 1.51–1.40 (m, 5H), 1.28–1.21 (m, 1H), 0.96 (d, *J* = 6.4 Hz, 3H). **¹³C NMR** (126 MHz, CDCl₃): 143.4, 142.9, 128.7, 128.3, 128.2, 125.56, 125.56, 113.0, 112.9, 112.3, 101.3, 68.6, 38.8, 36.5, 33.4, 32.4, 29.2, 23.3, 19.5 ppm.

HRMS (EI): Calcd. 350.1876 for C₂₆H₃₀O⁺ [M]⁺, found 350.1873.

6-Methyl-8-phenyloctanal (4at):

Following the **GP3**, the title compound was prepared from pentanal (21 mg) and Py S3 (79 mg) using 20 mol% Ni and 25 mol% L2. Purification using flash silica gel column chromatography (eluent: 15:1 hexane:EtOAc) gave the pure product as a colorless oil (9.8 mg, 45% yield).

¹H NMR (500 MHz, CDCl₃): 7.31–7.26 (m, 2H), 7.21–7.13 (m, 3H), 2.65 (ddd, *J* = 13.5, 10.5, 5.2 Hz, 1H), 2.55 (ddd, *J* = 13.6, 9.9, 6.1 Hz, 1H), 2.42–2.40 (td, *J* = 7.4, 1.9 Hz, 1H), 1.65–1.55 (m, 4H), 1.44 (td, *J* = 9.8, 5.7, 2.0 Hz, 2H), 1.32–1.28 (m, 3H), 1.22–1.13 (m, 1H), 0.93 (d, *J* = 6.4 Hz, 3H). **¹³C NMR** (126 MHz, CDCl₃): 128.3, 125.6, 43.9, 38.8, 36.6, 33.4, 32.3, 26.5, 22.4, 19.5 ppm.

HRMS (ESI) for: C₁₅H₂₂O⁺ [M+Na]⁺: calcd 241.1563, found 241.1566.

Methyl 4-(1-(2-(11-oxo-6,11-dihydrodibenzo[*b,e*]oxepin-2-yl)acetoxy)butan-2-yl)benzoate (4au):

Following the **GP2**, the title compound was prepared from methyl 4-bromobenzoate (21.5 mg) and Py S12 (108 mg, 1.5 equiv.). Purification using flash silica gel column chromatography (eluent: 15:1 hexane:EtOAc) gave the pure product as a colorless oil (26.5mg, 58% yield).

¹H NMR (500 MHz, CDCl₃): δ 7.94 (d, *J* = 2.3 Hz, 1H), 7.94-7.92 (m, 2H), 7.89 (d, *J* = 1.1 Hz, 1H), 7.56 (td, *J* = 7.5, 1.3 Hz, 1H), 7.47 (td, *J* = 7.6, 1.2 Hz, 1H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.25 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 1H), 5.18 (s, 2H), 4.26-4.25 (m, 2H), 3.88 (s, 3H), 3.54 (s, 2H), 2.89 (dd, *J* = 9.3, 6.8 Hz, 1H), 1.79-1.71 (m, 1H), 1.63 (s, 1H), 0.79 (t, *J* = 7.4 Hz, 3H). **¹³C NMR** (126 MHz, CDCl₃): δ 190.7, 171.1, 166.9, 160.4, 147.1, 140.4, 136.2, 135.6, 132.9, 132.1, 129.5, 129.2, 128.6, 127.9, 127.8, 127.6, 125.0, 121.0, 73.6, 68.1, 52.0, 46.6, 40.2, 25.2, 11.7 ppm. **HRMS** (ESI): Calcd. 481.1622 for C₂₆H₂₅NaO₆⁺ (M+Na)⁺, found 481.1618.

4.2 Site-selective alkylation by orthogonal halide activation

(3-(4-Bromophenyl)propyl)cycloheptane (6):

Following the **GP3**, the title compound was prepared from bromo-4-(3-bromopropyl)benzene (28 mg) and **1e** (98 mg, 2.0 equiv.) using 20 mol% Ni(diglyme), 25 mol% **12**, 3.0 equiv **3a** and 2.0 equiv. TBAI as additive. Purification using flash silica gel column chromatography (eluent: 10:1 hexane:EtOAc) gave the pure product as a colorless oil (16.2 mg, 55% yield).

¹H NMR (500 MHz, CDCl₃) δ: 7.26 (d, *J* = 8.3 Hz, 2H), 7.05 (d, *J* = 8.3 Hz, 2H), 2.52 (m, 2H), 1.69 (m, 8H), 1.54 (m, 5H), 1.25 (m, 2H), 1.11 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ: 142.7, 140.5, 128.4, 128.3, 128.2, 126.1, 25.6, 40.0, 32.3, 39.1, 38.0, 35.9, 34.6, 29.4, 28.5, 26.5 ppm.

HRMS (EI): Calcd. 294.0978 for C₁₂H₁₅Br⁺ [M]⁺, found 294.0983.

(3-(4-(4-Phenylbutan-2-yl)phenyl)propyl)cycloheptane (7):

Following the **GP2**, the title compound was prepared from **6** (29.4 mg) and **1b** (105 mg, 2.0 equiv.) using 20 mol% Ni(diglyme), 25 mol% **11** and 3.0 equiv **3a**. Purification using flash silica gel column chromatography (eluent: hexane:EtOAc) gave the pure product as a colorless oil (24.4 mg, 70% yield).

¹H NMR (500 MHz, CDCl₃) δ: 7.26 (m, 2H), 7.19 (m, 7H), 2.75 (m, 1H), 2.59 (m, 4H), 2.49 (m, 4H), 1.98 (m, 2H), 1.73 (m, 2H), 1.66 (m, 6H), 1.51 (m, 5H), 1.38 (m, 5H), 1.31 (m, 5H), 1.21 (m, 2H). **¹³C NMR** (126 MHz, CDCl₃) δ: 142.7, 140.5, 128.4, 128.3, 128.2, 126.1, 25.6, 40.0, 32.3, 39.1, 38.0, 35.9, 34.6, 29.4, 28.5, 26.5 ppm.

HRMS (EI) for: C₂₆H₃₆ [M]⁺: calcd 348.2811, found 348.2821.

(4-(3-Bromopropyl)phenyl)cycloheptane (8):

Following the **GP2**, the title compound was prepared from bromo-4-(3-bromopropyl)benzene (28 mg) and **1c** (98 mg, 2.0 equiv.) using 20 mol% Ni(diglyme), 25 mol% **11**, and 3.0 equiv **3a**. Purification using flash silica gel column chromatography (eluent: hexane:EtOAc) gave the pure product as a colorless oil (18.2 mg, 62% yield).

¹H NMR (500 MHz, CDCl₃) δ: 7.01 (m, 4H), 3.40 (t, *J* = 6.6 Hz, 2H), 2.73 (t, *J* = 7.4 Hz, 2H), 2.64 (t, *J* = 10.5, 3.7 Hz, 1H), 2.16 (d, *J* = 8.3, 6.6 Hz, 2H), 1.89 (dd, *J* = 13.4, 6.6, 3.1, 1.8 Hz, 2H), 1.79 (dd, *J* = 13.4, 6.4, 3.2 Hz, 2H), 1.53 (m, 6H), 1.53 (d, *J* = 9.7, 3.0 Hz, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ: 33.3, 27.9, 27.2.

HRMS (EI) for: C₁₆H₂₃Br⁺ [M]⁺: calcd 294.0978, found 294.0979.

(4-(4-Methyl-6-phenylhexyl)phenyl)cycloheptane (9):

Following the **GP3**, the title compound was prepared (**6** (29.4 mg) and **1b** (98 mg, 2.0 equiv.) using 20 mol% NiBr₂·glyme, 25 mol% **L2**, 3.0 equiv. **3a** and 2.0 equiv. TBAI as additive, Purification using flash silica gel column chromatography (solvent: hexane:EtOAc) gave the pure product as a colorless oil (46% yield).

¹H NMR (500 MHz, CDCl₃) δ: 7.26 (m, 2H), 7.17 (dd, 7.4, 3.4, 1.8 Hz, 3H), 7.12 (dd, 7.4, 3.4, 1.8 Hz, 3H), 7.06 (m, 4H), 2.64 (dd, 10.5, 6.9, 4.5 Hz, 2H), 2.59 (m, 3H), 1.93 (m, 2H), 1.78 (dp, *J* = 10.0, 3.3 Hz, 2H), 1.73 (m, 9H), 1.55 (m, 3H), 1.45 (m, 3H), 1.41 (m, 2H), 1.23 (tdd, *J* = 10.9, 6.1, 2.1 Hz, 1H), 0.93 (t, 6.4 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ: 147.3, 143.1, 139.9, 128.3, 128.2, 128.2, 126.5, 126.5, 125.5, 46.6, 38.8, 36.9, 36.6, 33.4, 32.4, 28.9, 28.0, 27.2 ppm.

HRMS (EI) for: C₂₆H₃₆[M]⁺: calcd 348.2812, found 348.2823.

4.3 Attempted deaminative alkylation using metal reductants

For **reaction A**, following the reported procedure, after the reaction was stirred at indicated time, quenched with EtOAc, mixture was analysed by GC-MS. Trace product was detected by GC-MS and the side products were also analysed.

For **reaction B**, following the reported procedure, after the reaction was stirred at indicated time, quenched with EtOAc, the mixture analysed by GC-MS. Trace product was detected by GC-MS and the side products were also analysed.

4.4 Attempted cross-coupling to access 4at using previous reductive methods

The reactions were performed according to the reported procedure. After the reaction mixture was stirred for the indicated time, the mixture was quenched with EtOAc and analyzed by GC-MS. No cross-coupling product was detected and the alkyl iodide was completely consumed.

5. Mechanistic Studies

5.1 Racemization experiment

To an oven-dried 5 mL vial equipped with a magnetic stir bar was added methyl 4-bromobenzoate (1.5 mg, 0.1 mmol), pyridinium salts (0.13 mmol, 51 mg, 0.2 mmol), and 4,4'-dimethoxy-2,2'-bipyridine (0.011 mmol). The vial was transferred to a dry glovebox. NiBr₂(diglyme) (0.01 mmol) was added to the vial, and the mixture was then dissolved in 1.0 mL DMA. The vial was tightly sealed and removed from the glovebox. The reaction was allowed to stir under 40 W blue LED irradiation for 16 h with fans to maintain the temperature below 30 °C (the vial was placed about 3 mm from the LEDs, see experimental setup). After that, the reaction was diluted with 6 mL EtOAc, and washed with saturated aq. NaCl (2×3 mL), the organic was separated and concentrated under reduced pressure. The residue was subjected to flash silica gel column chromatography to afford the pure **prod**.

Enantiomeric excess was determined by HPLC (IB column, hexane/*i*PrOH 90/10, 0.60 mL/min, 1254 nm): *t*₁ = 34.3 min, *t*₂ = 35.1 min. 0% ee.

HPLC spectra

Analysis Report

<Sample Information>

Sample Name	: 5-104-b	Sample Type	: Unknown
Sample ID	: 001		
Data Filename	: 5-104IB-3_15122020_001.lcd		
Method Filename	: IB0.6 mL-min 90-10-50 min.lcm		
Batch Filename	: 5-104IB-3.lcb		
Vial #	: 1-1		
Injection Volume	: 5 uL		
Date Acquired	: 12/15/2020 9:51:34 AM	Acquired by	: System Administrator
Date Processed	: 3/6/2021 4:52:53 PM	Processed by	: System Administrator

<Chromatogram>

<Peak Table>

PDA Ch1 254nm				
Peak#	Ret. Time	Area	Height	Area%
1	34.270	1564763	35125	50.168
2	35.117	1554273	33683	49.832
Total		3119036	68808	100.000

5.2 Radical inhibition experiment

To an oven-dried 5 mL vial equipped with a magnetic stir bar was added methyl 4-bromobenzoate (1.5 mg, 0.1 mmol), pyridinium salts (0.13 mmol), HE (51 mg, 0.2 mmol), TEMPO (31 mg, 0.2 mmol), and dimethoxy-2,2'-bipyridine (0.011 mmol). The vial was transferred to a fume hood. NiBr₂(diglyme) (0.01 mmol) was added to the vial, and the mixture was then dissolved in 1.0 mL DMA. The vial was tightly sealed and removed from the glovebox. The reaction was allowed to stir under 40 W blue LED irradiation for 16 h with fans to maintain the temperature below 30 °C (the vial was placed about 3 mm from the LEDs, see experimental setup) that, the reaction

mixture was analyzed by GC and the corresponding TEMPO adduct was detected by GC mass spectroscopy.

5.3 Synthesis of oxidative addition complex Ni-1

In a nitrogen filled glove box, a 50 mL round bottom flask containing a stirring bar was charged with $\text{Ni}(\text{COD})_2$ (138 mg, 0.5 mmol, 1.0 equiv), 4,4'-tert-butyl-2,2'-bipyridine (134 mg, 0.5 mmol, 1.0 equiv) and dry THF (5 mL) giving a dark purple mixture which was stirred overnight at 25°C. Methyl 4-bromobenzoate (1.1 g, 5 mmol, 10.0 equiv) was added and stirred for additional 4 h. Dry pentane (30 mL) was added to the deep red colored mixture and filtered. The resulting precipitate was washed with pentane (3 x 10 mL) and dried under vacuum to afford $\text{Ni}(\text{II})$ complex **Ni-1** (as a brown solid, 149 mg, 55% yield). The product was used without further purification. The complex was stored in a nitrogen filled glove box at 30°C. **^1H NMR** (500 MHz, CDCl_3) δ 7.81 (d, J = 14.5 Hz, 2H), 7.78 (d, J = 7.8 Hz, 2H), 7.59 (d, J = 7.8 Hz, 2H), 7.55 (s, 1H), 7.13 (d, J = 29.6 Hz, 2H), 3.88 (s, 3H), 1.42 (s, 3H), 1.42 (s, 3H), 1.42 (s, 3H). Spectral data was in agreement with the literature.¹¹

5.4 Stoichiometric reactions with Ni-1

To an oven-dried 5 mL vial equipped with a magnetic stir bar was added pyridinium salts (0.13 mmol) and HE (x equiv). The vial was transferred to a fume hood. Ni-1 (0.1 mmol) was added to the vial, and the mixture was then dissolved in 1.0 mL DMA. The vial was tightly sealed and removed from the fume hood. The reaction was allowed to stir under 40 W blue LED irradiation for 16 h with fans to maintain the temperature below 30 °C (the vial was placed about 3 mm from the LEDs, see experimental setup). After that, the reaction was diluted with 1 mL EtOAc, and then n-hexane (12 mg) as an internal standard was added. The mixture was then taken out for MS and GC analysis.

5.5 Catalytic competence of Ni-1

To an oven-dried 5 mL vial equipped with a magnetic stir bar was added pyridinium salts (0.13 mmol), HE (2.0 equiv) and L1 (2 mol%). The vial was transferred to a fume hood. Ni-1 (0.01 mmol) was added to the vial, and the mixture was then dissolved in 1.0 mL DMA. The vial was tightly sealed and removed from the fume hood. The reaction was allowed to stir under 40 W blue LED irradiation for 16 h with fans to maintain the temperature below 30 °C (the vial was placed about 3 mm from the LEDs, see experimental setup). After that, the reaction was diluted with EtOAc, and then n-hexane (12 mg) as an internal standard was added. The mixture was then taken out for MS and GC analysis.

5.6 UV/Vis Absorption spectra

The UV/Vis absorption spectra of DMA solutions of Hantzsch ester (5 mM), pyridinium salts (0.025 M), a mixture of HE (5 mM) and pyridinium salts (0.023 M) were recorded in 1 cm path quartz cuvettes using a 1800PC spectrophotometer. A mixture of 1 and 3 displayed a significant redshift in absorbance, confirming formation of the postulated EDA complex.

Figure S1 show the UV/Vis absorption spectra of DMA solutions of secondary alkyl pyridinium 1 and Hantzsch ester.

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7. NMR Spectra

¹H NMR (500 MHz, CDCl₃) for **4a**

¹³C NMR (126 MHz, CDCl₃) for **4a**

¹H NMR (500 MHz, CDCl₃) for **4c**

¹³C NMR (126 MHz, CDCl₃) for **4c**

¹H NMR (500 MHz, CDCl₃) for **4d**

¹³C NMR (126 MHz, CDCl₃) for **4d**

¹H NMR (500 MHz, CDCl₃) for **4e**

¹³C NMR (126 MHz, CDCl₃) for **4e**

¹H NMR (500 MHz, CDCl₃) for **4f**

¹³C NMR (126 MHz, CDCl₃) for **4f**

¹H NMR (500 MHz, CDCl₃) for **4g**

¹³C NMR (126 MHz, CDCl₃) for **4g**

¹H NMR (500 MHz, CDCl₃) for **4h**

¹³C NMR (126 MHz, CDCl₃) for **4h**

¹H NMR (500 MHz, CDCl₃) for **4i**

¹³C NMR (126 MHz, CDCl₃) for **4i**

¹H NMR (500 MHz, CDCl₃) for **4j**

¹³C NMR (126 MHz, CDCl₃) for **4j**

¹H NMR (500 MHz, CDCl₃) for **4k**

¹³C NMR (126 MHz, CDCl₃) for **4k**

¹H NMR (500 MHz, CDCl₃) for **41**

¹³C NMR (126 MHz, CDCl₃) for **41**

¹H NMR (500 MHz, CDCl₃) for 4m

¹³C NMR (126 MHz, CDCl₃) for 4m

¹H NMR (500 MHz, CDCl₃) for 4n-α

¹³C NMR (126 MHz, CDCl₃) for 4n-α

¹H NMR (500 MHz, CDCl₃) for 4n-β

¹³C NMR (126 MHz, CDCl₃) for 4n-β

¹H NMR (500 MHz, CDCl₃) for **4o**

¹³C NMR (126 MHz, CDCl₃) for **4o**

¹H NMR (400 MHz, CDCl₃) for 4p

¹³C NMR (101 MHz, CDCl₃) for 4p

¹H NMR (500 MHz, CDCl₃) for 4q

¹³C NMR (126 MHz, CDCl₃) for 4q

¹H NMR (500 MHz, CDCl₃) for **4r**

¹³C NMR (101 MHz, CDCl₃) for **4r**

¹H NMR (500 MHz, CDCl₃) for **4s**

¹³C NMR (126 MHz, CDCl₃) for **4s**

¹H NMR (500 MHz, CDCl₃) for **4t**

¹⁹F NMR (471 MHz, CDCl₃) for **4t**

¹³C NMR (126 MHz, CDCl₃) for **4t**

^1H NMR (500 MHz, CDCl_3) for **4u**

^{19}F NMR (471 MHz, CDCl_3) for **4u**

¹³C NMR (126 MHz, CDCl₃) for **4u**

157.412
155.453
144.282
144.252
141.975
128.968
128.342
128.296
126.653
125.808
116.432
116.267

38.807
38.696
33.727
22.369

¹H NMR (500 MHz, CDCl₃) for **4v**

¹³C NMR (126 MHz, CDCl₃) for **4v**

¹H NMR (500 MHz, CDCl₃) for **4w**

¹³C NMR (126 MHz, CDCl₃) for **4w**

¹H NMR (500 MHz, CDCl₃) for **4x**

¹³C NMR (126 MHz, CDCl₃) for **4x**

¹H NMR (500 MHz, CDCl₃) for **4y**

¹³C NMR (126 MHz, CDCl₃) for **4y**

¹H NMR (500 MHz, CDCl₃) for **4z**

¹³C NMR (126 MHz, CDCl₃) for **4z**

¹H NMR (500 MHz, CDCl₃) for 4aa

¹³C NMR (126 MHz, CDCl₃) for 4aa

¹H NMR (500 MHz, CDCl₃) for **4ab**

¹³C NMR (126 MHz, CDCl₃) for **4ab**

¹H NMR (400 MHz, CDCl₃) for 4ac

Mar05-2021-yiw-10.10.fid

¹³C NMR (101 MHz, CDCl₃) for 4ac

Mar05-2021-yiw-10.20.fid

¹H NMR (400 MHz, CDCl₃) for **4ad**

Feb21-2021-yiw-10-3, 10, fid

¹³C NMR (101 MHz, CDCl₃) for **4ad**

Feb22-2021-yiw-10-3, 10, fid

¹H NMR (500 MHz, CDCl₃) spectrum of compound **4ae**. The x-axis represents the chemical shift in ppm, ranging from 1.18 to 7.38. The spectrum shows several distinct signals with corresponding integration values.

Chemical Shift (ppm)	Integration
7.20 - 7.22	2.00
7.00 - 7.02	1.93
3.50 - 4.50	1.11, 9.10
2.00 - 3.00	2.08, 1.01, 0.95
1.20 - 1.60	1.37, 1.19, 1.25, 9.15, 2.74, 2.74, 1.11

ytw39-2C-Q224.3.fid
13C AVNE0500

170.59
170.29
144.20
132.72
132.62
127.25
98.73
80.61
67.50
66.90
66.19
42.67
37.58
36.50
30.91
30.12
28.07
19.76

f1 (ppm)

¹H NMR (500 MHz, CDCl₃) for **4af**

yiw39-3-H, 1, f1d
1H AVNEO 500

¹³C NMR (126 MHz, CDCl₃) for **4af**

yiw39-3-c, 3, f1d
13C AVNEO500

¹H NMR (500 MHz, CDCl₃) for **4b**

¹³C NMR (126 MHz, CDCl₃) for **4b**

¹H NMR (500 MHz, CDCl₃) for **4ag**

¹³C NMR (126 MHz, CDCl₃) for **4ag**

¹H NMR (500 MHz, CDCl₃) for 4ah

¹³C NMR (126 MHz, CDCl₃) for 4ah

¹H NMR (500 MHz, CDCl₃) for 4ai

¹³C NMR (126 MHz, CDCl₃) for 4ai

¹H NMR (500 MHz, CDCl₃) for 4aj

¹³C NMR (126 MHz, CDCl₃) for 4aj

¹H NMR (500 MHz, CDCl₃) for 4ak

¹³C NMR (126 MHz, CDCl₃) for 4ak

oq

DQ

¹H NMR (500 MHz, CDCl₃) for 4am

¹³C NMR (126 MHz, CDCl₃) for 4am

¹H NMR (500 MHz, CDCl₃) for 4an

¹³C NMR (126 MHz, CDCl₃) for 4an

¹H NMR (500 MHz, CDCl₃) for 4ao

¹³C NMR (126 MHz, CDCl₃) for 4ao

¹H NMR (500 MHz, CDCl₃) for 4ap

¹³C NMR (126 MHz, CDCl₃) for 4ap

¹H NMR (500 MHz, CDCl₃) for **4aq**

¹³C NMR (126 MHz, CDCl₃) for **4aq**

¹H NMR (500 MHz, CDCl₃) for 4ar

¹³C NMR (126 MHz, CDCl₃) for 4ar

¹H NMR (500 MHz, CDCl₃) for 4as

¹³C NMR (126 MHz, CDCl₃) for 4as

OC for 4at

Q for 4at

¹H NMR (500 MHz, CDCl₃) for 4au

¹³C NMR (126 MHz, CDCl₃) for 4au

^1H NMR (500 MHz, CDCl_3) for **6**

^{13}C NMR (126 MHz, CDCl_3) for **6**

¹H NMR (500 MHz, CDCl₃) for 7

¹³C NMR (126 MHz, CDCl₃) for 7

¹H NMR (500 MHz, CDCl₃) for **8**

¹³C NMR (101 MHz, CDCl₃) for **8**

yiw-62.11.fid
62

Chemical shifts (ppm): 147.88, 137.52, 128.42, 126.76, 46.61, 38.85, 34.21, 33.55, 33.25, 27.95, 27.19.

¹H NMR (500 MHz, CDCl₃) for 9

¹³C NMR (101 MHz, CDCl₃) for 9

Feb25-2021-yiw-72, 14, fid

¹H NMR (500 MHz, CDCl₃) for Ni-1