Supporting Information: A Widely Applicable Dual Catalytic System for Cross-Electrophile Coupling Enabled by Mechanistic Studies

David J. Charboneau,[a] Emily L. Barth,[a] Nilay Hazari,[a,*] Mycah R. Uehling[b] & Susan L. Zultanski[c,*]

[a]Department of Chemistry, Yale University, P. O. Box 208107, New Haven, Connecticut, 06520, USA. E-mail: nilay.hazari@yale.edu.

[b]Merck & Co., Inc., Discovery Chemistry, HTE and Lead Discovery Capabilities, Kenilworth, New Jersey, 07033, USA.

[c]Merck & Co., Inc., Department of Process Research and Development, Rahway, New Jersey, 07065, USA. E-mail: susan_zultanski@merck.com.

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SI. General Methods (Not Including High Throughput Experimentation)

Experiments were performed under an atmosphere of dinitrogen in an MBRAUN glovebox or using standard Schlenk techniques, unless specified otherwise. Purging of the glovebox atmosphere was not performed between uses of pentane, benzene, toluene, diethyl ether, 1,4-dioxane and tetrahydrofuran (THF); as such, trace amounts of the solvents may have been present in the box atmosphere and intermixed in the solvent bottles. 1,4-Dioxane, *N*,*N*-dimethylformamide (DMF), pentane, tetrahydrofuran (THF), benzene, and toluene were dried via passage through a column of activated alumina on an Inert Technologies PureSolv MD7 solvent purification system and subsequently stored under dinitrogen unless otherwise noted. Acetonitrile (CH_3CN) was purchased from Honeywell (Cat. No. CS017-56) and used without further purification. Methyl ethyl ketone (MEK) was purchased as <0.005% H_2O from EMD Chemicals then degassed and used without further purification. Other solvents used for catalysis, such as isopropyl acetate (IPAc, Sigma Aldrich), 2-methyltetrahydrofuran (2-MeTHF, Acros), and 1,2-dimethoxyethane (DME, Acros) were degassed then dried via passage through a small pipette of neutral activated alumina in a glovebox under an N_2 atmosphere until they reached <50 ppm H_2O content by KF titration. Neutral alumina was activated by heating at 250 °C under vacuum overnight. Deuterated solvents were obtained from Cambridge Isotope Laboratories and were dried by passage through a short column of neutral activated alumina. Chemicals were used as received unless otherwise stated. 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbbpy) was purchased from Sigma Aldrich or Santa Cruz at >97% purity. Substrates were purchased at ≥97% purity. All liquid substrates were degassed by sparging with dinitrogen or by three consecutive freeze-pump-thaw cycles, then handled inside of a nitrogen filled glovebox. Liquid substrates that had a yellow color instead of being colorless were purified by passage through a short column of neutral activated alumina prior to use. Tetrakis(dimethylamino)ethylene (TDAE) was purchased from Sigma-Aldrich, TCI, AstaTech, or Santa Cruz and was used without further purification. Co^{II}(Pc) was purchased from Sigma-Aldrich and used without further purification. The following compounds were synthesized according to literature procedures: (dtbbpy)Ni^{II}(*o*-tol)I,[1] (dtbbpy)$Ni^{II}Br_2$.[2]

SII. Instrumentation Methods (Not Including High Throughput Experimentation)

NMR spectra were recorded on Agilent-400, -500, or -600 MHz spectrometers at ambient probe temperatures unless otherwise stated. Chemical shifts for ^{1}H NMR spectra are reported with respect to residual protio solvent in ppm. Chemical shifts for other nuclei are referenced through the gyromagnetic ratio method described by Harris *et al.*[3] High resolution mass spectra were acquired with a Waters Xevo QToF Mass Spectrometer (spray needle held at 3kV, source temperature set to 125 °C, N_2 cone gas flow rate 24 L/h, N_2 desolvation gas flow rate 720 L/h). Liquid chromatography was used for sample separation with a gradient from 95% H_2O (0.1% formic acid) and 5% acetonitrile to 5% H_2O and 95% acetonitrile at a flow rate of 0.6 L/min over 3 minutes using an Acquity UPLC BEH C18 column (1.7 µm, 2.1 mm x 50 mm). In some instances, poor ionization of compounds precluded high resolution data collection, so low resolution gas chromatography/mass spectrometry or liquid chromatography/mass spectrometry was utilized. Low resolution gas chromatography/mass spectrometry was performed on an Agilent 6890N Network GC and an Agilent 5973 Mass Selective Detector system using the following parameters: flow rate 1.0 mL/min, column temperature 50 °C (held for 3 min), 20 °C/min increase to 300 °C (held for 2 min), total time 17.5 min. For information on liquid chromatography/mass spectroscopy see section SIV.

SIII. General Methods Used in High Throughput Experimentation

All coupling partners, catalysts, and reductants were dosed as mixtures in 1,4-dioxane inside a nitrogen filled glovebox. If the mixture in 1,4-dioxane was not soluble (slurry), the mixture was dosed while it was stirred. The 1,4-dioxane that was used was purchased from Millipore Sigma in an air-free, Sure/Seal^{TM} bottle, and used as is, after opening inside a nitrogen-filled glove box. Solutions of aryl and alkyl halide dissolved in 1,4-dioxane were prepared by independently weighing the aryl and alkyl halides into different dram vials under air (each with a stir bar), then bringing the vials inside a nitrogen filled glove box and adding 1,4-dioxane. The mixtures of Co^{II}(Pc) and TDAE were prepared by weighing Co^{II}(Pc) and TDAE into different dram vials (each with a stir bar) inside a nitrogen filled glovebox, then adding 1,4-dioxane. The mixture of (dtbbpy)$Ni^{II}Br_2$ was prepared by weighing $Ni^{II}Br_2$ (1 equiv) and dtbbpy (1 equiv) in a dram vial (with a stir bar) inside a nitrogen filled glove box, and adding 1,4-dioxane. The mixture was allowed to stir for 20 min at 25 °C before use. The concentration of the mixtures of each reaction component in 1,4-dioxane is outlined in section SXX.

SIV. Hardware and Instrumentation Methods for High Throughput Experimentation

Reactions were performed in a 96 well reaction block (Analytical Sales & Services, Inc. catalog # 96960) using 1 mL reaction vials (Analytical Sales & Services, Inc. catalog # 884001), a PFA sheet (Analytical Sales & Services, Inc. catalog #: 96967) and rubber mat (Analytical Sales & Services, Inc. catalog #: 96965) for sealing the block, and 96 parylene coated stir dowels (1.98mm diameter, 4.80 mm length, V&P Scientific, Inc. product # VP 711D-1) for stirring. The reaction block was stirred using a tumble stirrer (tumble stirrer: V&P Scientific, Inc. Model # VP710 S) and heating was applied using a heating jacket (V&P Scientific, Inc. Model VP 741ABZ-R-MB).

Figure S1. Representative image of a reaction block, reaction vessels, stir bar, PFA sheet, and rubber mat used in high throughput experimentation.

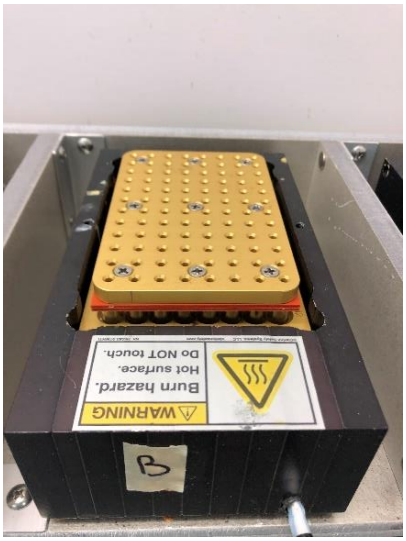


Figure S2. Representative image of a reaction block inside a heating jacket on a tumble stirrer used in high throughput experimentation.

UPLC/MS (ESI) was performed using a Waters Acquity UPLC I-Class system equipped with a binary pump, sample manager, column manager, sample organizer, a photodiode array detector, Single Quad Detector 2 with ESI source and MassLynx® software.

Analytical separations were performed using one of two methods (see below):

Method 1:
Inject volume: 1 μL
Column Temperature: 45 °C
UV scan: 210 – 400 nM
CORTECS UPLC C18 1.6 μM, 2.1 mm x 50 mm
Mobile Phase A: 0.1 % TFA in Water
Mobile Phase B: 0.1 % TFA in Acetonitrile
Details of Elution

Time (min)	Flow (mL/min)	% A	% B
0.00	0.700	95	5
1.70	0.700	0	100
1.95	0.700	0	100
1.96	0.700	95	100
2.00	0.700	95	5

Method 2:
Inject volume: 1 μL
Column temperature: 55 °C
UV scan: 210 – 500 nM
ACQUITY UPLC C18 BEH 1.7 μM, 1 mm x 50 mm
Mobile Phase A: 0.1 % TFA in Water
Mobile Phase B: 0.1 % TFA in Acetonitrile
Details of Elution

Time (min)	Flow (mL/min)	% A	% B
0.00	0.350	95	5
1.40	0.350	0	100
1.80	0.350	0	100
1.82	0.350	95	100
2.00	0.350	95	5

SV. General Procedure for Cross-Electrophile Coupling of Aryl and Alkyl Halides

General Information:

In general, aryl halides and alkyl halides were found to be unreactive with (dtbbpy)$Ni^{II}Br_2$ and Co^{II}(Pc) over hours at room temperature in the absence of TDAE. Therefore, reactions were typically set up by first generating a fresh stock solution of substrate with catalysts under an N_2 solution. However, if the substrates were a solid at room temperature, the solid was added directly to the reaction flask. In many solvents, the catalysts are not fully soluble, so the mixtures were sonicated into a fine suspension, which was then added as a slurry to a reaction vial equipped with a magnetic stir bar. TDAE was then added to initiate the reaction.

The quantity of TDAE utilized in a given reaction was determined by:

(mmol aryl halide + mmol alkyl halide)/2 + (0.1*mmol aryl halide) = mmol TDAE

In the above equation, the left term describes the amount of TDAE required to stoichiometrically reduce aryl and alkyl electrophiles. The right term shows that 10% excess of TDAE was employed relative to the aryl electrophile, which was employed to reduce Ni^{II} and Co^{II} catalysts to low-valent oxidation states (Ni^0 and Co^I).

In general, (dtbbpy)$Ni^{II}Br_2$ was employed as a well-defined precatalyst. However, comparable activity was observed when a slurry of premixed $Ni^{II}Br_2$ (anhydrous) and free dtbbpy in dioxane was utilized (See SXX).

Unless otherwise stated, all reported yields were performed in duplicate and quantified by ^{1}H NMR (*vide infra*) with the exception of isolated yields, which were quantified once by ^{1}H NMR and once by product isolation. In general, product yields for duplicate reactions agreed within 10% of one another regardless of quantification method.

Representative Procedure:

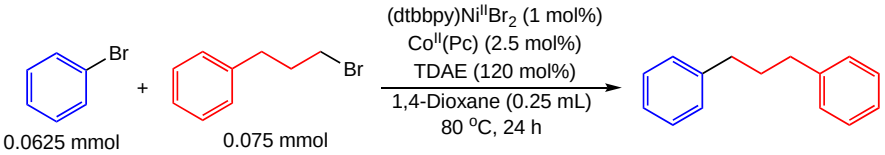


Figure S3. Cross-electrophile coupling of bromobenzene with 1-bromo-3-phenylpropane.

Outside of a glovebox to a 1 dram vial was added 1.2 mg (0.0025 mmol) (dtbbpy)$Ni^{II}Br_2$ and 3.6 mg (0.00625 mmol) Co^{II}(Pc). The vial was pumped into a glovebox containing an N_2 atmosphere, where 1 mL 1,4-dioxane was added via syringe transfer using a 1 mL disposable

syringe. To the same vial, 26.3 μL (0.25 mmol) bromobenzene and 45.6 μL (0.30 mmol) 1-bromo-3-phenylpropane were added via a 100 μL gas-tight Hamilton syringe. The vial was capped tightly with a PTFE seal cap and removed from the glovebox, sonicated until the mixture was a uniform suspension, then brought back into the glovebox. To a separate 1 dram vial equipped with a magnetic stir bar, 270 μL of the prepared suspension was added as a slurry via syringe transfer with a disposable 1 mL syringe, followed by 17.5 μL (0.075 mmol) TDAE via 50 μL gas-tight Hamilton syringe, which initiates the reaction. The reaction vial was capped tightly with a PTFE seal cap and stirred at 80 °C for 24 hours.

General Workup for ^{1}H NMR Yields:

The reaction vial was removed from heat, allowed to cool to room temperature, and diluted with 0.5 mL of ethyl acetate (EtOAc). The mixture was passed through a short silica plug (~1.5 inches) in a glass pipette, which was rinsed with 5 mL EtOAc. The filtrate was concentrated to dryness and the crude residue was taken up in $CDCl_3$ with added hexamethylbenzene as an internal standard. The reaction yields were determined using ^{1}H NMR spectroscopy.

SVI. Reactivity of (dtbbpy)Ni^{II}(*o*-tol)I with TDAE

General Information:

(dtbbpy)Ni^{II}(*o*-tol)I showed no decomposition in the absence of TDAE in the solvents in Table S1 over the measured course of the reaction with TDAE (<10 minutes for acetonitrile). Decomposition was measured as conversion to free ligand, which was the most significant decomposition product observed by ^{1}H NMR spectroscopy. Paramagnetic species were not observed during these reactions. The color of (dtbbpy)Ni^{II}(*o*-tol)I was deep red in nonpolar solvents, such as toluene and dioxane, but bright orange to pale red in more polar solvents, such as acetone, acetonitrile, and dimethylsulfoxide (DMSO). We hypothesize that the color difference arises from the iodide ligand being inner sphere in nonpolar solvents and outersphere in polar solvents so that complexes of the type $[(dtbbpy)Ni^{II}(o\text{-tol})(solv)]^+I^-$ are formed. In acetonitrile, ^{1}H NMR spectroscopy indicates that the dtbbpy ligand may also be displaced by acetonitrile.

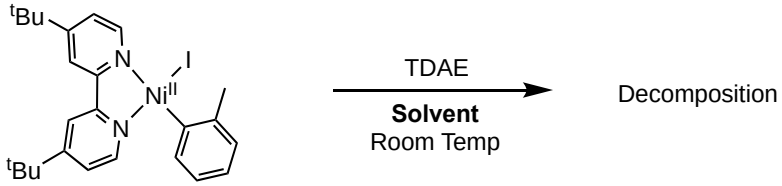
The data in Table S1 demonstrate that reduction of (dtbbpy)Ni^{II}(*o*-tol)I is slow in most solvents. In contrast, reduction of (dtbbpy)$Ni^{II}Br_2$ with TDAE to generate Ni^0 products has been previously demonstrated to occur rapidly at room temperature.[4]

Representative Procedure:

In a nitrogen-filled glovebox, to a 1 dram vial was added 0.0040 g (0.0073 mmol) (dtbbpy)Ni^{II}(*o*-tol)I, 600 μL of 1,4-dioxane, and 2.9 mg (0.014 mmol) TDAE. The solution was transferred to a J-young NMR tube and the reaction was monitored by ^{1}H NMR spectroscopy. For individual reaction conditions, see Table S1 below.

Reactivity Data:

Table S1. Reactivity of (dtbbpy)Ni^{II}(*o*-tol)I with TDAE in various solvents over time.



Solvent	Dielectric Constant (ε)	Solution Color Before TDAE Addition	^{1}H NMR After 12 Hours at Room Temperature with TDAE
Toluene	2.38	Dark Red	No Reaction
1,4-Dioxane	2.25	Dark Red	No Reaction
Acetone	20.7	Bright Orange	20% Conversion to New Signal
Acetonitrile	37.5	Bright Orange	Complete Conversion (in <10 min)
DMSO	46.7	Bright Orange	10% Conversion to New Signal

Representative ^{1}H NMR data in d_6-acetone:

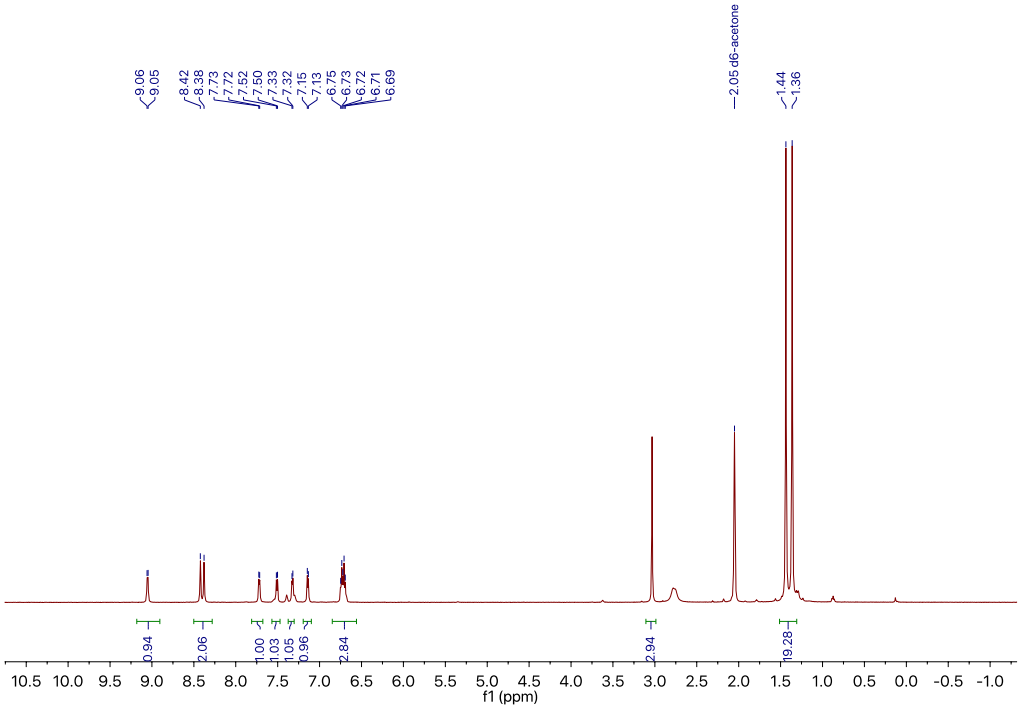


Figure S4. (dtbbpy)Ni^{II}(*o*-tol)I in d_6-acetone.

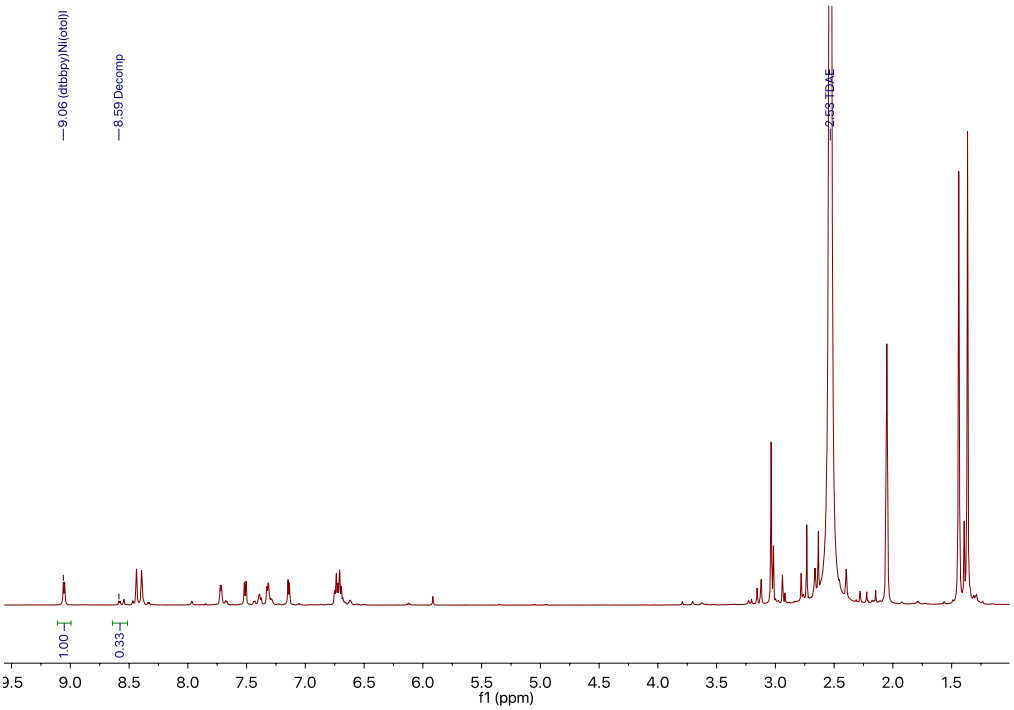


Figure S5. Reaction of (dtbbpy)Ni^{II}(*o*-tol)I with TDAE in d_6-acetone after 12 hours.

SVII. Varying (dtbbpy)Ni^{II}Br$_2$ Loading in Dual-Catalyzed Cross-Electrophile Coupling of Iodobenzene with Benzyl Chloride

General Information:

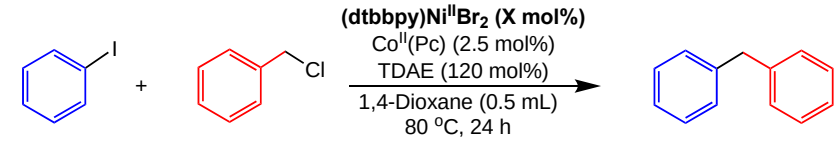
When varying the loading of (dtbbpy)Ni^{II}Br$_2$ while maintaining constant loading of Co^{II}(Pc), biphenyl is observed at high loading and iodobenzene is observed at low catalyst loadings, consistent with our hypotheses (Table S2).

Procedure:

See section SV for representative experimental setup and workup. For individual reaction conditions, see Table S2, below.

Data:

Table S2. Dual catalyzed cross-electrophile coupling of iodobenzene with benzyl chloride using varying amounts of (dtbbpy)Ni^{II}Br$_2$.



0.0625 mmol 0.075 mmol

(dtbbpy)Ni^{II}Br$_2$ (X mol%)	Product Yield (%)	Phenyl Iodide (%)	Biphenyl (%)	PhI Mass Balance (%)	Benzyl Chloride (%)
1.75	52	38	<1	90	<1
3.5	61	27	<1	88	<1
7	75	14	1	91	<1
14	85	2	8	103	<1

SVIII. Stoichiometric C(sp^2)-C(sp^3) Bond Formation with (dtbbpy)Ni^{II}(*o*-tol)I

Representative Procedure:

In a nitrogen filled glovebox, to a 1 dram vial equipped with a magnetic stir bar was added 6.8 mg (0.013 mmol) (dtbbpy)Ni^{II}(*o*-tol)I, 1.1 mg (0.0019 mmol) Co^{II}(Pc), 1.5 mL 1,4-dioxane, 3.3 mg (0.026 mmol) benzyl chloride, then 5.2 mg (0.026 mmol) TDAE. The vial was fit with a PTFE cap and stirred at room temperature for one hour. The reaction was then diluted with 0.5 mL of ethyl acetate (EtOAc). The mixture was passed through a short silica plug (~1.5 inches) in a glass pipette, which was rinsed with 5 mL EtOAc. The filtrate was concentrated to dryness and the crude residue was taken up in $CDCl_3$ with added hexamethylbenzene as an internal standard. The reaction yields were determined by ^1H NMR spectroscopy. For individual reaction conditions, see Table 2 in the manuscript.

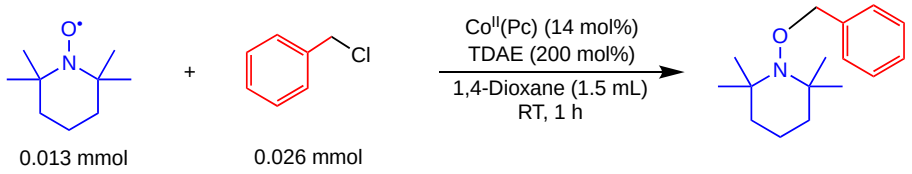
SIX. Radical Trapping Experiments with TEMPO

Representative Procedure:

In a nitrogen filled glovebox, to a 1 dram vial equipped with a magnetic stir bar was added 2.0 mg (0.013 mmol) TEMPO, 1.1 mg (0.0019 mmol) Co^{II}(Pc), 1.5 mL 1,4-dioxane, 3.3 mg (0.026 mmol) benzyl chloride, then 5.2 mg (0.026 mmol) TDAE. The vial was fit with a PTFE cap and stirred at room temperature for one hour. The reaction was then diluted with 0.5 mL of ethyl acetate (EtOAc). The mixture was passed through a short silica plug (~1.5 inches) in a glass pipette, which was rinsed with 5 mL EtOAc. The filtrate was concentrated to dryness and the crude residue was taken up in $CDCl_3$ with added hexamethylbenzene as an internal standard. The reaction yields were determined by ^1H NMR spectroscopy. For individual reaction conditions, see Table S3 below.

Data:

Table S3. Stoichiometric reaction of TEMPO with benzyl chloride under various reaction conditions.



0.013 mmol 0.026 mmol

Deviation From Conditions	Product Yield (%)
None	41
No Co^{II}(Pc)	<1
No Co^{II}(Pc) and no TDAE	<1
100 mol% Co^{II}(Pc) and no TDAE	<1

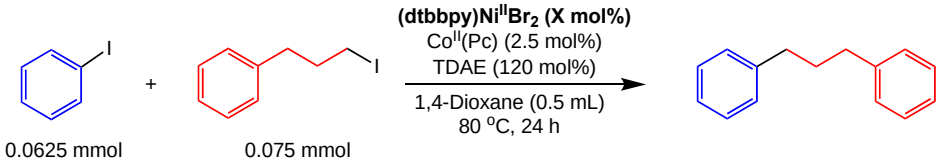
SX. Optimization of Cross-Electrophile Coupling of Phenyl Iodide with 1-Iodo-3-Phenylpropane

Procedure:

See section SV for representative experimental setup and workup. For individual reaction conditions, see Table S4 below.

Data:

Table S4. Optimization of dual catalyzed cross-electrophile coupling of iodobenzene with 1-iodo-3-phenylpropane.



(dtbbpy)Ni^{II}Br$_2$ (X mol%)	Product Yield (%)	Phenyl Iodide (%)	Biphenyl (%)	PhI Mass Balance (%)	AlkI (%)
1.75	92	<1	6	104	<1
3.5	81	<1	11	103	<1
7	58	<1	20	98	<1

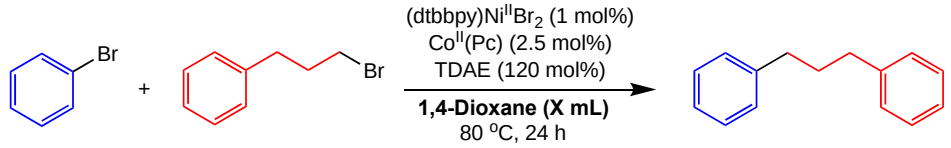
SXI. Optimization of Concentration

Procedure:

See section SV for representative experimental setup and workup. For individual reaction conditions, see Table S5 below. Higher concentrations were not utilized because, at these concentrations, as TDAE oxidized and precipitated out of solution, insufficient stirring of the thick mixture was observed.

Data:

Table S5. Optimization of dual catalyzed cross-electrophile coupling of bromobenzene with 1-bromo-3-phenylpropane.



0.0625 mmol 0.075 mmol

1,4-Dioxane (X mL)	Product Yield (%)
0.5	84
0.25	**87**

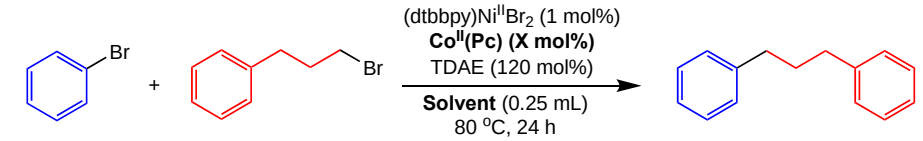
SXII. Solvent Screen

Procedure:

See section SV for representative experimental setup and workup. For individual reaction conditions, see Table S6 below.

Data:

Table S6. Solvent screen for dual-catalyzed cross-electrophile coupling of bromobenzene with 1-bromo-3-phenylpropane.



0.0625 mmol 0.075 mmol

Solvent	**Yield (%) X = 2.5%**	**Yield (%) X = 0%**
1,4-Dioxane	87	<1
Isopropylacetate	72	<1
2-MeTHF	83	<1
Dimethoxyethane	56 (79)[a]	<1
Methyl ethyl ketone	13 (66)[b]	<1

[a]Reaction performed with 1 mol% Co^{II}(Pc). [b]Reaction performed with 0.25 mol% Co^{II}(Pc).

SXIII. Optimization of Temperature

Procedure:

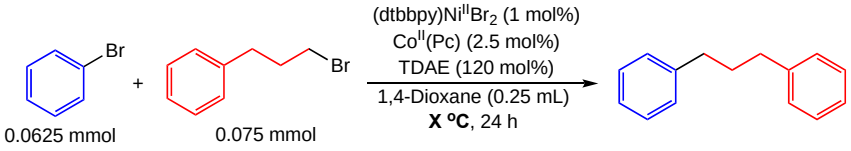
See section SV for representative experimental setup and workup. For individual reaction conditions, see Table S7 below.

General Discussion:

The majority of cross-electrophile coupling reactions between aryl and unactivated alkyl bromides require elevated temperatures, although in some instances room temperature reactivity has been achieved.[5] Under our optimized conditions, catalysis is performed at 80 ºC. Below 80 ºC, product yield diminishes substantially.

Data:

Table S7. Dual-catalyzed cross-electrophile coupling of bromobenzene with 1-bromo-3-phenylpropane at varying temperature.



Temperature	Product Yield (%)
Room Temperature	2
40 ºC	3
60 ºC	46
80 ºC	87

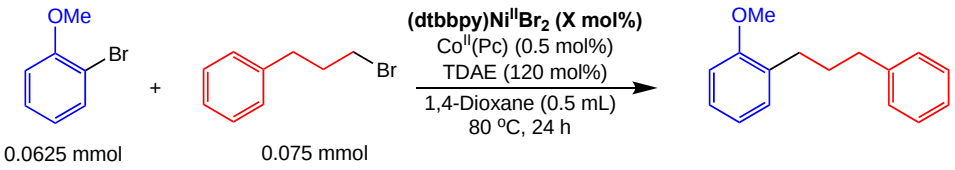
SXIV. Effect of Aryl Halide Ortho-Substitution on Optimization of Catalyst Loadings

Procedure:

See section SV for representative experimental setup and workup. For individual reaction conditions, see Tables S8 and S9 below.

Data:

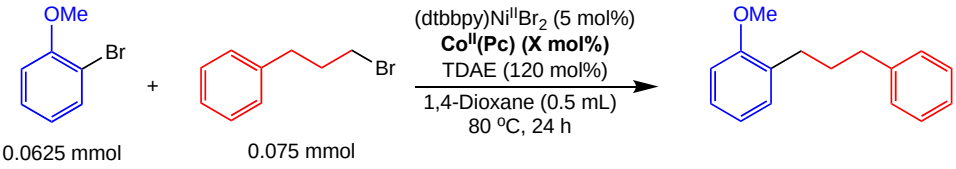
Table S8. Dual catalyzed cross-electrophile coupling of 2-bromoanisole with 1-bromo-3-phenylpropane using varying (dtbbpy)$Ni^{II}Br_2$.



0.0625 mmol 0.075 mmol

(dtbbpy)$Ni^{II}Br_2$ (X mol%)	Product Yield (%)	ArBr (%)	Biaryl (%)	ArBr Mass Balance (%)	AlkBr (%)
2.5	88	15	<1	103	29
5	91	<1	<1	91	15
10	92	<1	<1	92	6

Table S9. Dual catalyzed cross-electrophile coupling of 2-bromoanisole with 1-bromo-3-phenylpropane using varying Co^{II}(Pc).



0.0625 mmol 0.075 mmol

Co^{II}(Pc) (X mol%)	Product Yield (%)	ArBr (%)	Biaryl (%)	ArBr Mass Balance (%)	AlkBr (%)
0.5	91	<1	<1	91	15
1	87	7	<1	94	10
2.5	83	5	<1	87	12
5	83	6	<1	89	11

SXV. Additional Reactions for Two-Component Cross-Electrophile Coupling

Procedure:

See section SV for representative experimental setup and workup. For individual reaction conditions, see Figures S6 and S7 below.

Aryl Halide Substrates:

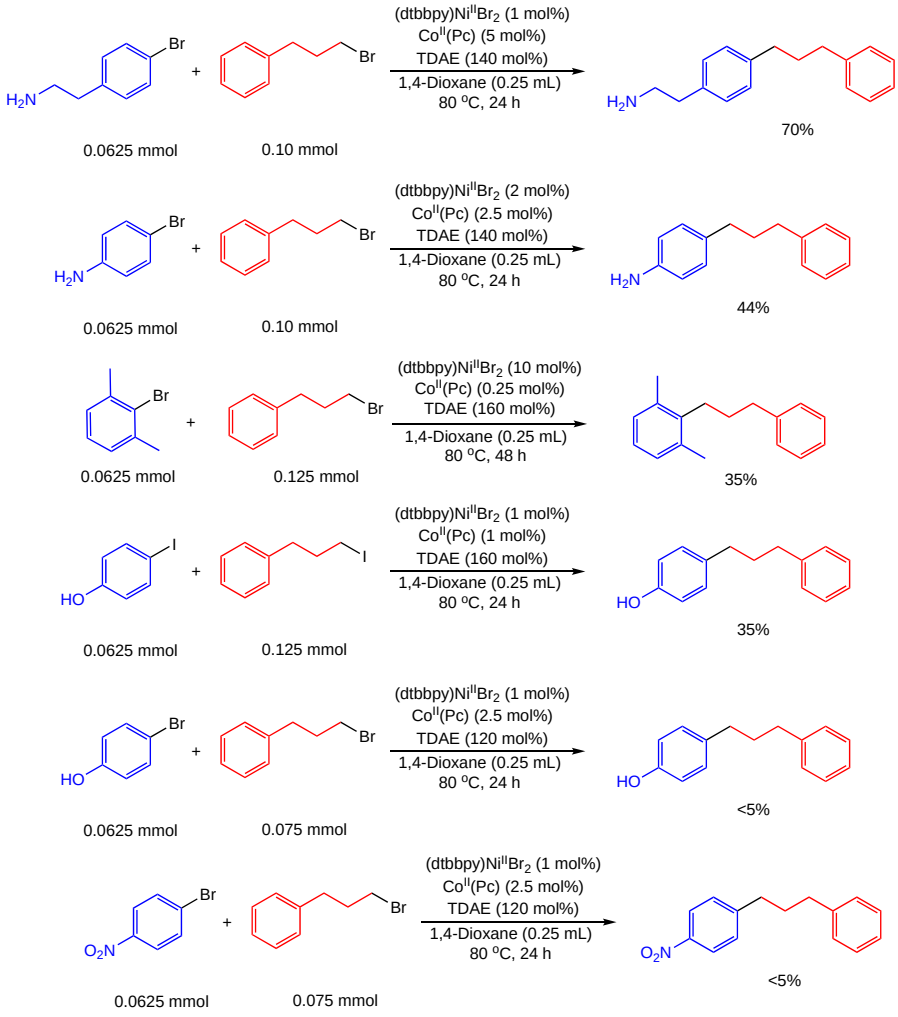


Figure S6. Additional reactions for two-component cross-electrophile coupling aryl halide substrate scope.

Alkyl Halide Substrates:

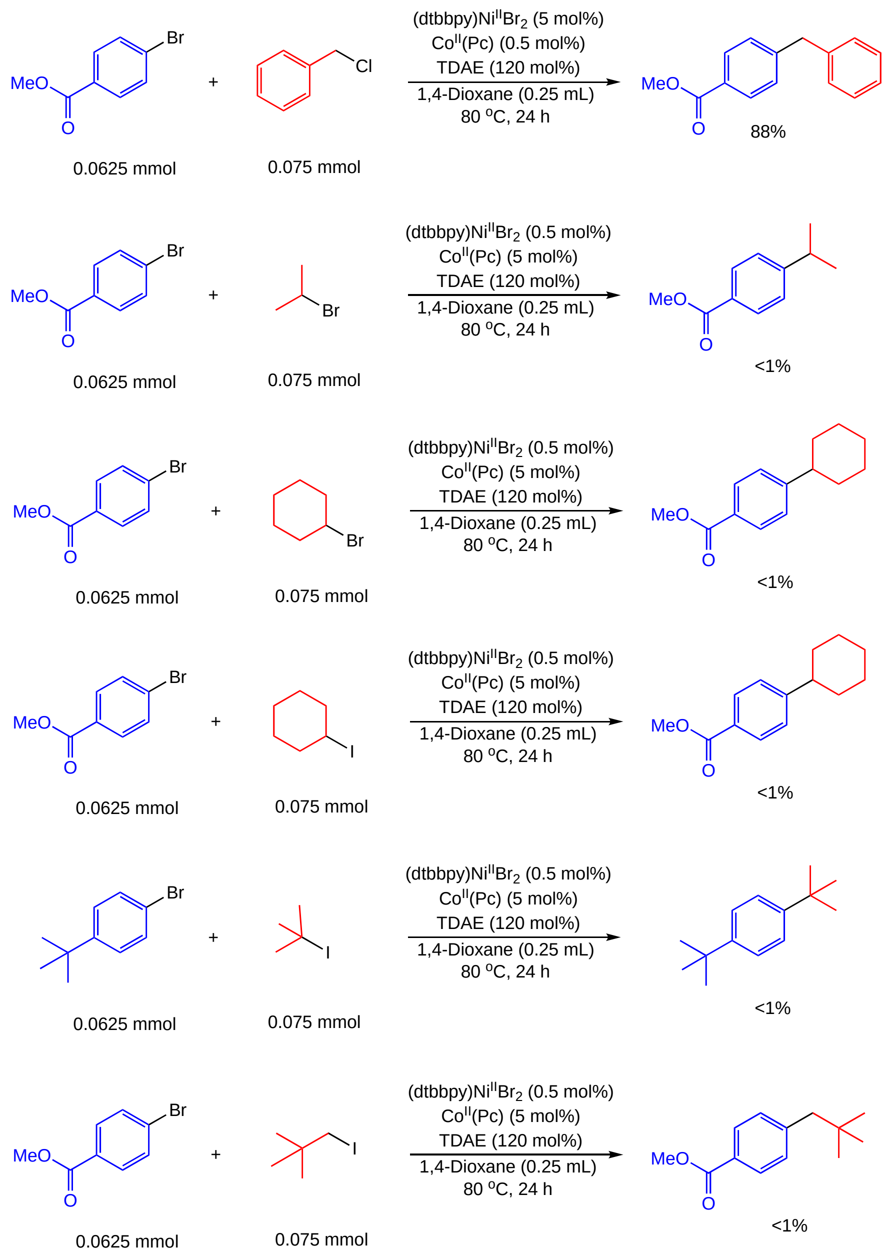


Figure S7. Additional reactions for two-component cross-electrophile coupling alkyl halide substrate scope.

SXVI. Representative Optimizations of Substrates in Figure 4

Procedure:

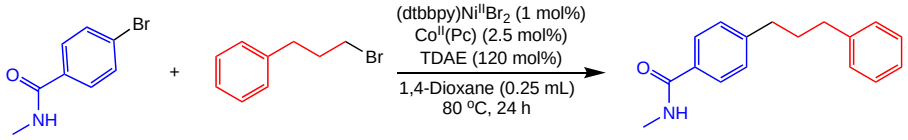
See section SV for representative experimental setup and workup. For individual reaction conditions, see Tables S10-S14 below.

General Information:

These data are to demonstrate the methods by which substrates in Figure 4 of the manuscript were optimized and that the general optimization strategy can be applied to a wide range of substrates. Representative optimization sequences are provided and, in some instances, superfluous data points are omitted.

Data and Analysis:

Table S10. Optimization of dual catalyzed cross-electrophile coupling of 4-bromo-*N*-methylbenzamide (**4i**) with 1-bromo-3-phenylpropane.

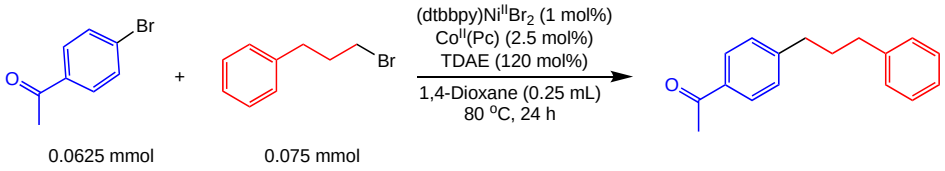


0.0625 mmol 0.075 mmol

Deviation From Conditions	Product Yield (%)	ArBr (%)	ArH (%)	Biaryl (%)	AlkBr (%)
None	62	<1	<1	12	18
5 mol% Co	**82**	**<1**	**<1**	**7**	**8**

Using our standard catalyst loadings for bromobenzene (**4a**), 1 mol% (dtbbpy)Ni^{II}Br$_2$ and 2.5 mol% Co^{II}(Pc), 4-bromo-*N*-methylbenzamide (**4i**) was coupled with 1-bromo-3-phenylpropane in 62% yield. Under these conditions, alkyl bromide was left unreacted upon complete consumption of the aryl electrophile. Therefore, in accord with the strategy outlined in Figure 3, the loading of Co^{II}(Pc) was increased to 5 mol%, resulting in an 82% yield. Further optimization was not attempted, however, using 5 mol% Co^{II}(Pc), alkyl bromide still remained after consumption of the aryl bromide, indicating that higher yields could be obtained by either increasing Co^{II}(Pc) loading or decreasing (dtbbpy)Ni^{II}Br$_2$ loadings.

Table S11. Optimization of dual catalyzed cross-electrophile coupling of 4-bromoacetophenone (**4g**) with 1-bromo-3-phenylpropane.

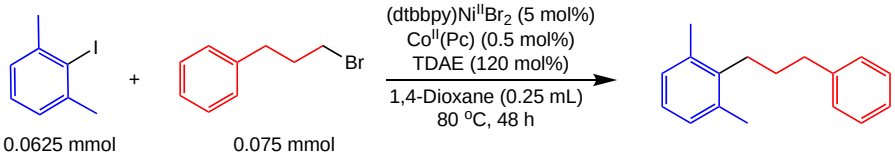


0.0625 mmol 0.075 mmol

Deviation From Conditions	Product Yield (%)	ArBr (%)	ArH (%)	Biaryl (%)	AlkBr (%)
None	80	17	<1	<1	20
36 h	**93**	**6**	**<1**	**1**	**2**

Using our standard catalyst loadings for bromobenzene (**4a**), 1 mol% (dtbbpy)Ni^{II}Br$_2$ and 2.5 mol% Co^{II}(Pc), 4-bromoacetophenone (**4g**) was coupled with 1-bromo-3-phenylpropane in 80% yield. Under these conditions, alkyl bromide and aryl bromide remained unreacted, indicating that the reaction had not reached completion. Therefore, the reaction was allowed to run for 36 hours, resulting in a 93% yield.

Table S12. Optimization of dual catalyzed cross-electrophile coupling of 2-iodo-1,3-dimethylbenzene (**4r**) with 1-bromo-3-phenylpropane.



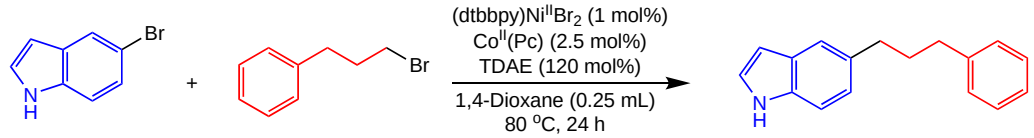
0.0625 mmol 0.075 mmol

Deviation From Conditions	Product Yield (%)	ArBr (%)	ArH (%)	Biaryl (%)	AlkBr (%)
None	37	54	<1	<1	20
10 mol% Ni, 0.125 mmol AlkBr, 160 mol% TDAE	**88**	**<1**	**<1**	**<1**	**<1**

Based on reactivity observed with mono-*ortho*-substituted aryl halide substrates, which required a higher ratio of (dtbbpy)Ni^{II}Br$_2$ to Co^{II}(Pc), we started reaction optimization for the coupling of 2-iodo-1,3-dimethylbenzene (**4r**) with 1-bromo-3-phenylpropane at 5 mol% (dtbbpy)Ni^{II}Br$_2$ and 0.5 mol% Co^{II}(Pc). Additionally, the reaction was performed for 48 hours

owing to the expected sluggish oxidative addition of **4r**. Under these conditions, a 37% yield was observed. While both alkyl bromide and aryl bromide were present at the end of the reaction, the rate of alkyl bromide consumption outpaced the rate of aryl bromide consumption. Therefore, the loading of (dtbbpy)$Ni^{II}Br_2$ was increased and the loadings of alkyl bromide and TDAE were increased. It is probable that high yields could also be obtained in this reaction without increasing the equivalents of alkyl bromide, however, these reactions were not attempted.

Table S13. Optimization of dual catalyzed cross-electrophile coupling of 5-bromoindole (**4j**) with 1-bromo-3-phenylpropane.

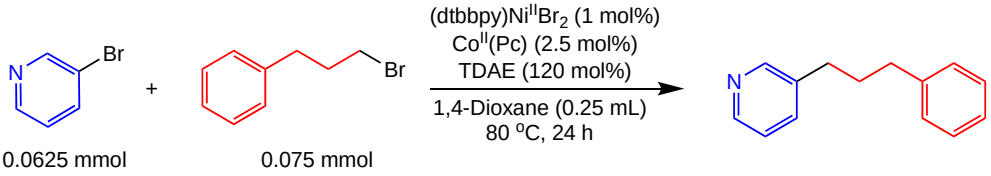


0.0625 mmol 0.075 mmol

Deviation From Conditions	Product Yield (%)	ArBr (%)	ArH (%)	Biaryl (%)	AlkBr (%)
None	64	20	6	<1	15
36 hours	68	24	6	<1	2
0.1 mmol AlkBr, 140 mol% TDAE, 36h	**81**	**<1**	**12**	**1**	**<1**

Using our standard catalyst loadings for bromobenzene (**4a**), 1 mol% (dtbbpy)$Ni^{II}Br_2$ and 2.5 mol% Co^{II}(Pc), 5-bromoindole (**4j**) was coupled with 1-bromo-3-phenylpropane in 64% yield. Under these conditions, alkyl bromide and aryl bromide remained unreacted, indicating that the reaction had not reached completion. Therefore, the reaction was allowed to run for 36 hours, resulting in a modest increase in yield to 68%. After 36 hours, alkyl bromide was fully consumed but aryl bromide remained unreacted. According to our general strategy, the nickel loading should be increased or the cobalt loading should be decreased. However, another alternative solution for reaction optimization when alkyl bromide is consumed more quickly than aryl bromide is to increase the loadings of alkyl bromide and TDAE. In this case, when the loadings of alkyl bromide and TDAE are increased, the yield was improved to 81%.

Table S14. Optimization of dual catalyzed cross-electrophile coupling of 3-bromopyridine (**4v**) with 1-bromo-3-phenylpropane.



0.0625 mmol 0.075 mmol

Deviation From Conditions	Product Yield (%)	ArBr (%)[a]	ArH (%)	Biaryl (%)	AlkBr (%)
None	52	16	<1	<1	3
0.1 mmol AlkBr, 140% TDAE	65	12	<1	<1	7
5 mol% Ni, 0.1 mmol AlkBr, 140% TDAE	**80**	**<1**	**<1**	**1**	**<1**

[a]3-bromopyridine is volatile enough to be partially removed through evaporation during workup. Therefore, values reported represent the lower limit of unreacted aryl bromide in catalysis.

Using our standard catalyst loadings for bromobenzene (**4a**), 1 mol% (dtbbpy)Ni^{II}Br$_2$ and 2.5 mol% Co^{II}(Pc), 3-bromopyridine (**4v**) was coupled with 1-bromo-3-phenylpropane in 52% yield. Under these conditions, aryl bromide was left unreacted upon complete consumption of the alkyl electrophile. According to our optimization guidelines, the options for improving the reaction yield are to: (1) increase the loading of (dtbbpy)Ni^{II}Br$_2$, (2) decrease the loading of Co^{II}(Pc), or (3) increase the loadings of alkyl bromide and TDAE. Through option (3), increasing the loadings of alkyl bromide and TDAE, the yield was improved to 65%. However, aryl bromide still remained after near consumption of alkyl bromide. In addition to option (3), using option (1), increasing the loading of (dtbbpy)Ni^{II}Br$_2$, an 80% yield was obtained.

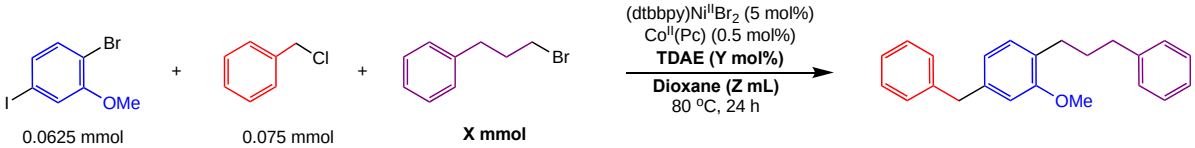
SXVII. Optimization of Single-Step One-Pot Three-Component Coupling

Procedure:

See section SV for representative experimental setup and workup. For individual reaction conditions, see Table S15 below.

Reaction Optimization Data:

Table S15. Reaction optimization of single-step one-pot cross-electrophile coupling of 1-bromo-4-iodo-2-methoxybenzene with 1-bromo-3-phenylpropane and benzyl chloride.



0.0625 mmol | 0.075 mmol | **X mmol**

1-bromo-3-phenylpropane (X mmol)	**TDAE (X mol%)**	**1,4-Dioxane (Z mL)**	**Product Yield (%)**
0.075	240	0.5	48
0.075	240	0.25	59
0.10	**260**	**0.25**	**76**
0.125	280	0.25	68

SXVIII. Procedure for and Optimization of Two-step One-Pot Three-Component Component Coupling for ^{1}H NMR Yields

Representative Procedure:

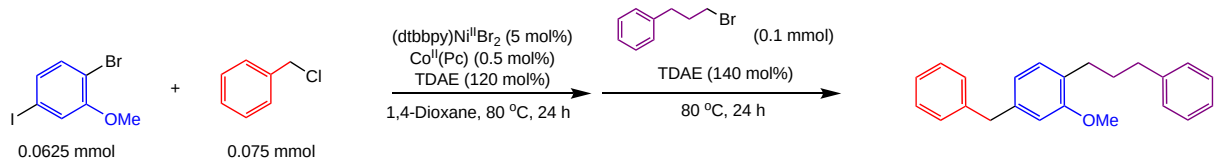


Figure S8. Two-step three-component cross-electrophile coupling of 1-bromo-4-iodo-2-methoxybenzene with 1-bromo-3-phenylpropane and benzyl chloride.

Outside of a glovebox 1.4 mg (0.0025 mmol) Co^{II}(Pc) was added to a 1 dram vial. The vial was pumped into a glovebox containing an N_2 atmosphere, where 2 mL 1,4-dioxane was added via syringe transfer using a 1 mL disposable syringe. To the same vial, 69.0 μL (0.6 mmol) benzyl chloride was added via a 100 μL gas-tight Hamilton syringe. The vial was capped tightly with a PTFE seal cap and removed from the glovebox, sonicated until the mixture was homogeneous, then brought back into the glovebox. Outside of a glovebox, 19.6 mg (0.0625 mmol) 1-bromo-4-iodo-2-methoxybenzene and 1.5 mg (0.00313 mmol) (dtbbpy)Ni^{II}Br$_2$ were weighed into a separate 1 dram vial equipped with a magnetic stir bar, which was pumped into a glovebox. Next, 260 μL of the prepared Co^{II}(Pc) solution was added via syringe transfer with a disposable 1 mL syringe, followed by 17.5 μL (0.075 mmol) TDAE via 50 μL gas-tight Hamilton syringe. The reaction vial was capped tightly with a PTFE seal cap and stirred at 80 °C for 24 hours. Next, the reaction vial was removed from heat and pumped into a nitrogen filled glovebox, where the cap was removed and 14.3 μL (0.1 mmol) ethyl 4-bromobutyrate was added via 50 μL gas-tight Hamilton syringe transfer followed by addition of 20.2 μL (0.0875 mmol) TDAE. The reaction was then tightly capped and stirred at 80 °C for 24 hours. The reaction vial was removed from heat, allowed to cool to room temperature, and diluted with 0.5 mL of ethyl acetate (EtOAc). The mixture was passed through a short silica plug (~1.5 inches) in a glass pipette, which was rinsed with 5 mL EtOAc. The filtrate was concentrated to dryness and the crude residue was taken up in $CDCl_3$ with added hexamethylbenzene as an internal standard. The reaction yields were determined by ^{1}H NMR spectroscopy. For individual reaction conditions, see Table 4 in the manuscript.

General Information:

Two-step three-component reactions were optimized by initially performing the first alkylation at the iodide site of the bromo(iodo)arene to ensure high yields, then performing the combination of the two alkylation reactions. See below for representative example.

Representative Data for Quantifying the First Alkylation Reaction of a Bromo(iodo)arene in a Discrete Step Followed by Two-Step One-Pot Cross-Electrophile Coupling:

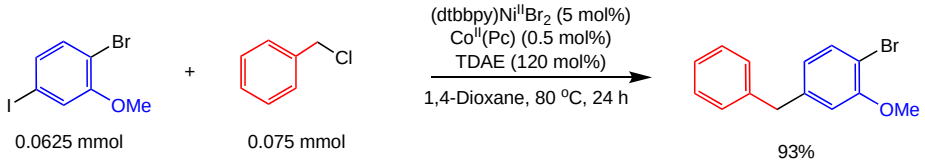


Figure S9. Cross-electrophile coupling of 1-bromo-4-iodo-2-methoxybenzene with benzyl chloride.

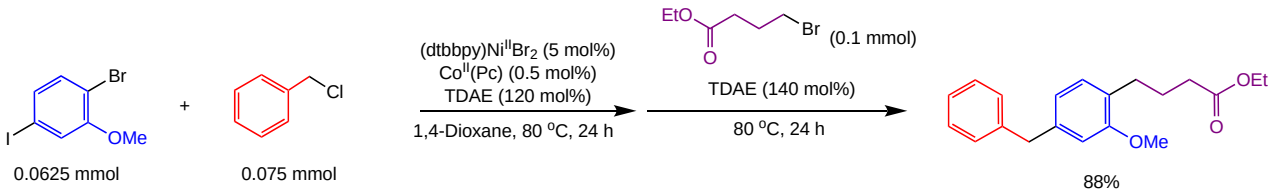


Figure S10. Cross-electrophile coupling of 1-bromo-4-iodo-2-methoxybenzene with benzyl chloride.

SXIX. Additional Reactions for Three-Component Cross-Electrophile Coupling

Procedure:

See section SXVIII for representative experimental setup and workup. For individual reaction conditions, see Figure S11 below.

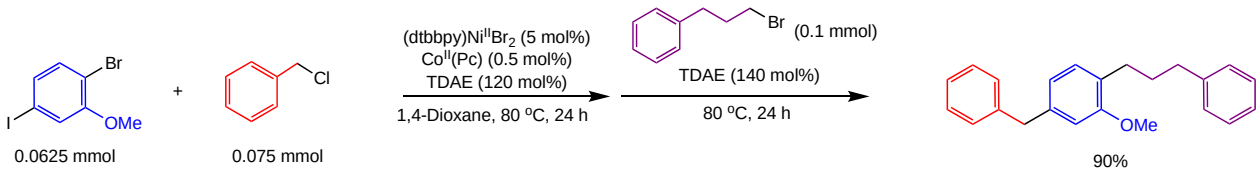


Figure S11. Additional reactions for alkyl halide substrate scope.

SXX. High Throughput Experimentation for Optimization of Drug-Like Aryl Halides

Representative Procedure:

Using Eppendorf pipettes in a nitrogen filled glove box, each 1 mL reaction vial (containing a parylene coated stir dowel) was charged with a 1,4-dioxane mixture of aryl halide (50 μL, 10 μmol, 1 equiv, 0.2 M), (dtbbpy)$Ni^{II}Br_2$ (12.5 μL, 0.5 μmol, 0.05 equiv, 0.04 M, *for 5 mol% loading, volumes scaled appropriately for other loadings*), Co^{II}(Pc) (12.5 μL, 0.5 μmol, 0.05 equiv, 0.04 M, *for 5 mol% loading, volumes scaled appropriately for other loadings*), alkyl halide (16 μl, 16 μmol, 1.6 equiv, 1 M), and TDAE (14 μL, 14 μmol, 1.4 equiv, 1 M). The final concentration of all reactions was 0.1 M. If multiple catalyst loadings were used on the same reaction block (different volumes of catalyst added to different vials), after the dosing of TDAE, 1,4-dioxane was added to vials, where required, to reach a final concentration of 0.1 M. The reaction plate was then sealed and placed in a preheated (80 °C) tumble stirrer. The reaction block was stirred at 80 °C for 36 hours. At this time, the reaction block was allowed to cool to 25 °C and removed from the tumble stirrer and glove box. The plate was centrifuged, opened to air, and diluted with 100 μL DMSO. The plate was then sealed, and the mixtures were stirred for 5 minutes on a tumble stirrer. The plate was opened, and 4 μL of the crude material was diluted in 200 μL DMSO. These solutions were used for analytical analysis. The reaction mixtures were analyzed by comparing the UV210 peak area for the product, aryl halide, protodehalogenation product, and aryl homocoupling product. Reactions that had the most product relative to aryl halide starting material and associated byproducts were repeated and the yield measured using ^1H NMR calibrated with hexamethylbenzene external standard. See section SXXVII for NMR yields.

Representative Schematics of HTE Plate Design for Reaction Optimization:

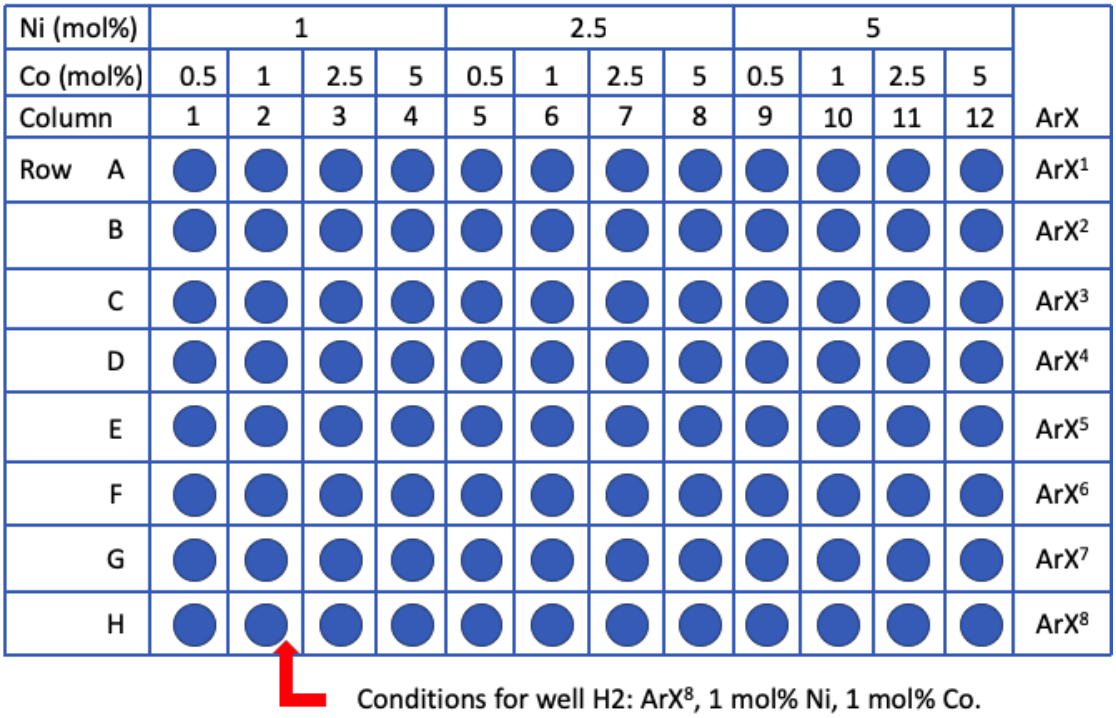
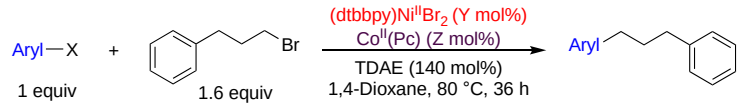


Figure S12. Generic scheme for reaction optimization of drug-like aryl halides using HTE. Table represents a 12x8 well plate (see Figure S1).



Y = 1 mol% Z = 0.5 mol% Aryl = 1	Y = 1 mol% Z = 1 mol% Aryl = 1	Y = 1 mol% Z = 2.5 mol% Aryl = 1	Y = 1 mol% Z = 5 mol% Aryl = 1	Y = 2.5 mol% Z = 0.5 mol% Aryl = 1	Y = 2.5 mol% Z = 1 mol% Aryl = 1	Y = 2.5 mol% Z = 2.5 mol% Aryl = 1	Y = 2.5 mol% Z = 5 mol% Aryl = 1	Y = 5 mol% Z = 0.5 mol% Aryl = 1	Y = 5 mol% Z = 1 mol% Aryl = 1	Y = 5 mol% Z = 2.5 mol% Aryl = 1	Y = 5 mol% Z = 5 mol% Aryl = 1
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Y = 1 mol% Z = 0.5 mol% Aryl = 7	Y = 1 mol% Z = 1 mol% Aryl = 7	Y = 1 mol% Z = 2.5 mol% Aryl = 7	Y = 1 mol% Z = 5 mol% Aryl = 7	Y = 2.5 mol% Z = 0.5 mol% Aryl = 7	Y = 2.5 mol% Z = 1 mol% Aryl = 7	Y = 2.5 mol% Z = 2.5 mol% Aryl = 7	Y = 2.5 mol% Z = 5 mol% Aryl = 7	Y = 5 mol% Z = 0.5 mol% Aryl = 7	Y = 5 mol% Z = 1 mol% Aryl = 7	Y = 5 mol% Z = 2.5 mol% Aryl = 7	Y = 5 mol% Z = 5 mol% Aryl = 7
Y = 1 mol% Z = 0.5 mol% Aryl = 8	Y = 1 mol% Z = 1 mol% Aryl = 8	Y = 1 mol% Z = 2.5 mol% Aryl = 8	Y = 1 mol% Z = 5 mol% Aryl = 8	Y = 2.5 mol% Z = 0.5 mol% Aryl = 8	Y = 2.5 mol% Z = 1 mol% Aryl = 8	Y = 2.5 mol% Z = 2.5 mol% Aryl = 8	Y = 2.5 mol% Z = 5 mol% Aryl = 8	Y = 5 mol% Z = 0.5 mol% Aryl = 8	Y = 5 mol% Z = 1 mol% Aryl = 8	Y = 5 mol% Z = 2.5 mol% Aryl = 8	Y = 5 mol% Z = 5 mol% Aryl = 8

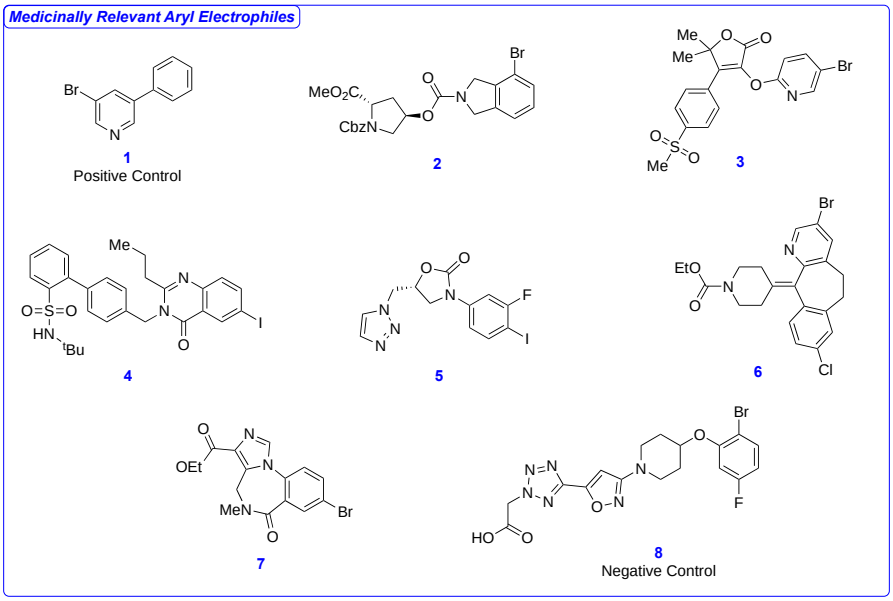


Figure S13. Example experimental design for HTE optimization of drug-like aryl halides. Table represents a 12x8 well plate (See Figure S1).

SXXI. Additional Reactions for Drug-Like Aryl Halides Cross-Electrophile Coupling

Procedure:

See section SXX for representative experimental setup, permutations of attempted reaction optimization conditions, and data analysis.

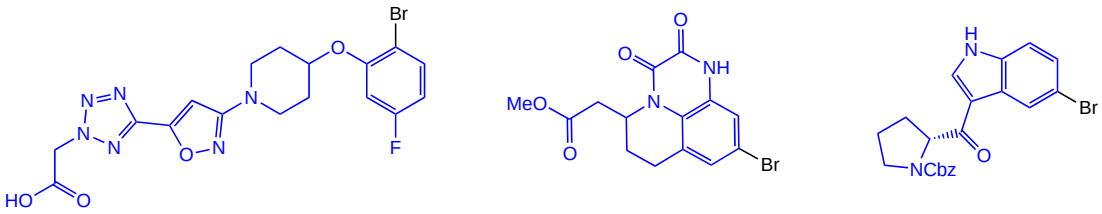


Figure S14. Drug-like aryl halides that did not show conversion to product when reacted with 1-bromo-3-phenylpropane.

SXXII. Parallel Library Synthesis Using Substrate 5f

Procedure for ^{1}H NMR Yields:

Reactions to obtain ^{1}H NMR yields were performed on 0.03 mmol scale. See SV for representative experimental setup and workup.

Procedure for High Throughput Experimentation:

See SXX for representative experimental setup. Values are reported as area percent of product relative to all known species derived from **5f** as determined by UV-Visible spectroscopy (see section SXX for details). The species observed include **5f**, the cross-electrophile coupling product of **5f**, the homocoupled product of **5f** (Aryl-Aryl), and the protodehalogenated product of **5f** (Aryl-H).

Data:

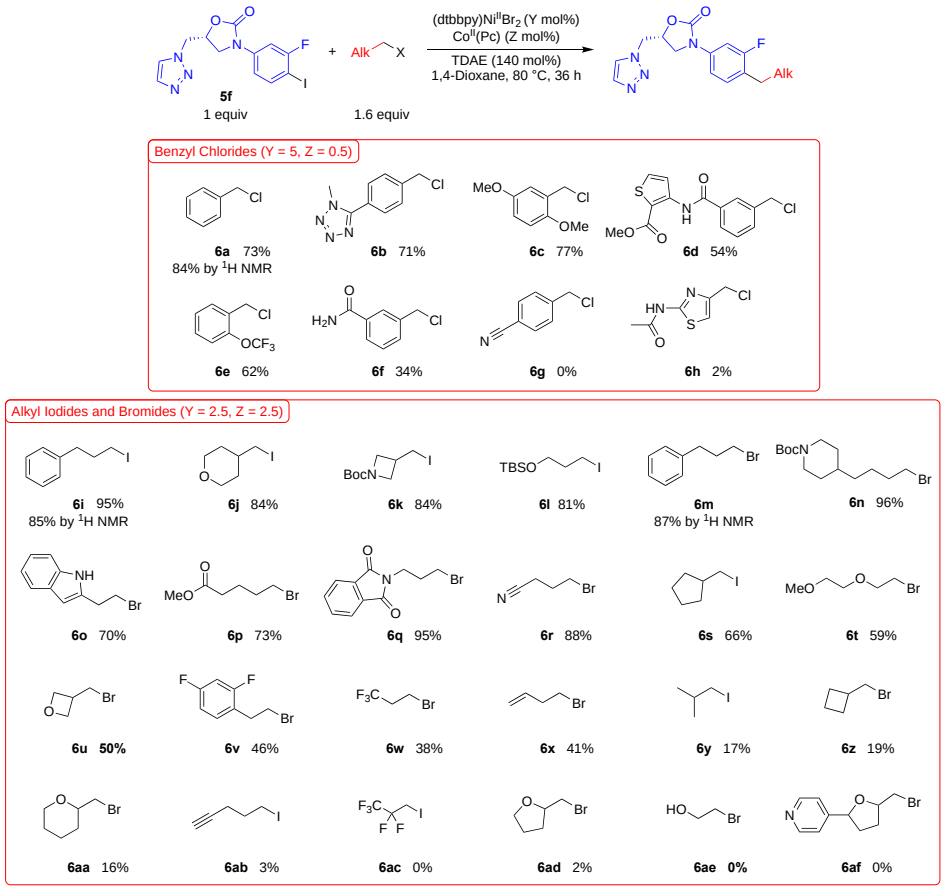


Figure S15. Dual catalyzed cross-electrophile coupling reactions between **5f** and a series of benzyl chlorides, alkyl iodides, and alkyl bromides. Values are reported as the conversion to product relative to all known species derived from **5f** determined by UV-Visible spectroscopy. NMR yields were determined by integration of ^{1}H NMR spectra against a hexamethylbenzene external standard.

SXXIII. Procedure and General Information for 3 mmol Scale Reaction of 5f with 1-Iodo-3-Phenylpropane

Procedure:

A 100-mL round bottom flask with a Kontes seal was charged with a stir bar, aryl halide **5f** (1.165 g, 3 mmol, 1.0 equiv), (dtbbpy)$Ni^{II}Br_2$ (36.2 mg, 2.5 mol %), and Co^{II}(Pc) (42.9 mg, 2.5 mol %). The flask was then moved into a nitrogen-filled glovebox. To the flask was then added 30 mL 1,4-dioxane and 1-iodo-3-phenylpropane (0.772 mL, 4.8 mmol, 1.6 equiv). The flask was then sealed and removed from the glovebox and sonicated for approximately 5 minutes or until the mixture was a fine slurry. The flask was then moved back into the glovebox and TDAE (0.977 mL, 4.2 mmol, 1.4 equiv) was added. The flask was quickly removed from the glovebox, and placed into an oil bath with a thermocouple. The reaction was stirred at 80 °C for 36 hours, during which time the color was deep blue and a precipitate formed (Figure S16). After 36 hours, the flask was opened and about 30 mL EtOAc was added. The reaction mixture was filtered through a celite pad, which was rinsed with EtOAc (3 x 30 mL). The filtrate was then concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel in 100% EtOAc. The clean fractions were collected and concentrated under reduced pressure until about 10 mL of EtOAc remained. Pentane was then added, which caused the precipitation of an off-white solid. The solid was collected via filtration, washed with pentane, and dried on a high vacuum line. The product was obtained in 64% yield (729 mg) (see general information below for further details, including discussion of isolated yield on large scale relative to ^{1}H NMR yield on small scale).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J*=15.2 Hz, 2H), 7.30-7.23 (m, 3H), 7.20-7.11 (m, 4H), 7.01-6.99 (m, 1H), 5.06 (sextet, *J*=4.4 Hz, 1H), 4.79-4.74 (m, 2H), 4.14 (t, *J*=9.1 Hz, 1H), 3.92-3.88 (m, 1H), 2.66-2.62 (m, 4H), 1.91 (quintet, *J*=7.8 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 161.97, 160.34, 153.37, 142.05, 136.7 (d, *J*=10.6 Hz), 134.77 (br s), 130.99 (d, *J*=6.7 Hz), 128.50 (d, *J*=9.4 Hz), 125.95, 125.52 (d, *J*=16.5 Hz), 125.21 (br s), 113.67 (d, *J*=3.3 Hz), 106.5 (d, *J*=28.2 Hz), 70.51, 52.11, 47.38, 35.52, 31.70, 28.29. ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ -115.75 (quartet, *J*=8.9 Hz). (HRMS) TOF MS ES+ (*m/z*) $[M+H]^+$ calculated for $[C_{21}H_{21}FN_4O_2+H]^+$ 381.1721; found 381.1727.

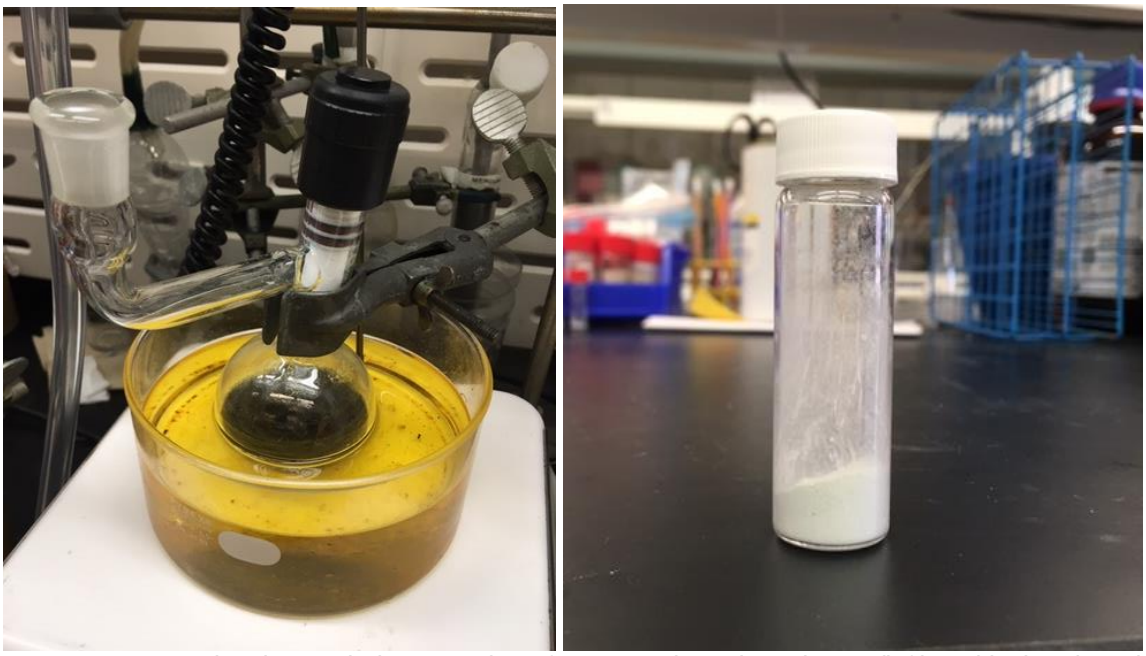


Figure S16. Image showing scaled-up reaction after approximately 24 hours (left) and isolated product (right).

General Information:

When the reaction was performed on a 3 mmol scale, ^{19}F NMR analysis of the crude reaction mixture showed 95:5 ratio of product to starting material, with no other species present (Figure S17). This result is consistent with the 96:4 ratio of product to starting material observed by ^{19}F NMR analysis of the crude reaction mixture when the same reaction was performed on 0.03 mmol scale (Figure S18). These data suggest that our reaction conditions can be readily used to scale up synthetic protocols for medicinally relevant substrates. However, there was a discrepancy in product yield between the 85% yield obtained on 0.03 mmol scale, which was determined by ^{1}H NMR integration of the crude reaction mixture against a hexamethylbenzene external standard, with the 64% yield obtained on 3 mmol scale, which was determined by the mass of the isolated product after purification. We propose that this discrepancy is likely due to the fact that product was lost during purification for the quantification of the 3 mmol scale reaction. One possible explanation is that significant amounts of product remained in solution after filtration and the filtrate was not recovered.

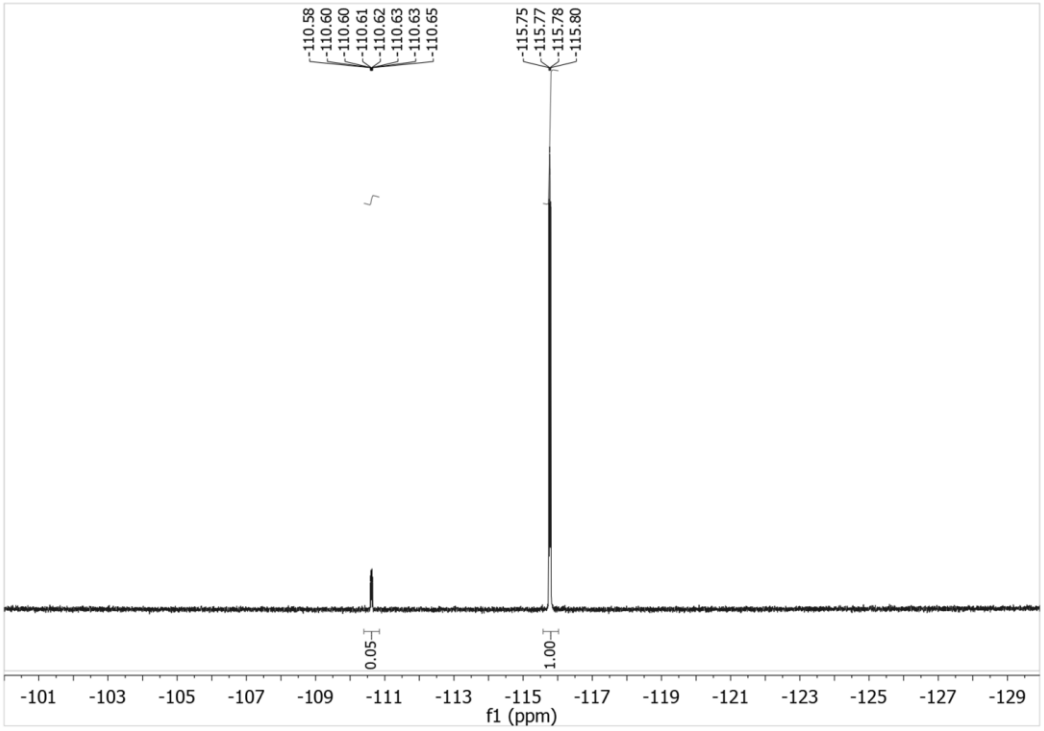


Figure S17. ^{19}F NMR spectrum ($CDCl_3$) of crude reaction mixture for product derived from the cross-electrophile coupling of **5f** with 1-iodo-3-phenylpropane on a 3 mmol scale.

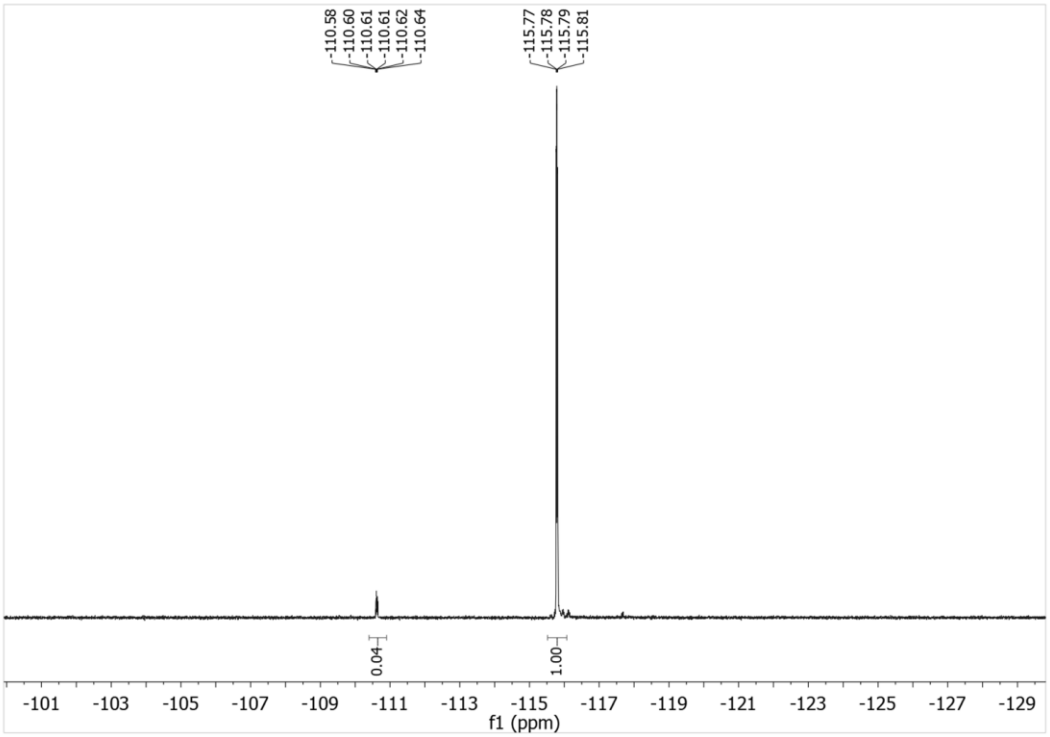


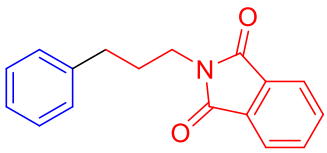
Figure S18. ^{19}F NMR spectrum ($CDCl_3$) of crude reaction mixture for product derived from the cross-electrophile coupling of **5f** with 1-iodo-3-phenylpropane on a 0.03 mmol scale.

SXXIV. Isolation Procedures and Characterization for Products of Two-Component Cross-Electrophile Coupling

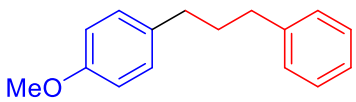
Procedure for Isolation Scale Reactions of Following Substrates:

See section SV for representative experimental setup. Reactions were typically performed on 0.1875 mmol scale of aryl electrophile (other reagents scaled linearly). See Figure 4 in the manuscript for individual reaction conditions. The reaction vial was removed from heat, allowed to cool to room temperature, and diluted with 0.5 mL of ethyl acetate (EtOAc). The mixture was passed through a short celite plug (~1.5 inches) in a glass pipette, which was rinsed with 5 mL EtOAc. The filtrate was concentrated to dryness and the crude residue was purified by silica gel column chromatography.

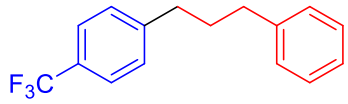
Aryl Electrophiles



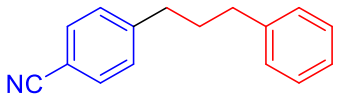
2-(3-phenylpropyl)isoindoline-1,3-dione, derived from **4a**: Eluent: gravity column in 10% EtOAc in petroleum ether. White solid, 83% yield (41.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.82 (m, 2H), 7.71-7.70 (m, 2H), 7.27-7.24 (m, 2H), 7.25 (t, *J*=7.4 Hz, 2H), 7.20 (d, *J*=7.1 Hz, 2H), 7.14 (t, *J*=7.2 Hz, 1H), 3.75 (t, *J*=7.2 Hz, 2H), 2.69 (t, *J*=8.0 Hz, 2H), 2.04 (quintet, *J*=8.0 Hz, 2H). The ^{1}H NMR data are consistent with a previous literature report.[6]



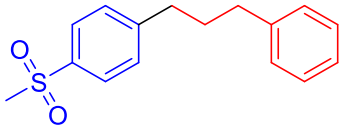
1-phenyl-3-(4-methoxyphenyl)propane, derived from **4b**: Eluent: 5% EtOAc in hexanes. Colorless oil, 70% yield (42.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, 2H), 7.20-7.18 (m, 3H), 7.11 (d, *J*=8.5 Hz, 2H), 6.84 (d, *J*=8.5 Hz, 2H), 3.79 (s, 3H), 2.67-2.59 (m, 4H), 1.94 (quintet, *J*=7.8 Hz, 2H). The ^{1}H NMR data are consistent with a previous literature report.[7]



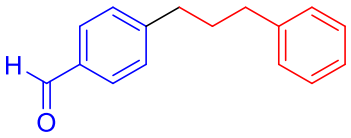
1-phenyl-3-(4-trifluoromethylphenyl)propane, derived from **4c**: Eluent: 100% pentane. Colorless oil, 88% yield (43.6 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J*=8.0 Hz, 2H), 7.32-7.29 (m, 4H), 7.23-7.19 (m, 3H), 2.74-2.65 (m, 4H), 1.99 (quintet, *J*=7.8 Hz, 2H). ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ -62.29 (s). The ^{1}H NMR data are consistent with a previous literature report.[8]



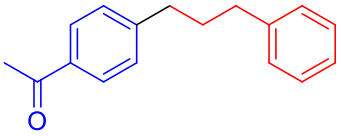
4-(3-phenylpropyl)benzonitrile, derived from **4d**: Eluent: 5% EtOAc in hexanes. Colorless oil, 86% yield (35.7 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J*=8.1 Hz, 2H), 7.32-7.26 (m, 4H), 7.22-7.17 (m, 3H), 2.72-2.64 (m, 4H), 1.97 (quintet, *J*=7.8 Hz, 2H). The ^{1}H NMR data are consistent with a previous literature report.[8]



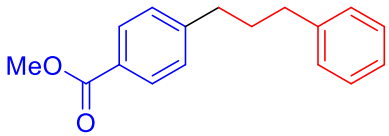
1-(methylsulfonyl)-4-(3-phenylpropyl)benzene, derived from **4e**: Eluent: 30% EtOAc in hexanes. Pale yellow oil, 93% yield (47.7 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J*=7.9 Hz, 2H), 7.37 (d, *J*=8.0 Hz, 2H), 7.31-7.26 (m, 2H), 7.22-7.17 (m, 3H), 3.04 (s, 3H), 2.74 (t, *J*=7.7 Hz, 2H), 2.66 (t, *J*=7.7 Hz, 2H), 1.99 (quintet, *J*=7.9 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 149.09, 141.71, 138.19, 129.51, 128.57, 128.53, 127.62, 126.13, 44.74, 35.45, 35.43, 32.66. (LRMS) GCMS EI (*m/z*) $[M]^+$ calculated for $[C_{16}H_{18}O_2S]^+$ 274.1; found 274.1.



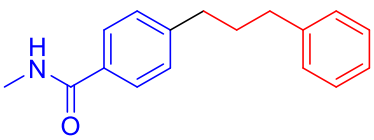
4-(3-phenylpropyl)benzaldehyde, derived from **4f**: Eluent: 5% EtOAc in hexanes. Colorless oil, 88% yield (37.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.79 (d, *J*=8.1 Hz, 2H), 7.32 (d, *J*=8.0 Hz, 2H), 7.29-7.24 (m, 2H), 7.20-7.15 (m, 3H), 2.71 (t, *J*=7.7 Hz, 2H), 2.65 (t, *J*=7.7 Hz, 2H), 1.98 (quintet, *J*=7.8 Hz, 2H). The ^{1}H NMR data are consistent with a previous literature report.[9]



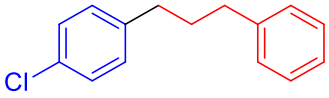
4-(3-phenylpropyl)benzophenone, derived from **4g**: Eluent: 5% EtOAc in hexanes. Colorless oil, 89% yield (39.7 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J*=8.1 Hz, 2H), 7.31-7.27 (m, 4H), 7.21-7.17 (m, 3H), 2.73-2.64 (m, 4H), 2.59 (s, 3H), 1.98 (quintet, *J*=7.9 Hz, 2H). The ^{1}H NMR data are consistent with a previous literature report.[10]



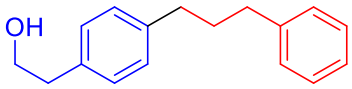
4-(3-phenylpropyl)methyl-benzoate, derived from **4h**: Eluent: 5% EtOAc in hexanes. Colorless oil, 88% yield (41.9 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J*=8.0 Hz, 2H), 7.30-7.27 (t, *J*=7.4 Hz, 2H), 7.25 (d, *J*=8.1 Hz, 2H), 7.21-7.17 (m, 3H), 3.90 (s, 3H), 2.70 (t, *J*=7.8 Hz, 2H), 2.65 (t, *J*=7.8 Hz, 2H), 1.98 (quintet, *J*=7.7 Hz, 2H). The ^{1}H NMR data are consistent with a previous literature report.[11]



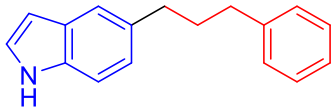
***N*-methyl-4-(3-phenylpropyl)benzamide**, derived from **4i**: Eluent: 70% EtOAc in hexanes. White solid, 75% yield (35.5 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J*=8.1 Hz, 2H), 7.30-7.26 (m, 2H), 7.24-7.16 (m, 5H), 6.16 (br s, 1H), 3.00 (d, *J*=4.9 Hz, 3H), 2.66 (quintet, *J*=8.0 Hz, 4H), 1.96 (quintet, *J*=7.8 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.31, 146.14, 142.08, 132.31, 128.73, 128.54, 128.48, 127.03, 125.97, 35.46, 35.35, 32.80, 26.93. (LRMS) GCMS EI (*m/z*) $[M]^+$ calculated for $[C_{17}H_{19}NO]^+$ 253.2; found 253.2.



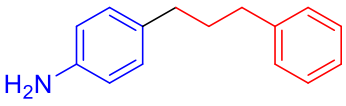
1-chloro-4-(3-phenylpropyl)benzene, derived from **4j**: Eluent: 100% pentane. Colorless oil, 67% yield (43.3 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.31-7.29 (m, 2H), 7.25-7.22 (m, 3H), 7.16 (d, J= 8.3 Hz, 2H), 2.71-2.66 (m, 4H), 1.99 (quintet, J= 7.8 Hz, 2H). The ^{1}H NMR data are consistent with a previous literature report.[12]



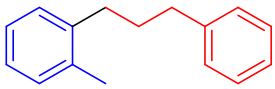
2-(4-(3-phenylpropyl)phenyl)ethanol, derived from **4k**: Eluent: 5% EtOAc in hexanes. Colorless oil, 70% yield (31.5 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (quartet, *J*=7.2 Hz, 2H), 7.21-7.18 (m, 3H), 7.15 (s, 4H), 3.85 (t, *J*=6.5 Hz, 2H), 2.84 (t, *J*=6.6 Hz, 2H), 2.65 (quartet, *J*=7.3 Hz, 4H), 1.96 (quintet, *J*=7.8 Hz, 2H), 1.46 (br s, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 142.39, 140.60, 135.83, 129.10, 128.80, 128.56, 128.43, 125.86, 63.87, 38.92, 35.58, 35.16, 33.08. (LRMS) GCMS EI (*m/z*) $[M]^+$ calculated for $[C_{17}H_{20}O]^+$ 240.2; found 240.2.



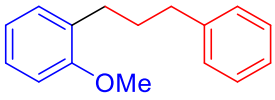
5-(3-phenylpropyl)-1*H*-indole, derived from **4l**: Eluent: 22% EtOAc in hexanes. Pale yellow oil, 73% yield (32.1 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (br s, 1H), 7.44 (s, 1H), 7.30-7.23 (m, 3H), 7.20-7.15 (m, 4H), 7.03 (d, *J*=8.3 Hz, 1H), 6.48 (br s, 1H), 2.75 (t, *J*=7.9 Hz, 2H), 2.67 (t, *J*=7.9 Hz, 2H), 2.01 (quintet, *J*=7.8 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 142.77, 134.46, 133.80, 128.61, 128.38, 128.18, 125.75, 124.37, 120.02, 110.87, 102.40, 35.70, 35.63, 33.86. (LRMS) GCMS EI (*m/z*) $[M]^+$ calculated for $[C_{17}H_{17}N]^+$ 235.1; found 235.2.



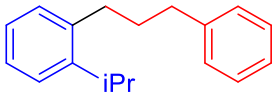
4-(3-phenylpropyl)aniline, derived from **4m**: Eluent: Gradient of 35-40% EtOAc in hexanes. Pale yellow oil, 71% yield (28.1 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.24 (m, 2H), 7.17 (d, *J*=6.8 Hz, 3H), 6.96 (d, *J*=8.1 Hz, 2H), 6.61 (d, *J*=8.1 Hz, 2H) 3.50 (br s, 2H), 2.62 (t, *J*=7.7 Hz, 2H), 2.54 (t, *J*=7.7 Hz, 2H), 1.89 (quintet, *J*=7.8 Hz, 2H). The ^{1}H NMR data are consistent with a previous literature report.[13]



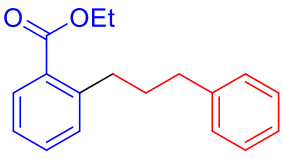
2-(3-phenylpropyl)toluene, derived from **4n**: Eluent: gradient of 0-5% diethyl ether in pentane. Colorless oil, 77% yield (30.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, *J*=7.6 Hz, 2H), 7.22-7.18 (m, 3H), 7.14-7.10 (m, 4H), 2.71 (t, *J*=7.6 Hz, 2H), 2.65 (t, *J*=7.6 Hz, 2H), 2.28 (s, 3H), 1.93 (quintet, *J*=7.9 Hz, 2H). The ^{1}H NMR data are consistent with a previous literature report.[1]



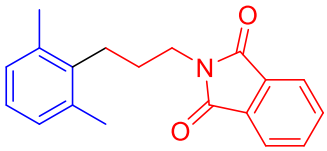
1-phenyl-3-(2-methoxyphenyl)propane, derived from **4o**: Eluent: gradient of 0-5% diethyl ether in pentane. Colorless oil, 76% yield (33.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (m, 2H), 7.21-7.12 (m, 5H), 6.90-6.83 (m, 2H), 3.80 (s, 3H), 2.67 (t, *J*=7.7 Hz, 4H), 1.93 (quintet, *J*=7.8, 2H). The ^{1}H NMR data are consistent with a previous literature report.[14]



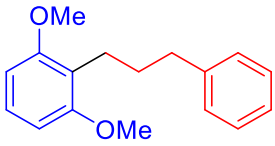
1-phenyl-3-(2-isopropylphenyl)propane, derived from **4p**: Eluent: Gradient of 0-3% diethyl ether in pentane. Colorless oil, 83% yield (37.1 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.26 (m, 3H), 7.22-7.18 (m, 4H), 7.14-7.09 (m, 2H), 3.11 (septet, *J*=6.9 Hz, 1H), 2.71 (quartet, *J*=7.9 Hz, 4H), 1.93 (quintet, *J*=7.9 Hz, 2H), 1.22 (d, *J*=6.9 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 146.69, 142.40, 139.15, 129.46, 128.54, 128.44, 126.40, 125.90, 125.65, 125.39, 36.03, 33.36, 32.57, 28.69, 24.19. (LRMS) GCMS EI (*m/z*) $[M]^+$ calculated for $[C_{18}H_{22}]^+$ 238.2; found 238.2.



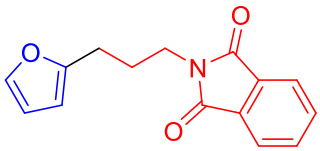
2-(3-phenylpropyl)ethyl-benzoate, derived from **4q**: Eluent: 5% EtOAc in hexanes. Colorless oil, 77% yield (38.7 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J*=7.4 Hz, 1H), 7.40 (t, *J*=8.6 Hz, 1H), 7.30-7.16 (m, 7H), 4.34 (quartet, *J*=7.1 Hz, 2H), 3.01 (t, *J*=7.9 Hz, 2H), 2.70 (t, *J*=7.9 Hz, 2H), 1.95 (quintet, *J*=7.9 Hz, 2H), 1.39 (t, *J*=7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.99, 143.99, 142.47, 131.83, 130.99, 130.70, 130.12, 128.55, 128.39, 125.94, 125.82, 60.92, 36.07, 34.29, 33.53, 14.45. (LRMS) GCMS EI (*m/z*) $[M]^+$ calculated for $[C_{18}H_{20}O_2]^+$ 268.1; found 268.1.



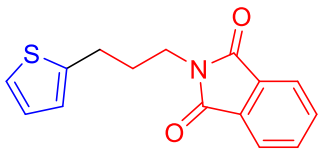
2-(3-(2,6-dimethylphenyl)propyl)isoindoline-1,3-dione, derived from **4r**: Eluent: gravity column in 10% EtOAc in petroleum ether. White solid, 87% yield (47.8 mg). ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.87-7.85 (m, 2H), 7.73-7.71 (m, 2H), 6.98 (s, 3H), 3.82 (t, *J*=7.3 Hz, 2H), 2.69-2.66 (m, 2H), 2.29 (s, 6H), 1.89-1.83 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.49, 138.08, 136.00, 134.04, 132.18, 128.25, 125.90, 123.33, 38.45, 27.84, 27.14, 19.83. (LRMS) GCMS EI (*m/z*) $[M]^+$ calculated for $[C_{19}H_{19}NO_2]^+$ 293.1; found 293.1.



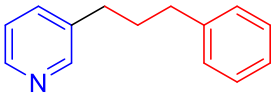
3-(3-phenylpropyl)-2,6-dimethoxybenzene, derived from **4s**: Eluent: 4% EtOAc in hexanes. Colorless oil, 73% yield (48.1 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, *J*=7.3 Hz, 2H), 7.21 (d, *J*=7.9 Hz, 2H), 7.15 (t, *J*=7.3 Hz, 1H), 7.11 (t, *J*=8.3 Hz, 1H), 6.53 (d, *J*=8.3 Hz, 1H), 3.78 (s, 6H), 2.72 (t, *J*=7.7 Hz, 2H), 2.66 (t, *J*=7.7 Hz, 2H), 1.82 (quintet, *J*=7.9 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 158.45, 143.21, 128.52, 128.21, 126.71, 125.53, 119.16, 103.77, 55.77, 36.11, 30.79, 22.99. (LRMS) GCMS EI (*m/z*) $[M]^+$ calculated for $[C_{17}H_{20}O_2]^+$ 256.2; found 256.1.



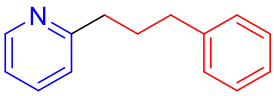
2-(3-(2-furanyl)propyl)isoindoline-1,3-dione, derived from **4t**: Eluent: gravity column in 10% EtOAc in petroleum ether. White solid, 72% yield (34.3 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.83 (m, 2H), 7.72-7.70 (m, 2H), 7.26 (s, 1H), 6.23 (t, *J*=1.9 Hz, 1H), 6.04 (d, *J*=2.8 Hz, 1H), 3.76 (t, *J*=7.2 Hz, 2H), 2.70 (t, *J*=7.5 Hz, 2H), 2.05 (quintet, *J*=7.2 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.43, 154.78, 141.11, 133.99, 132.21, 123.27, 110.19, 105.32, 37.59, 26.90, 25.59. (LRMS) GCMS EI (*m/z*) $[M]^+$ calculated for $[C15H13NO_3]^+$ 255.1; found 255.1.



2-(3-(2-thiophenyl)propyl)isoindoline-1,3-dione, derived from **4u**: Eluent: gravity column in 10% EtOAc in petroleum ether. White solid, 73% yield (37.1 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.83 (m, 2H), 7.71-7.70 (m, 2H), 7.09 (d, *J*=5.1 Hz, 1H), 6.88 (t, *J*=4.9 Hz, 1H), 6.83 (br s, 1H), 3.77 (t, *J*=7.1 Hz, 2H), 2.90 (t, *J*=7.7 Hz, 2H), 2.09 (quintet, *J*=7.4 Hz, 2H). The ^{1}H NMR data are consistent with a previous literature report.[15]

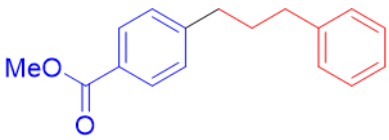


3-(3-phenylpropyl)pyridine, derived from **4v**: Eluent: 50% EtOAc in hexanes. Colorless oil, 71% yield (26.3 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 2H), 7.49 (d, *J*=7.7 Hz, 1H), 7.29 (quartet, *J*=7.4 Hz, 2H), 7.22-7.17 (m, 4H), 2.66 (quartet, *J*=7.7 Hz, 4H), 1.97 (quintet, *J*=7.8 Hz, 2H). The ^{1}H NMR data are consistent with a previous literature report.[16]

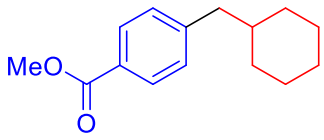


2-(3-phenylpropyl)pyridine, derived from **4w**: Eluent: 20% EtOAc and 1% Et_3N in hexanes. Colorless oil, 41% yield (37.0 mg). Isolated yield accounts for a roughly 1% impurity of 4,4'-ditertbutyl-2,2'-bipyridine. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J*=4.4 Hz, 1H), 7.58 (td, *J*=7.7, 1.7 Hz, 1H), 7.29-7.26 (m, 2H), 7.20-7.16 (m, 3H), 7.13 (d, *J*=7.8, 1H), 7.11-7.08 (m, 1H), 2.83 (t, *J*=7.8 Hz, 2H), 2.69 (t, *J*=7.8 Hz, 2H), 2.08 (quintet, *J*=7.8, 2H). The ^{1}H NMR data are consistent with a previous literature report.[17]

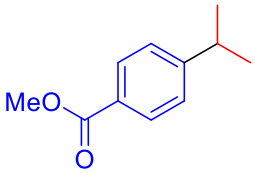
Alkyl Electrophiles



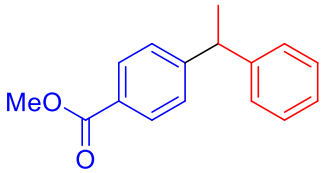
4-(3-phenylpropyl)methyl-benzoate, derived from **4x**: Eluent: 10% EtOAc in hexanes. Colorless oil, 82% yield (39.2 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J*=8.1 Hz, 2H), 7.28 (t, *J*=7.4 Hz, 2H), 7.24 (d, *J*=8.0 Hz, 2H), 7.20-7.17 (m, 3H), 3.90 (s, 3H), 2.70 (t, *J*=7.8 Hz, 2H), 2.65 (t, *J*=7.8 Hz, 2H), 1.97 (quintet, *J*=7.6 Hz, 2H). The ^{1}H NMR data are consistent with a previous literature report.[11]



Methyl 4-(cyclohexylmethyl)benzoate, derived from **4y**: Eluent: gravity column in 10% EtOAc in hexanes. Colorless oil, 87% yield (40.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J= Hz, 2H), 7.20 (d, J= Hz, 2H), 3.90 (s, 3H), 2.53 (d, J= Hz, 2H), 1.69-1.64 (m, 5H), 1.57-1.51 (m, 1H), 1.22-1.13 (m, 3H), 0.97-0.91 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.34, 147.13, 129.30, 127.74, 52.07, 44.24, 39.77, 33.23, 26.59, 26.37. (LRMS) GCMS EI (*m/z*) $[M]^+$ calculated for $[C_{15}H_{20}O_2]^+$ 232.2; found 232.2.

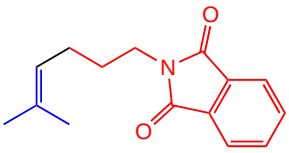


Methyl 4-isopropylbenzoate, derived from **4z**: Eluent: 40% EtOAc in hexanes by preparative TLC. Pale yellow oil, 54% yield (18.1 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J*=8.3 Hz, 2H), 7.29 (d, *J*= 8.2 Hz, 2H), 3.90 (s, 3H), 2.96 (quintet, *J*=6.9 Hz, 1H), 1.27 (d, *J*=6.9 Hz, 6H). The ^{1}H NMR data are consistent with a previous literature report.[18]



Methyl 4-(1-phenylethyl)benzoate, derived from **4aa**: Eluent: 5% EtOAc in hexanes. Colorless oil, 46% yield (20.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J*=8.3 Hz, 2H), 7.31-7.28 (m, 4H), 7.22-7.19 (m, 3H), 4.21 (quartet, *J*=7.2 Hz, 1H), 3.90 (s, 3H), 1.66 (d, *J*=7.2 Hz, 3H). The ^{1}H NMR data are consistent with a previous literature report.[19]

Vinyl Electrophiles

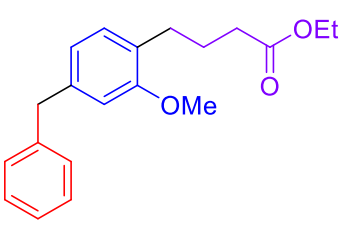


2-(5-methylhex-4-enyl)isoindoline-1,3-dione: Eluent: 10% EtOAc in hexanes. Colorless oil, 74% yield (33.8 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.80 (m, 2 H), 7.71–7.67 (m, 2 H), 5.12–5.06 (m, 1 H), 3.67 (t, J = 7.1 Hz, 2 H), 2.03 (q, J = 7.1 Hz, 2 H), 1.71 (quint, J = 7.6 Hz, 2 H), 1.61 (s, 3 H), 1.57 (s, 3 H). The ^{1}H NMR data are consistent with a previous literature report.[20]

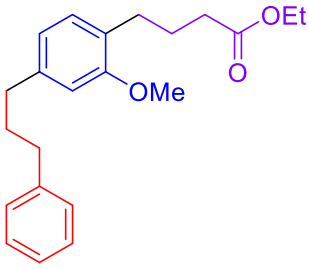
SXXV. Isolation Procedures and Characterization for Products of Two-step One-Pot Three-Component Component Coupling

Procedure:

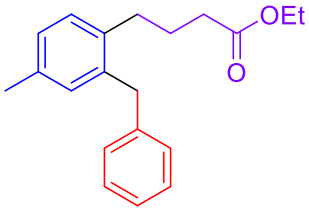
See section SXVIII for representative experimental setup, but reactions were performed on 0.125 mmol scale of aryl electrophile (other reagents scaled linearly). See Table 4 in manuscript for individual reaction conditions. The reaction vial was removed from heat, allowed to cool to room temperature, and diluted with 0.5 mL of ethyl acetate (EtOAc). The mixture was passed through a short celite plug (~1.5 inches) in a glass pipette, which was rinsed with 5 mL EtOAc. The filtrate was concentrated to dryness and the crude residue was purified by silica gel column chromatography.



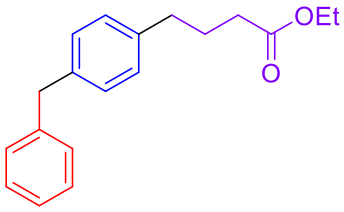
Ethyl 4-(4-benzyl-3-methoxyphenyl)butanoate, Table 4, Entry 1: Eluent: 10% EtOAc in hexanes. Colorless oil, 82% yield (32.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 7.21-7.19 (m, 3H), 7.03 (d, *J*=7.5 Hz, 1H), 6.71 (d, *J*=7.6 Hz, 1H), 6.66 (s, 1H), 4.11 (quartet, *J*=7.1 Hz, 2H), 3.95 (s, 2H), 3.76 (s, 3H), 2.61 (t, *J*=7.6 Hz, 2H), 2.31 (t, *J*=7.7 Hz, 2H), 1.90 (quintet, *J*=7.5 Hz, 2H), 1.24 (t, *J*=7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 173.92, 157.64, 141.30, 140.37, 130.06, 128.99, 128.57, 127.67, 126.17, 120.94, 111.12, 60.29, 55.31, 42.07, 34.11, 29.37, 25.23, 14.41. (LRMS) GCMS EI (*m/z*) $[M]^+$ calculated for $[C_{20}H_{24}O_3]^+$ 312.2; found 312.2.



Ethyl 4-(3-methoxy-4-(3-phenylpropyl)phenyl)butanoate, Table 4, Entry 2: Eluent: 5% EtOAc in hexanes. Colorless oil, 84% yield (35.8 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (quartet, *J*=6.8 Hz, 2H), 7.19-7.15 (m, 3H), 7.00 (d, *J*=7.5 Hz, 1H), 6.69 (d, *J*=7.6 Hz, 1H), 6.64 (s, 1H), 4.10 (quartet, *J*=7.1 Hz, 2H), 3.78 (s, 3H), 2.67-2.58 (m, overlapping signals, 6H), 2.30 (t, *J*=7.7 Hz, 2H), 1.98-1.85 (m, 4H), 1.23 (t, *J*=7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 173.92, 157.54, 142.44, 141.67, 129.93, 128.58, 128.43, 127.29, 125.86, 120.36, 110.70, 60.27, 55.33, 35.65, 34.13, 33.08, 29.37, 25.29, 14.41. (LRMS) GCMS (*m/z*) EI $[M]^+$ calculated for $[C_{22}H_{28}O_3]^+$ 340.2; found 340.2.



Ethyl 4-(2-benzyl-4-methylphenyl)butanoate, Table 4, Entry 3: Eluent: 5% EtOAc in hexanes. Colorless oil, 91% yield (26.6 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.24 (m, 2H), 7.19-7.15 (m, 1H), 7.12-7.06 (m, 3H), 7.00 (d, *J*=7.8 Hz, 1H), 6.93 (s, 1H), 4.10 (quartet, *J*=7.1 Hz, 2H), 3.99 (s, 2H), 2.57 (t, *J*=8.1 Hz, 2H), 2.30-2.26 (m, overlapping signals, 5H), 1.81 (quintet, *J*=7.7 Hz, 2H), 1.23 (t, *J*=7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 173.59, 141.11, 138.34, 136.94, 135.81, 131.43, 129.52, 128.80, 128.49, 127.42, 126.02, 60.38, 38.85, 34.13, 31.92, 26.19, 21.13, 14.39. (LRMS) GCMS EI (*m/z*) $[M]^+$ calculated for $[C_{20}H_{24}O_2]^+$ 296.2; found 296.1.



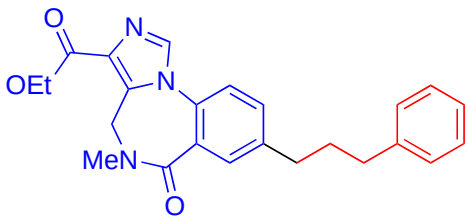
Ethyl 4-(4-benzylphenyl)butanoate, Table 4, Entry 4: Eluent: 8% EtOAc in hexanes. Colorless oil, 70% yield (24.8 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H), 7.21-7.18 (m, 3H), 7.10 (s, 4H), 4.12 (quartet, *J*=7.1 Hz, 2H), 3.95 (s, 2H), 2.62 (t, *J*=7.5 Hz, 2H), 2.31 (t, *J*=7.5 Hz, 2H), 1.94 (quintet, *J*=7.5 Hz, 2H), 1.25 (t, *J*=7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 173.64, 141.40, 139.28, 138.87, 129.04, 128.71, 128.57, 126.15, 60.38, 41.69, 34.88, 33.86, 26.71, 14.40. (LRMS) GCMS EI (*m/z*) $[M]^+$ calculated for $[C_{19}H_{22}O_2]^+$ 282.2; found 282.1.

SXXVI. Isolation Procedures and Characterization for Products of Two-Component Cross-Electrophile Coupling with Drug-Like Aryl Halides

General Information:

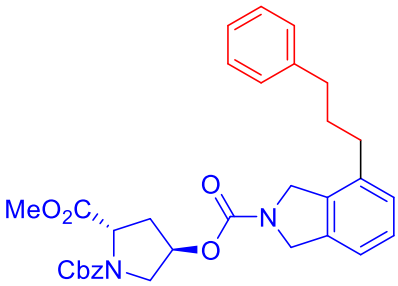
Products derived from the cross-electrophile coupling of 1-bromo-3-phenylpropane with aryl halides **5a** and **5f** were isolated using silica gel chromatography according to the corresponding procedures (see below for product derived from **5a** and see section SXXIII for product derived from **5f**).

Products derived from the cross-electrophile coupling of 1-bromo-3-phenylpropane with all other drug-like aryl halides were isolated from purification of the combined fractions for a given aryl halide from HTE experiments (see section SXX for representative HTE experimental setup). This mixture was purified by initial filtration using a 0.45 μM syringe filter and followed by preparatory scale reverse-phase HPLC (aqueous phase: 8% NH_4OH, organic phase: MeCN, column: Waters XBridge Prep C18, 5 μM, 19x100 mm, unless otherwise specified). The isolated products were used to confirm the ^{1}H NMR yields reported in Figure 5 (see section SXXVII). The products were purified using mass-directed purification, with priority weighted on purity, not material recovery, so in some cases, only milligram quantities of products were isolated, obscuring the physical appearance of some samples. In these cases, the sample is described as: "oil (residue)".

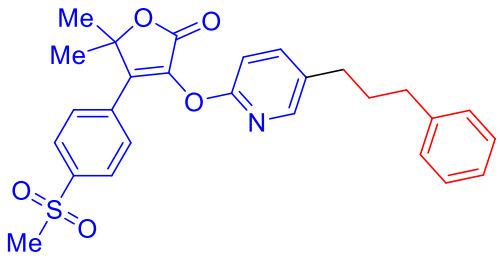


Product derived from 5a, Figure 5: The isolation scale experimental setup follows that is described in section SV on a 0.100 mmol scale of aryl halide (all other reagents scaled linearly), see Figure 5 exact reaction conditions. The reaction vial was removed from heat, allowed to cool to room temperature, and diluted with 0.5 mL of ethyl acetate (EtOAc). The mixture was passed through a short celite plug (~1.5 inches) in a glass pipette, which was rinsed with 5 mL EtOAc. The filtrate was concentrated to dryness and the crude residue was purified by silica gel column chromatography. Eluent: 100% EtOAc. Off-white powder, 72% yield (29.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J*=6.6 Hz, 2H), 7.42 (d, *J*=8.2 Hz, 1H), 7.33-7.26 (m, 3H), 7.20-7.16 (m, 3H), 5.17 (br s, 1H), 4.42-4.35 (br m, overlapping signals, 3H), 3.23 (s, 3H), 2.74 (t, *J*=7.6 Hz, 2H), 2.68 (t, *J*=7.6 Hz, 2H), 2.01 (quintet, *J*=7.7 Hz, 2H),

1.44 (t, *J*=7.2 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 166.77, 163.21, 143.36, 141.72, 135.68, 135.00, 132.83, 132.38, 130.05, 129.01, 128.64, 128.51, 126.06, 121.89, 61.05, 42.51, 35.97, 35.45, 34.84, 32.64, 14.52. (HRMS) TOF MS ES+ (*m/z*) $[M+H]^+$ calculated for $[C_{24}H_{25}N_3O_2+H]^+$ 404.1969; found 404.1962.

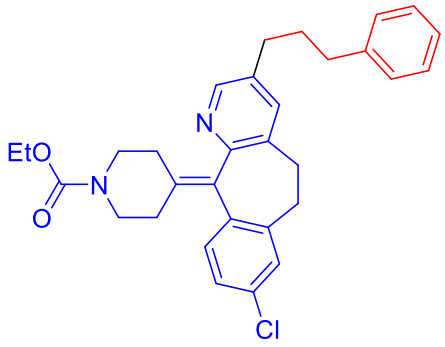


Product derived from 5b, Figure 5: Pale yellow oil. Purification method: 25 mL/min, 12-minute run, ramp from 52% to 82% MeCN. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38-7.25 (m, 7H), 7.24-7.10 (m, 6H), 5.20 (br s, 1H), 5.15-4.98 (m, overlapping signals, 2H), 4.66-4.56 (m, 3H), 4.52-4.41 (m, 2H), 3.77-3.63 (m, overlapping signals, 3H), 3.58 (d, *J*=7.1 Hz, 1H), 2.61 (quartet, *J*=7.7 Hz, 2H), 2.55 (t, *J*=7.8 Hz, 1H), 2.48-2.42 (br m, overlapping with DMSO, 1H), 2.28-2.17 (m, 1H), 1.84 (quintet, *J*=7.7 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (151 MHz, DMSO-d_6) δ 172.45, 172.09, 154.07, 153.48, 153.42, 153.39, 153.37, 141.80, 141.70, 136.73, 136.68, 136.64, 136.48, 136.42, 136.15, 135.26, 134.77, 128.36, 128.33, 128.27, 127.86, 127.84, 127.80, 127.73, 127.37, 126.97, 125.75, 120.26, 120.24, 73.19, 72.49, 66.44, 66.40, 66.27, 57.74, 57.66, 57.30, 57.23, 52.68, 52.42, 52.24, 52.18, 52.11, 52.09, 51.08, 50.41, 36.29, 36.21, 35.26, 35.17, 34.88, 34.68, 31.98, 31.56, 31.17, 30.96. Complexity observed in ^{1}H NMR and ^{13}C NMR due to presence of rotamers and possibly diastereomers.[21] (LRMS) LCMS ES+ (*m/z*) $[M+H]^+$ calculated for $[C_{32}H_{34}N_2O_6+H]^+$ 543.2; found 543.5.

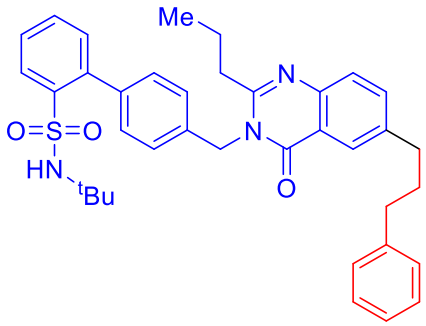


Product derived from 5c, Figure 5: colorless oil (residue). Purification method: 25 mL/min, 8-minute run, ramp from 45% to 80% MeCN. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.97 (m, 2H), 7.94 (d, *J*=2.3 Hz, 1H), 7.77-7.76 (m, 2H), 7.53 (dd, *J*=8.4, 2.4 Hz, 1H), 7.30-7.27 (m, 2H), 7.21-7.16 (m, 3H), 6.93 (d, *J*=8.4 Hz, 1H), 3.05 (s, 3H), 2.65 (t, *J*=7.7 Hz, 2H), 2.59 (t, *J*=7.9 Hz, 2H), 1.92 (quintet, *J*=7.8 Hz, 2H), 1.76 (s, 6H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 166.06, 159.82, 148.20, 146.93, 141.79, 141.36, 140.08, 138.16, 135.16, 133.66, 129.09, 128.53, 128.52, 128.00, 126.06, 110.76, 84.42, 44.49, 35.36, 32.72, 31.66, 26.55. (LRMS) LCMS ES+ (*m/z*)

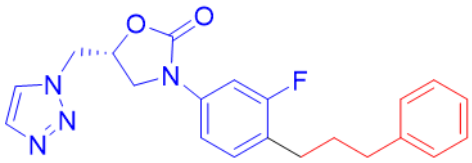
$[M+H]^+$ calculated for $[C_{27}H_{27}NO_5S]^+$ 478.17; found 478.0.



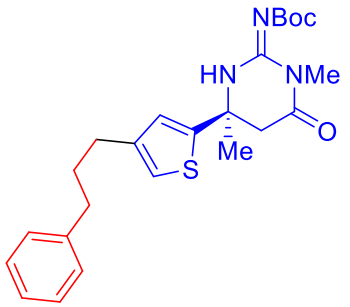
Product derived from 5d, Figure 5: Yellow oil. Purification method: 25 mL/min, 8-minute run, ramp from 65% to 98% MeCN. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J*=7.1 Hz, 1H), 7.26-7.21 (m, 3H), 7.17-7.11 (m, 4H), 7.10-7.08 (m, 2H), 4.11 (quartet, *J*=7.7 Hz, 2H), 3.79 (br s, 2H), 3.39-3.33 (m, 1H), 3.31-3.25 (m, 1H), 3.11-3.06 (m, 2H), 2.82-2.72 (m, 2H), 2.63 (t, *J*=8.0 Hz, 2H), 2.56 (t, *J*=8.0 Hz, 2H), 2.49-2.44 (m, 1H), 2.32-2.29 (br m, 3H), 1.91 (quintet, *J*=7.7 Hz, 2H), 1.22 (t, *J*=7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 155.62, 154.37 (br s), 146.69 (br s), 141.82, 139.78, 138.18, 137.77 (br s), 137.61 (br s), 136.22, 134.06 (br s), 132.95, 130.53, 128.97, 128.51, 128.50, 126.29, 126.03, 61.44, 44.91, 35.48, 32.59, 32.15, 31.75, 31.70, 30.90, 30.66, 14.82. (HRMS) TOF MS ES+ (*m/z*) $[M+H]^+$ calculated for $[C_{31}H_{33}ClN_2O_2+H]^+$ 501.2303; found 501.2300.



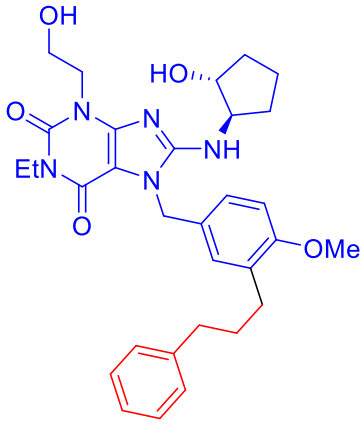
Product derived from 5e, Figure 5: Light brown solid. Purification method: 25 mL/min, 8-minute run, ramp from 65% to 98% MeCN. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (d, *J*=7.9 Hz, 1H), 7.99 (s, 1H), 7.70-7.68 (m, 1H), 7.63-7.58 (m, 2H), 7.57-7.53 (m, 1H), 7.38 (d, *J*=8.2 Hz, 2H), 7.28 (t, *J*=7.2 Hz, 3H), 7.23-7.16 (m, 5H), 6.57 (s, 1H), 5.45 (br s, 2H), 2.79-2.74 (m, 4H), 2.63 (t, *J*=7.8 Hz, 2H), 1.95 (quintet, *J*=7.6 Hz, 2H), 1.75 (sextet, *J*=7.4 Hz, 2H), 0.95-0.92 (m, overlapping signals, 12H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 161.65, 156.52, 145.32, 142.06, 141.82, 140.55, 139.59, 138.77, 135.84, 135.17, 132.59, 131.76, 129.64, 128.31, 128.29, 128.05, 127.75, 126.92, 125.76, 125.56, 125.19, 119.63, 53.34, 45.35, 35.73, 34.66, 34.41, 32.62, 29.29, 19.45, 13.57. (HRMS) TOF MS ES+ (*m/z*) $[M+H]^+$ calculated for $[C_{37}H_{41}N_3O_3S+H]^+$ 608.2941; found 608.2947.



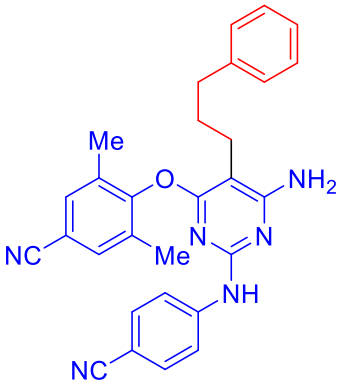
Product derived from 5f, Figure 5: see section SXXIII for purification and characterization data.



Product derived from 5g, Figure 5: white solid. Purification method: 25 mL/min, 12-minute run, ramp from 53% to 83% MeCN. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.29-7.26 (m, 2H), 7.20-7.16 (m, 3H), 7.08 (s, 1H), 6.93 (s, 1H), 3.33 (s, 1H), 3.19-3.11 (m, 2H), 3.04 (s, 3H), 2.57 (t, *J*=7.8 Hz, 2H), 2.52 (t, overlapping with DMSO, *J*=7.7 Hz, 2H), 1.84 (quintet, *J*=7.9 Hz, 2H), 1.68 (s, 3H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d$_6$) δ 167.66, 163.11, 156.85, 148.17, 142.45, 141.85, 128.31, 128.27, 125.72, 125.23, 119.74, 78.55, 52.90, 44.42, 34.76, 31.48, 29.49, 29.45, 27.91. (HRMS) TOF MS ES+ (*m/z*) [M+H]$^{+}$ calculated for [$C_{24}H_{31}N_3O_3S$+H]$^{+}$ 442.2159; found 442.2164.



Product derived from 5h, Figure 5: white solid. Purification method: 25 mL/min, 12-minute run, ramp from 40% to 70% MeCN. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.28-7.25 (m, 2H), 7.18-7.16 (m, 4H), 7.12-7.10 (m, 1H), 6.96 (d, J= Hz, 1H), 6.89 (d, J= Hz, 1H), 5.22 (s, 2H), 4.81 (t, J= Hz, 1H), 4.78 (d, J= Hz, 1H), 3.98-3.94 (m, 3H), 3.91-3.82 (m, 3H), 3.72 (s, 3H), 3.60 (quartet, J= Hz, 2H), 2.56 (t, J= Hz, 2H), 2.05-1.98 (m, 1H), 1.85-1.74 (m, 3H), 1.66-1.56 (m, 2H), 1.48-1.42 (m, 2H), 1.05 (t, J= Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d$_6$) δ 156.44, 153.42, 152.54, 150.39, 148.66, 141.95, 129.52, 128.98, 128.84, 128.22, 126.43, 125.66, 110.58, 101.14, 76.12, 61.42, 57.76, 55.32, 44.73, 44.56, 35.11, 34.89, 32.39, 30.82, 29.88, 28.92, 20.55, 13.31. (HRMS) TOF MS ES+ (*m/z*) [M+H]$^{+}$ calculated for [$C_{31}H_{39}N_5O_5$+H]$^{+}$ 562.3024; found 562.3029.



Product derived from 5i, Figure 5: white solid. First purification: 0.1% TFA aqueous phase, 25 mL/min, 12-minute run, ramp from 45% to 75% MeCN (column: Waters Sunfire Prep C18, 5 μM, 19x100 mm). Second purification: 0.8% NH_4OH aqueous phase, 25 mL/min, 15 minute run, 48% to 78% MeCN. ^1H NMR (400 MHz, DMSO-d_6) δ 9.33 (s, 1H), 7.71 (s, 2H), 7.50 (d, *J*=8.6 Hz, 2H), 7.36 (d, *J*=8.9 Hz, 2H), 7.28-7.25 (t, *J*=7.3 Hz, 2H), 7.22 (d, *J*=6.9 Hz, 2H), 7.15 (t, *J*=7.1 Hz, 1H), 6.67 (s, 2H) 2.73-2.69 (t, *J*=8.0 Hz, 2H), 2.66-2.63 (t, *J*=7.6 Hz, 2H), 2.08 (s, 6H), 1.82 (quintet, *J*=7.2 Hz, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 165.02, 164.23, 156.11, 154.67, 145.50, 142.37, 132.89, 132.36, 132.28, 128.30, 128.12, 125.65, 119.68, 118.82, 117.56, 107.65, 101.14, 91.39, 35.12, 30.27, 22.26, 15.93. (HRMS) TOF MS ES+ (*m/z*) $[M+H]^+$ calculated for $[C_{29}H_{26}N_6O+H]^+$ 475.2241; found 475.2246.

SXXVII. Procedure for ^{1}H NMR Yields of Products from Two-Component Cross-Electrophile Coupling with Drug-Like Aryl Halides

Procedure:

See section SV for representative experimental setup and workup, but reactions were performed on 0.03 mmol scale of aryl electrophile at 0.1 M in 1,4-dioxane for 36 hours (other reagents scaled linearly). For individual reaction conditions, see Figure 5 in the manuscript.

General Comments:

Optimized reaction conditions were determined through HTE (see section SXX), so reactions to determine ^{1}H NMR yields were not performed in duplicate as long as results agreed well with data obtained from HTE optimization. In the case of aryl halide **5i**, the reaction was optimized using ^{1}H NMR yields beyond the initial optimization performed using HTE. As a result, this reaction was performed in duplicate to report a yield as the average of two trials.

SXXVIII. NMR Spectra of Isolated Products

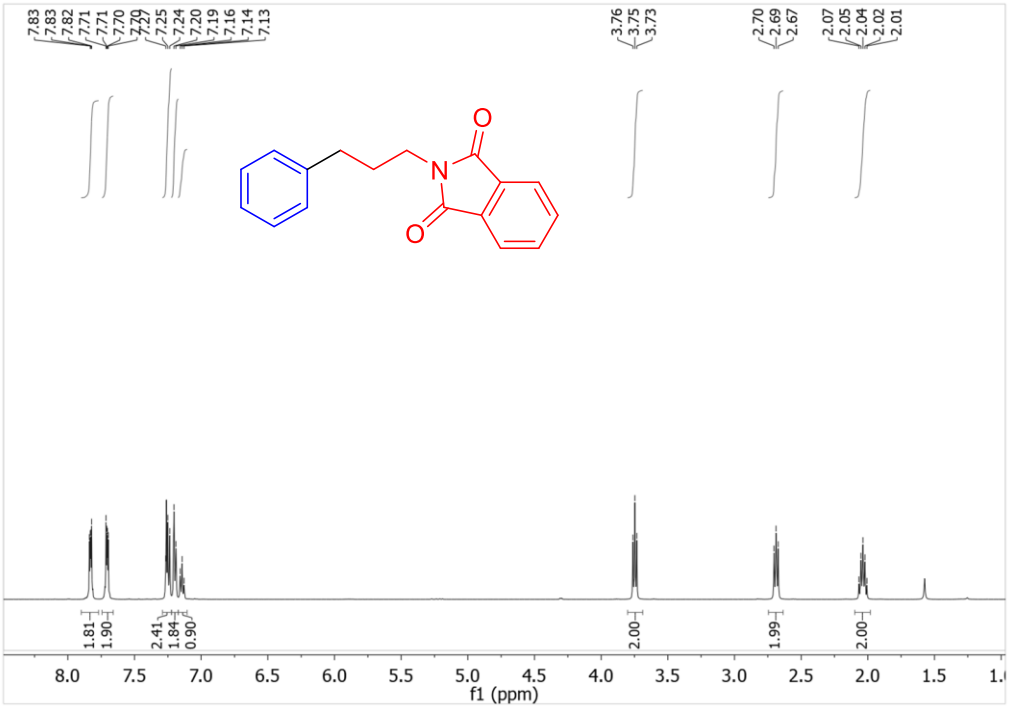


Figure S19. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 2-(3-phenylpropyl)isoindoline-1,3-dione, derived from substrate **4a**.

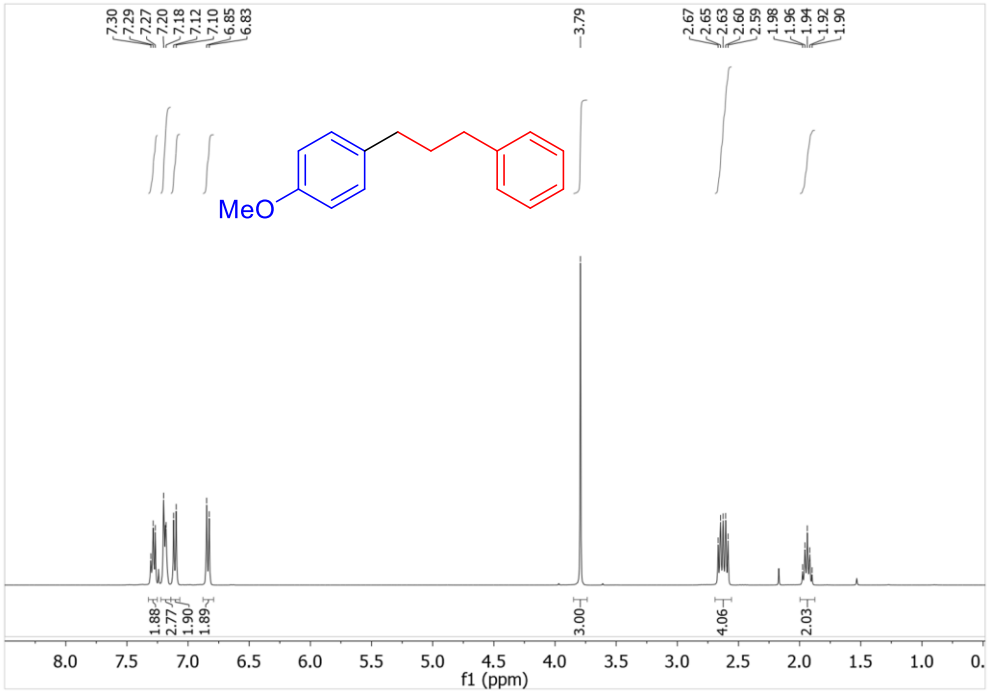


Figure S20. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 1-phenyl-3-(4-methoxyphenyl)propane, derived from substrate **4b**.

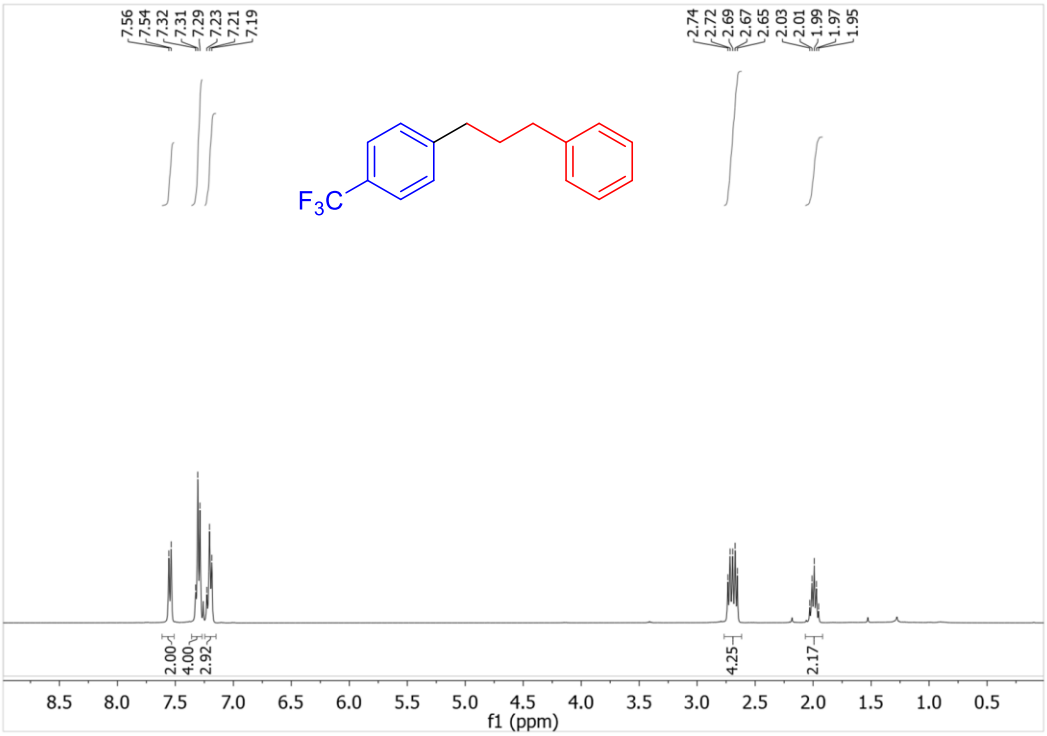


Figure S21. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 1-phenyl-3-(4-trifluoromethylphenyl)propane, derived from substrate **4c**.

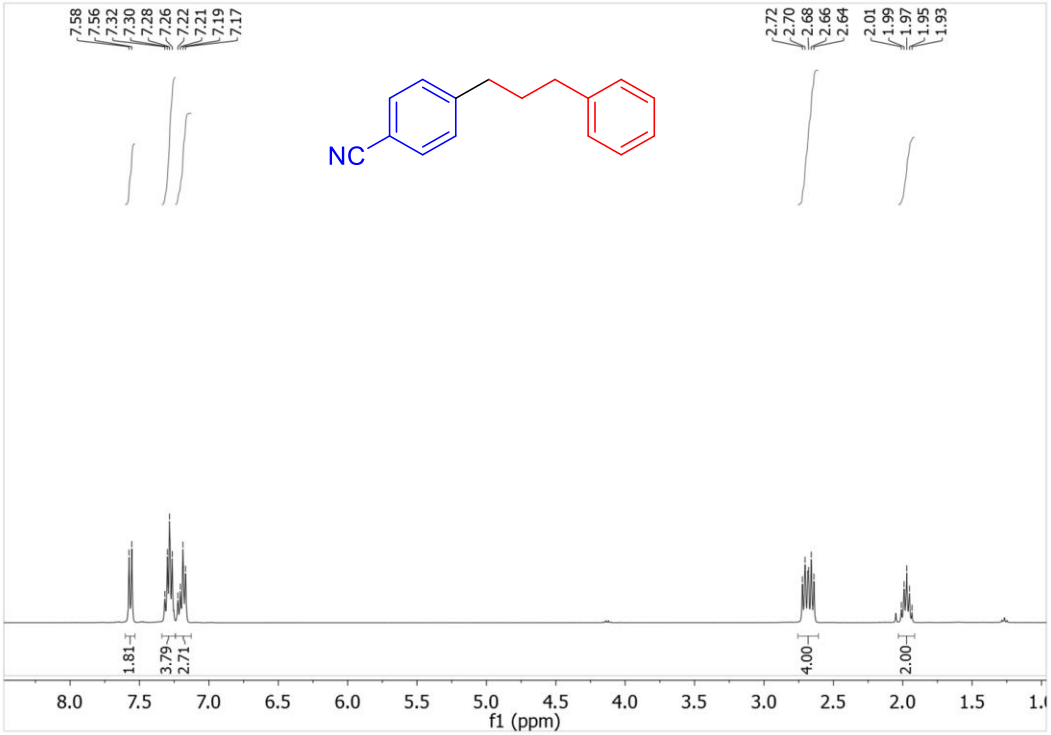


Figure S22. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4-(3-phenylpropyl)benzonitrile, derived from substrate **4d**.

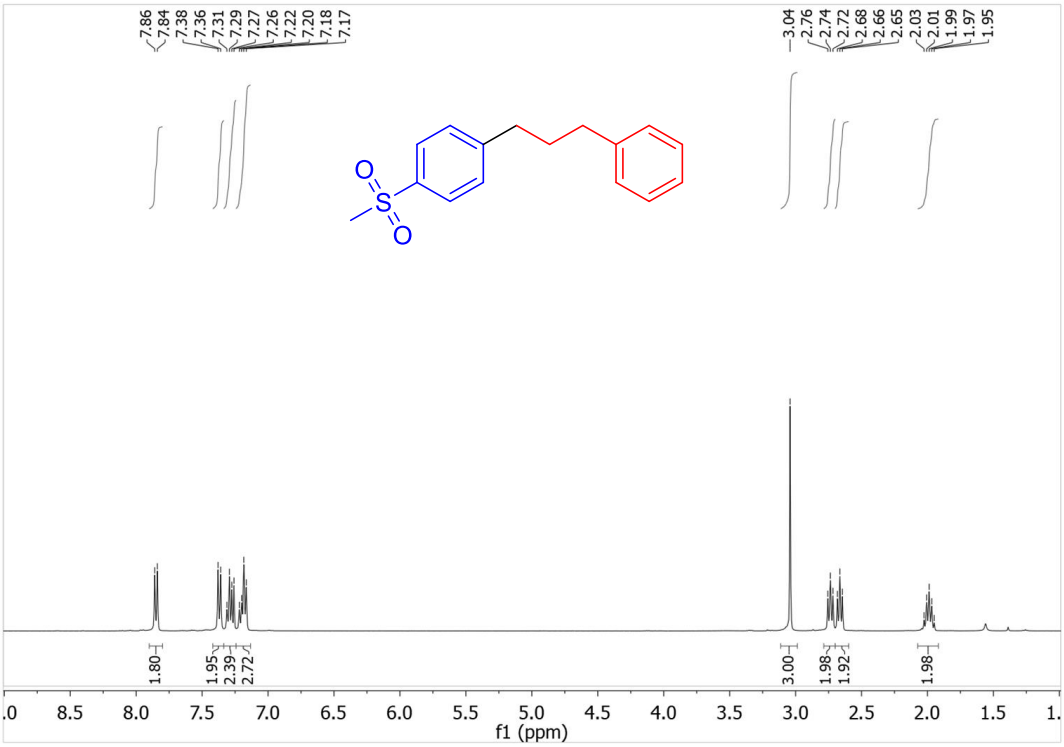


Figure S23. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 1-(methylsulfonyl)-4-(3-phenylpropyl)benzene, derived from substrate **4e**.

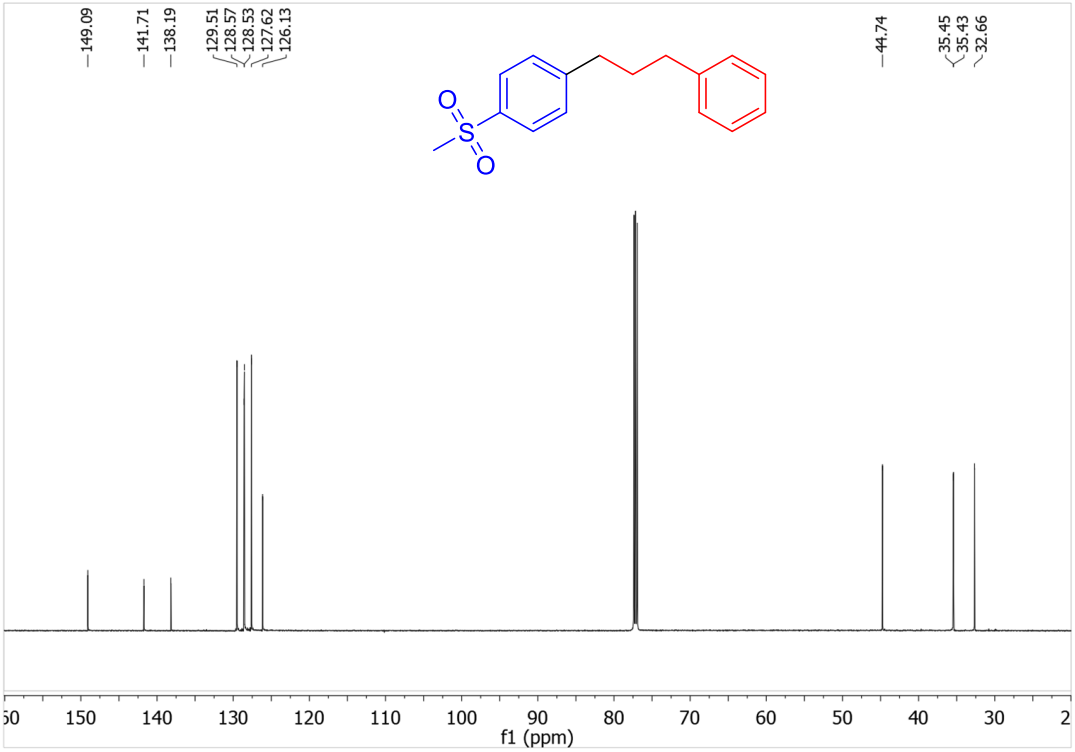


Figure S24. $^{13}C\{^{1}H\}$ NMR spectrum (151 MHz, $CDCl_3$) of 1-(methylsulfonyl)-4-(3-phenylpropyl)benzene, derived from substrate **4e**.

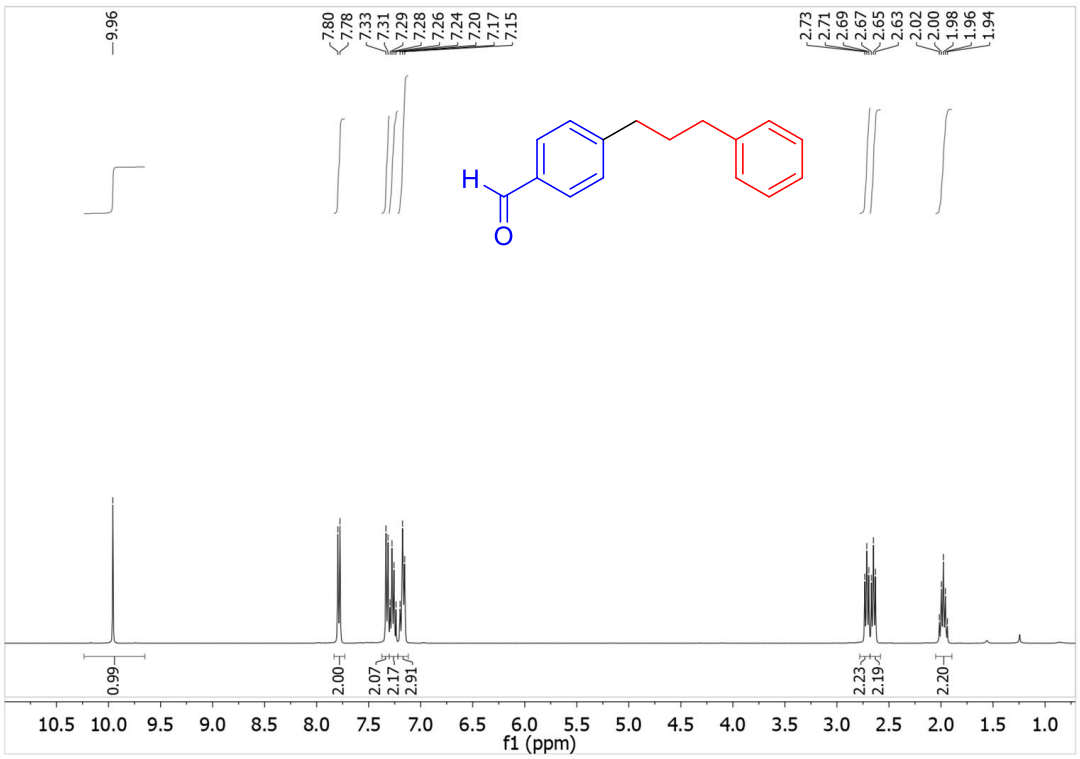


Figure S25. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4-(3-phenylpropyl)benzaldehyde, derived from substrate **4f**.

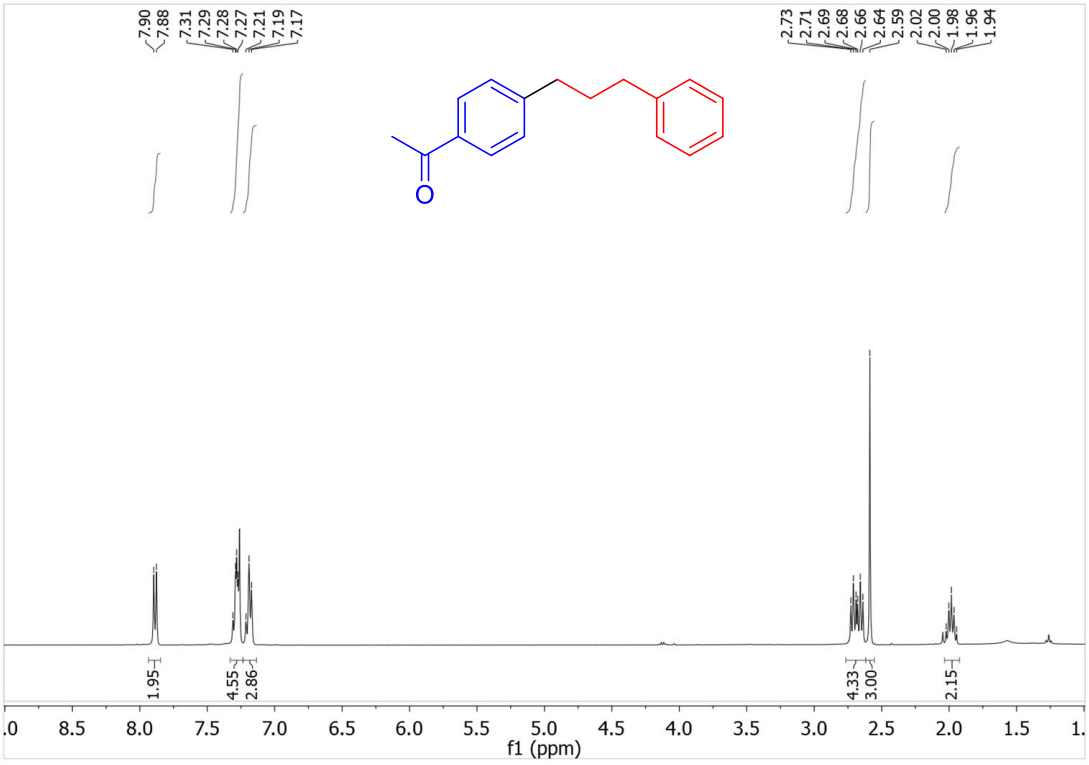


Figure S26. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4-(3-phenylpropyl)benzophenone, derived from substrate **4g**.

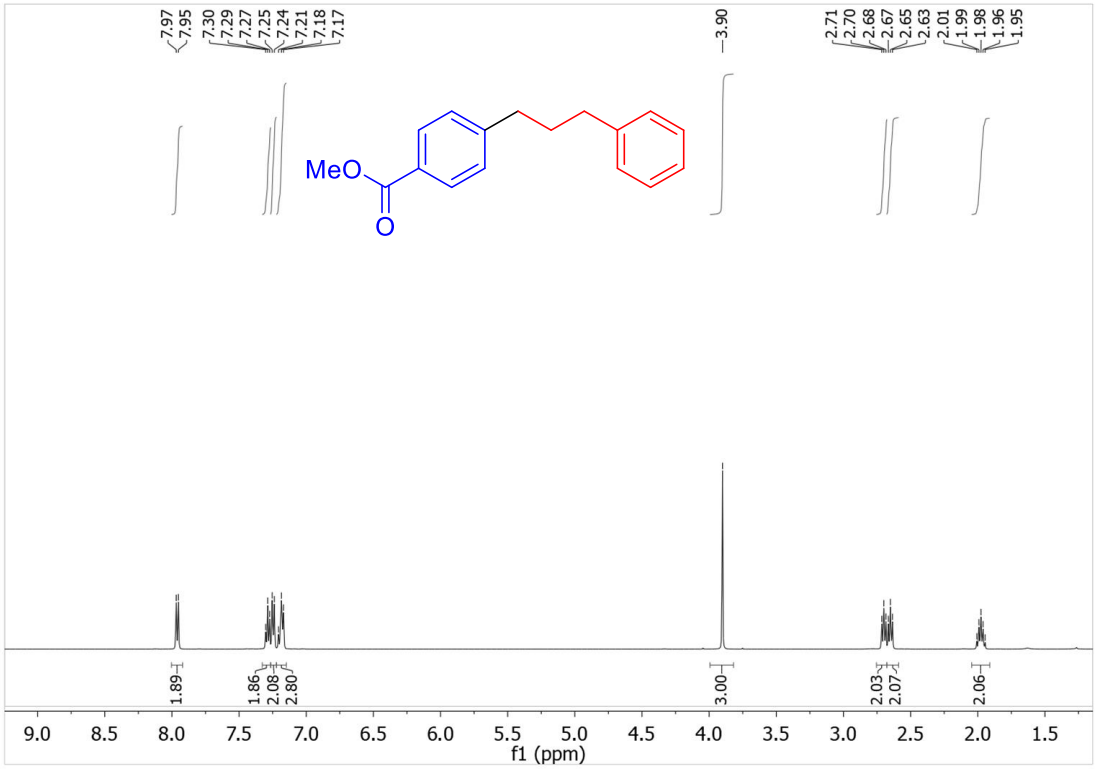


Figure S27. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4-(3-phenylpropyl)methyl-benzoate, derived from substrate **4h**.

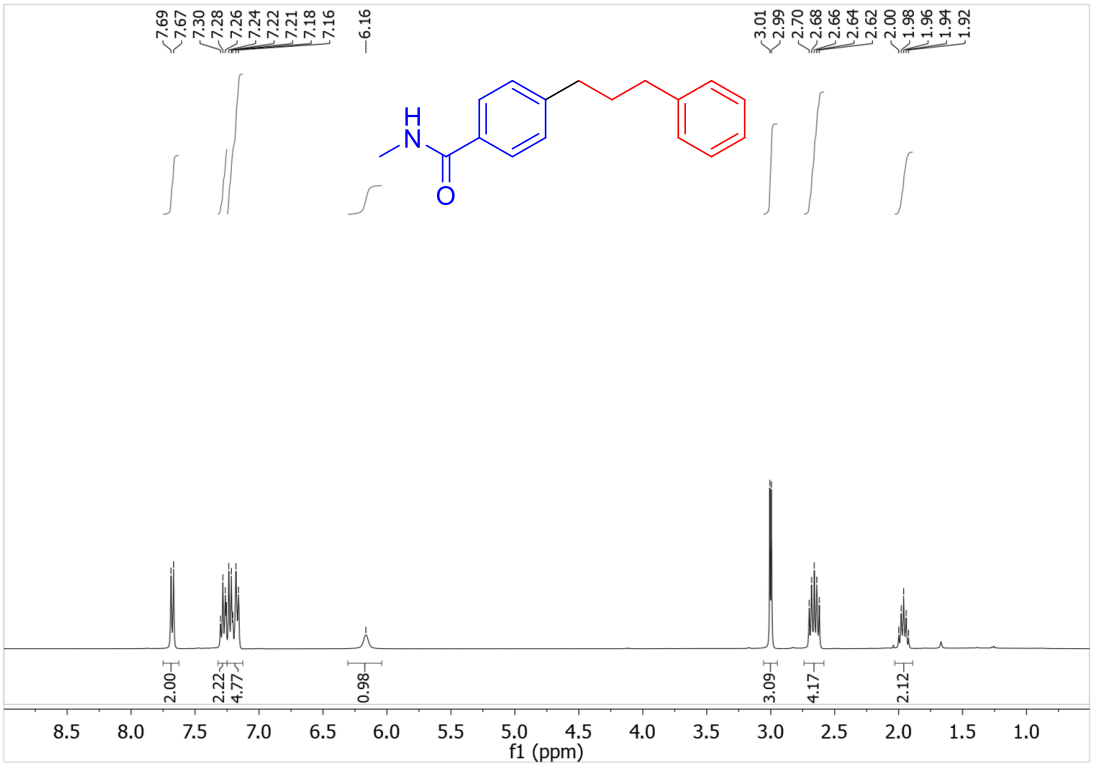


Figure S28. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of *N*-methyl-4-(3-phenylpropyl)benzamide, derived from substrate **4i**.

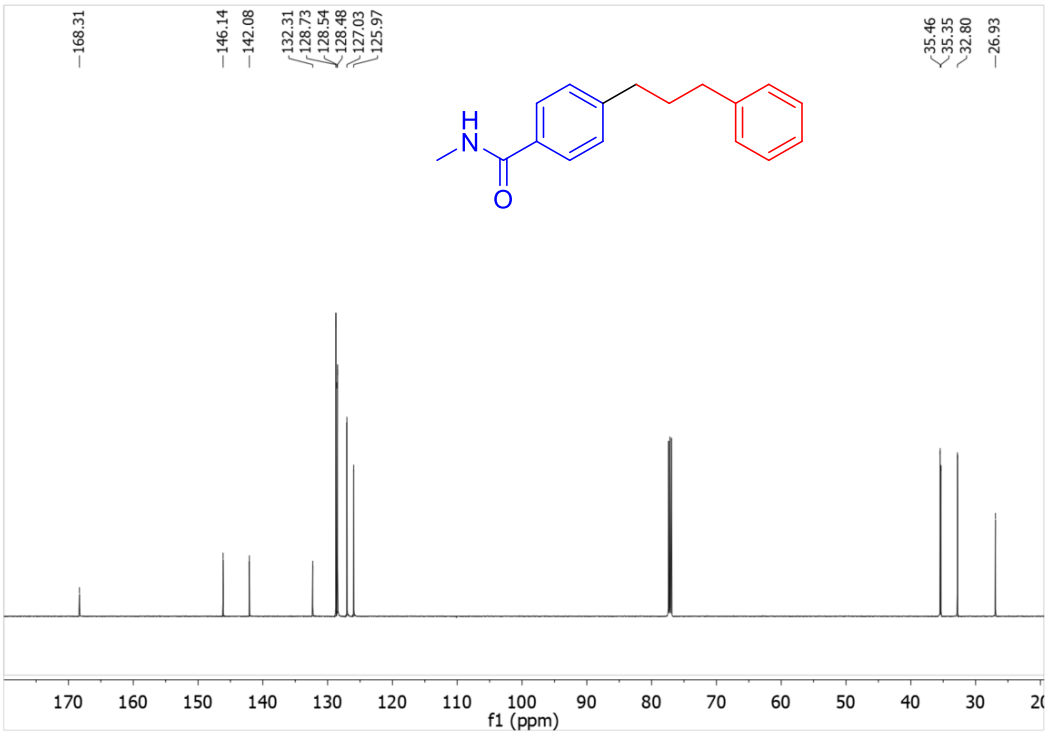


Figure S29. $^{13}C\{^{1}H\}$ NMR spectrum (151 MHz, $CDCl_3$) of *N*-methyl-4-(3-phenylpropyl)benzamide, derived from substrate **4i**.

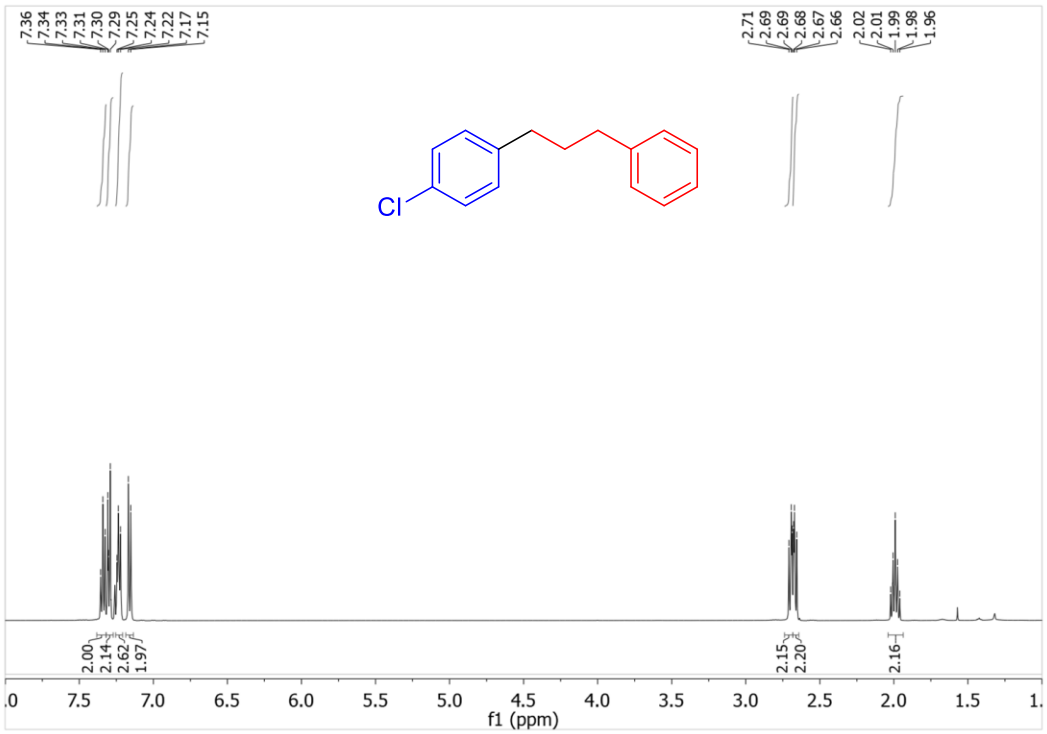


Figure S30. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 1-chloro-4-(3-phenylpropyl)benzene, derived from substrate **4j**.

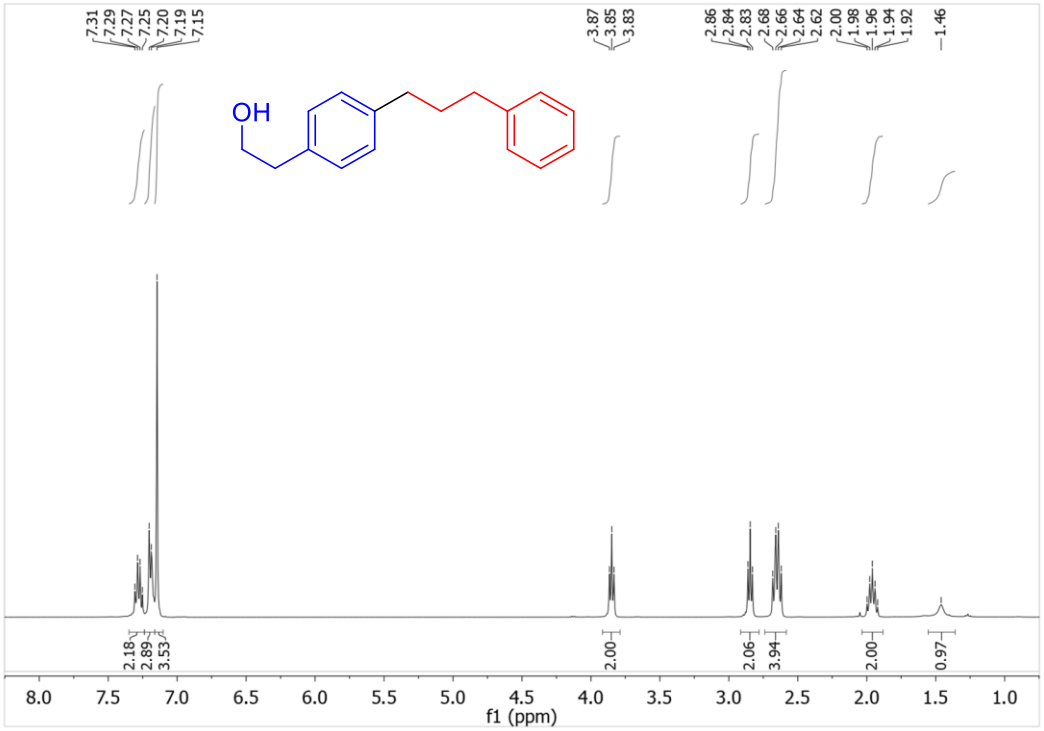


Figure S31. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 2-(4-(3-phenylpropyl)phenyl)ethanol, derived from substrate **4k**.

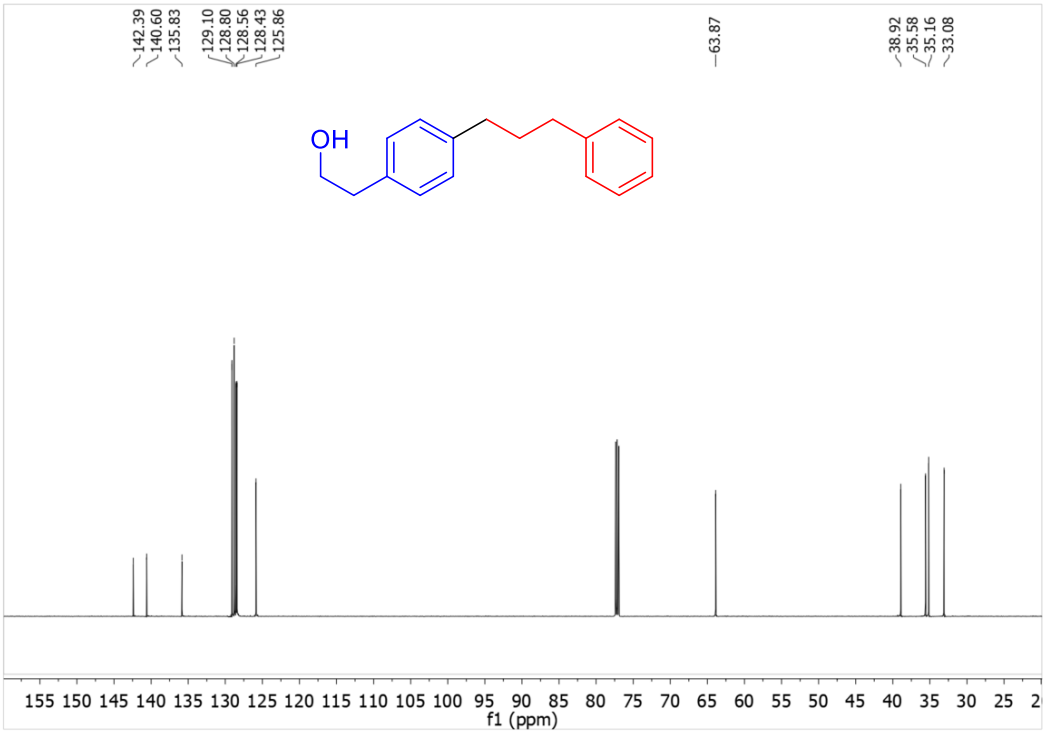


Figure S32. $^{13}C\{^{1}H\}$ NMR spectrum (151 MHz, $CDCl_3$) of 2-(4-(3-phenylpropyl)phenyl)ethanol, derived from substrate **4k**.

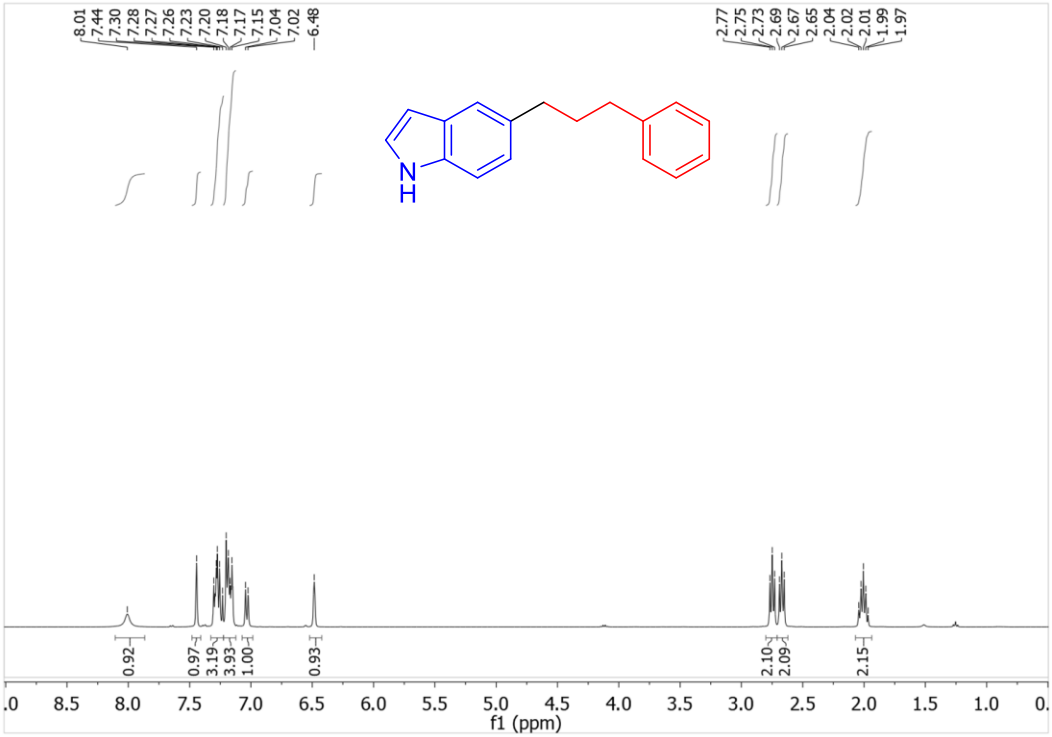


Figure S33. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 5-(3-phenylpropyl)-1*H*-indole, derived from substrate **4l**.

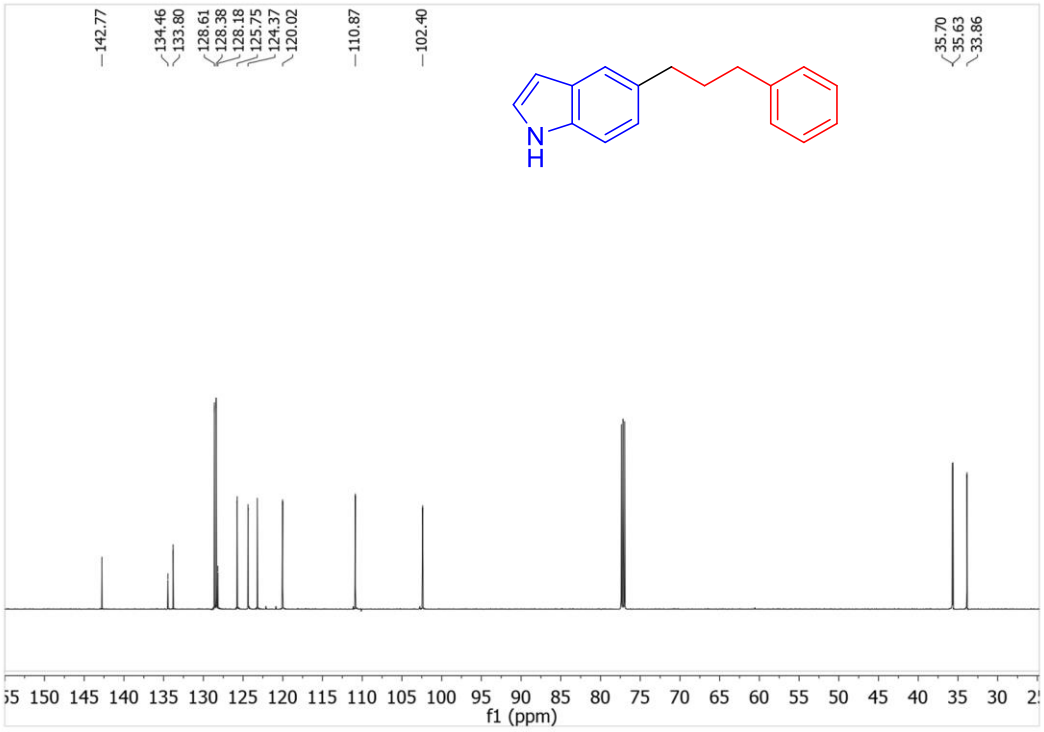


Figure S34. $^{13}C\{^{1}H\}$ NMR spectrum (151 MHz, $CDCl_3$) of 5-(3-phenylpropyl)-1*H*-indole, derived from substrate **4l**.

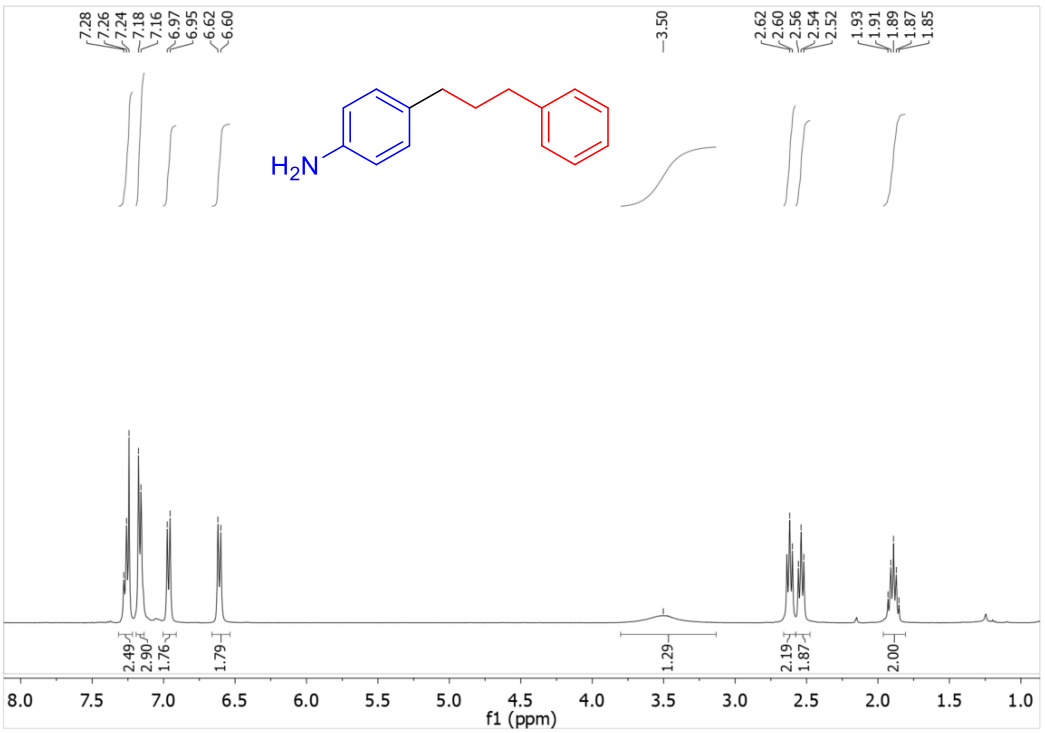


Figure S35. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4-(3-phenylpropyl)aniline, derived from substrate **4m**.

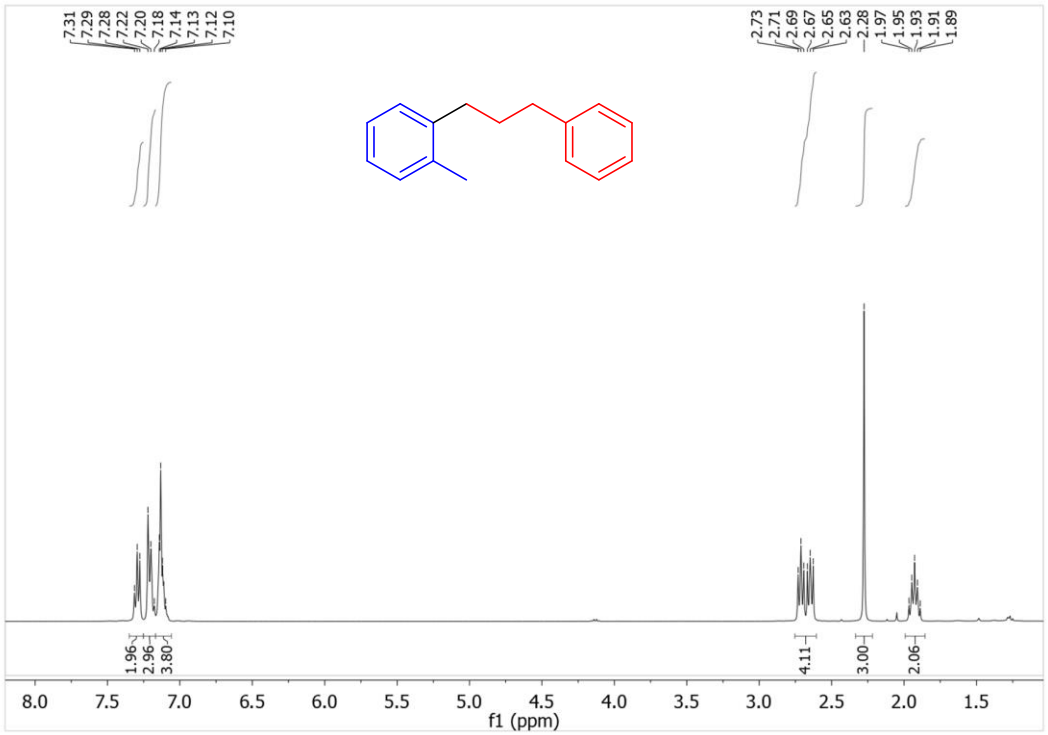


Figure S36. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 2-(3-phenylpropyl)toluene, derived from substrate **4n**.

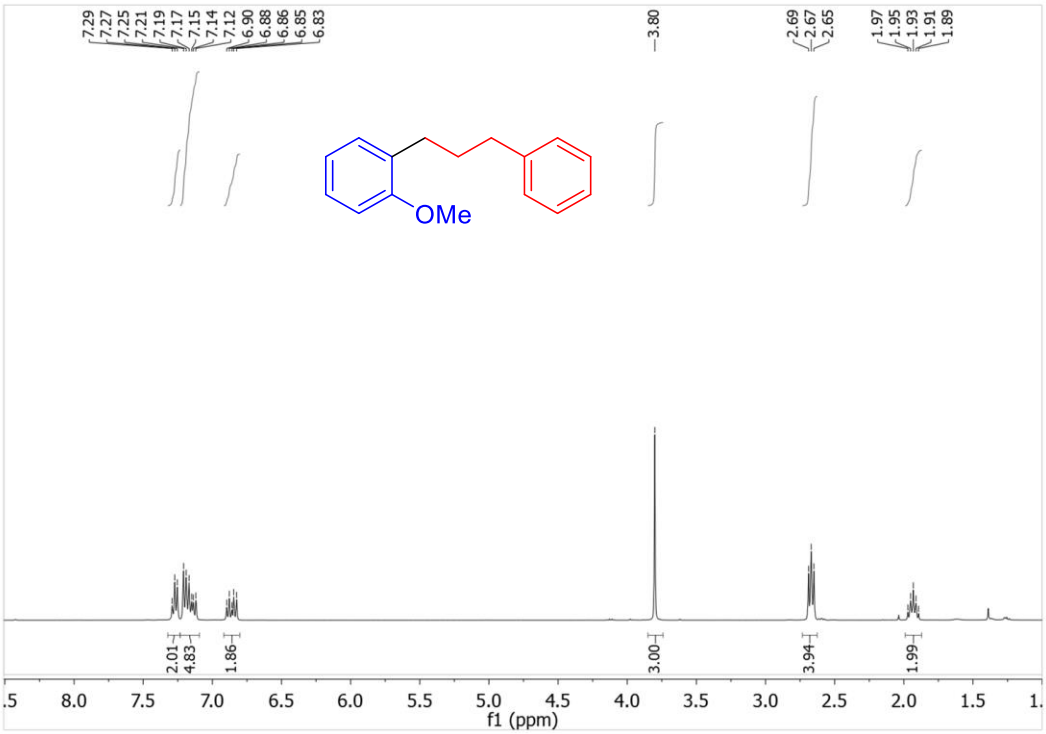


Figure S37. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 1-phenyl-3-(2-methoxyphenyl)propane, derived from substrate **4o**.

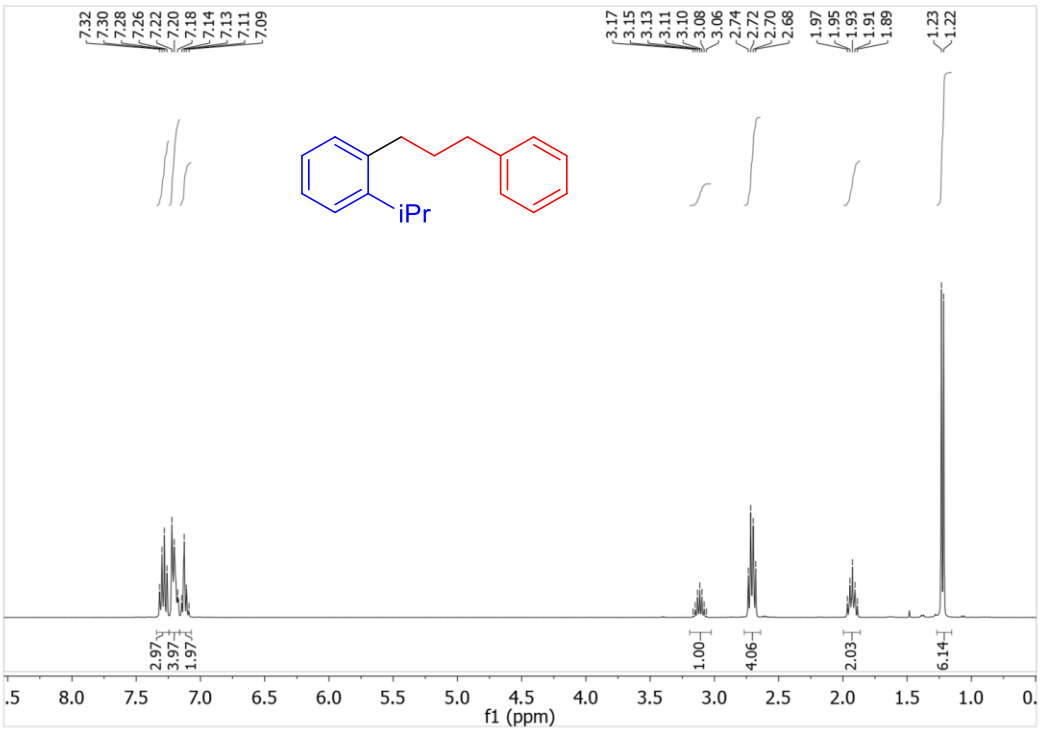


Figure S38. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 1-phenyl-3-(2-isopropylphenyl)propane, derived from substrate **4p**.

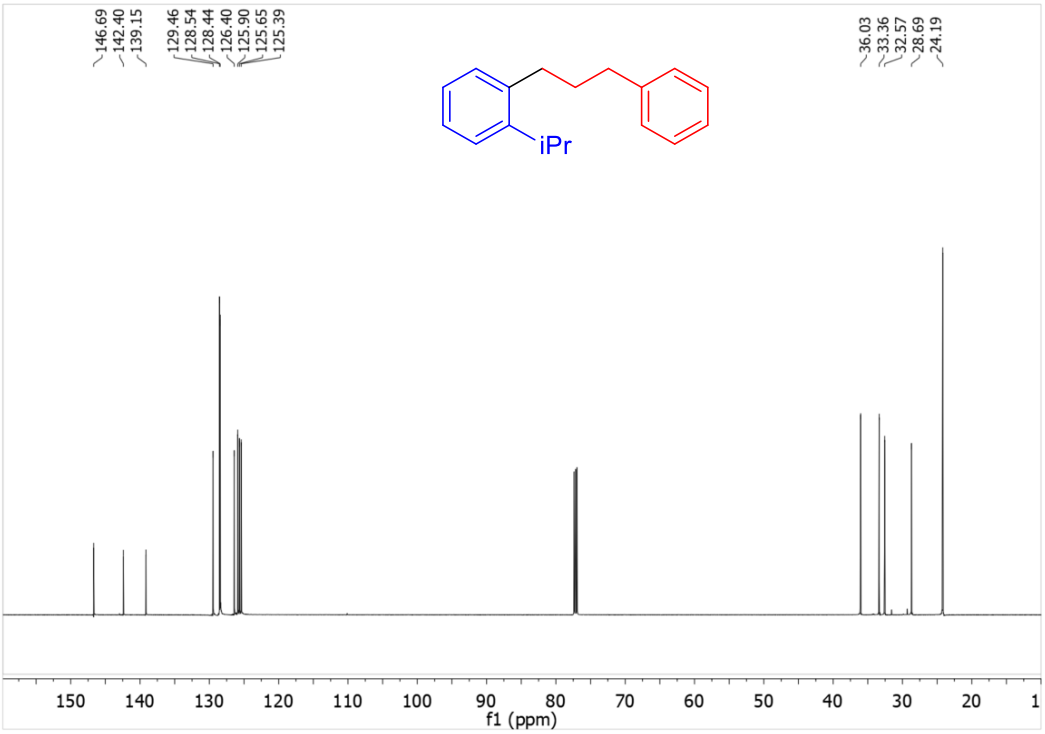


Figure S39. $^{13}C\{^{1}H\}$ NMR spectrum (151 MHz, $CDCl_3$) of 1-phenyl-3-(2-isopropylphenyl)propane, derived from substrate **4p**.

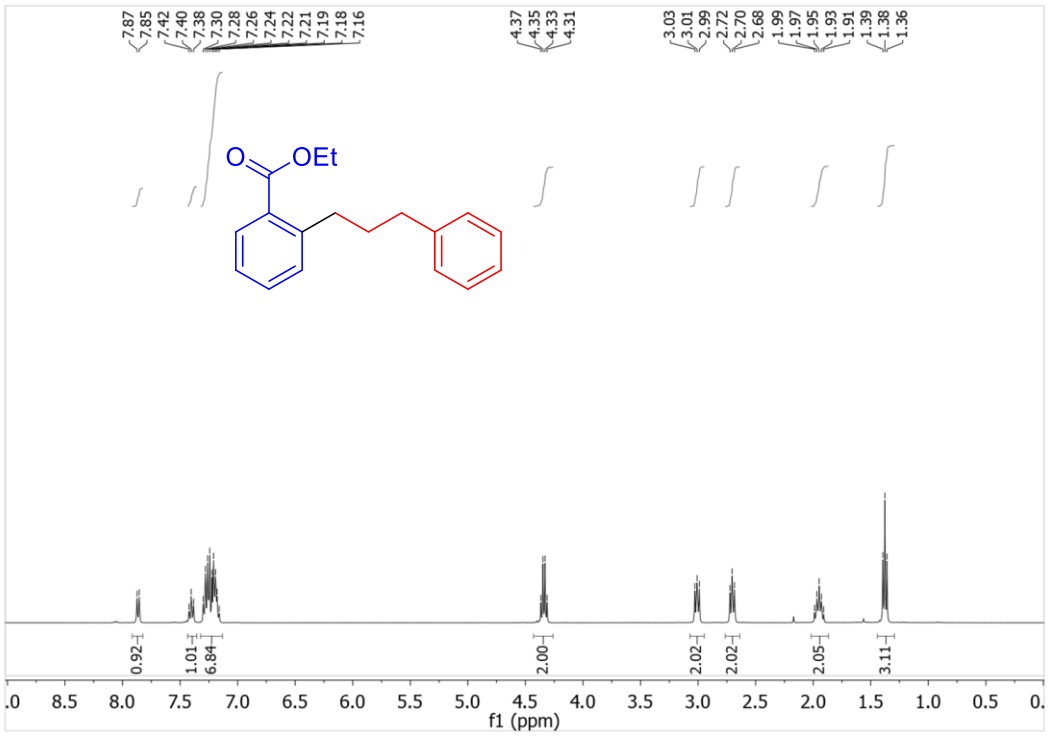


Figure S40. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 2-(3-phenylpropyl)ethylbenzoate, derived from substrate **4q**.

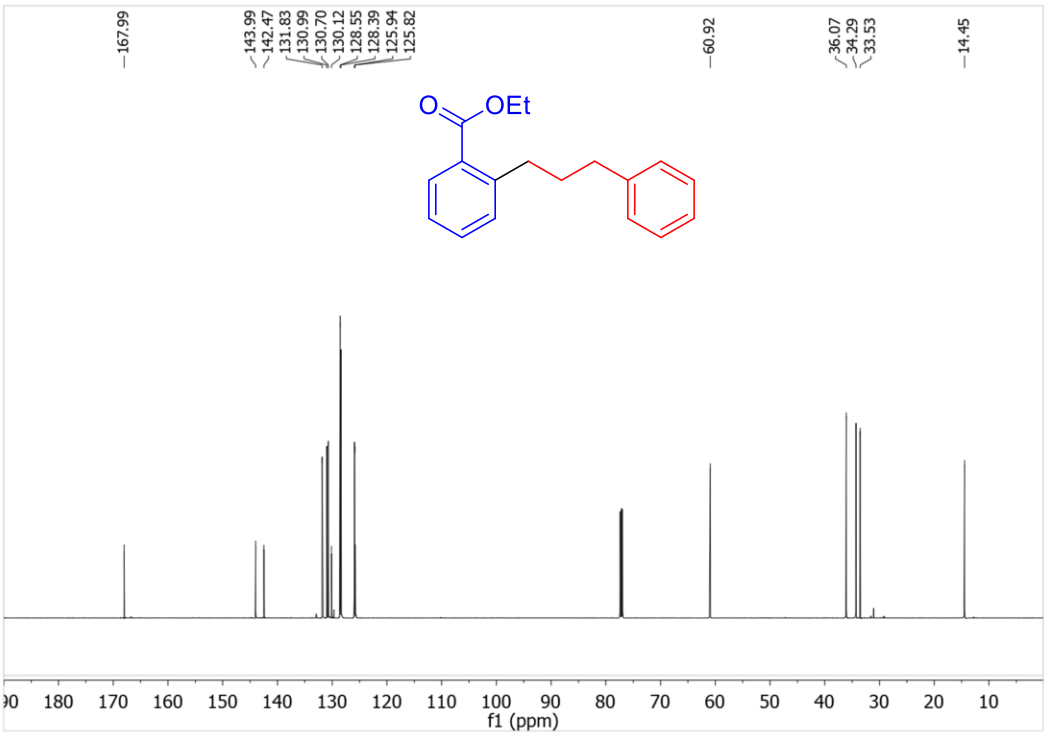


Figure S41. $^{13}C\{^{1}H\}$ NMR spectrum (151 MHz, $CDCl_3$) of 2-(3-phenylpropyl)ethylbenzoate, derived from substrate **4q**.

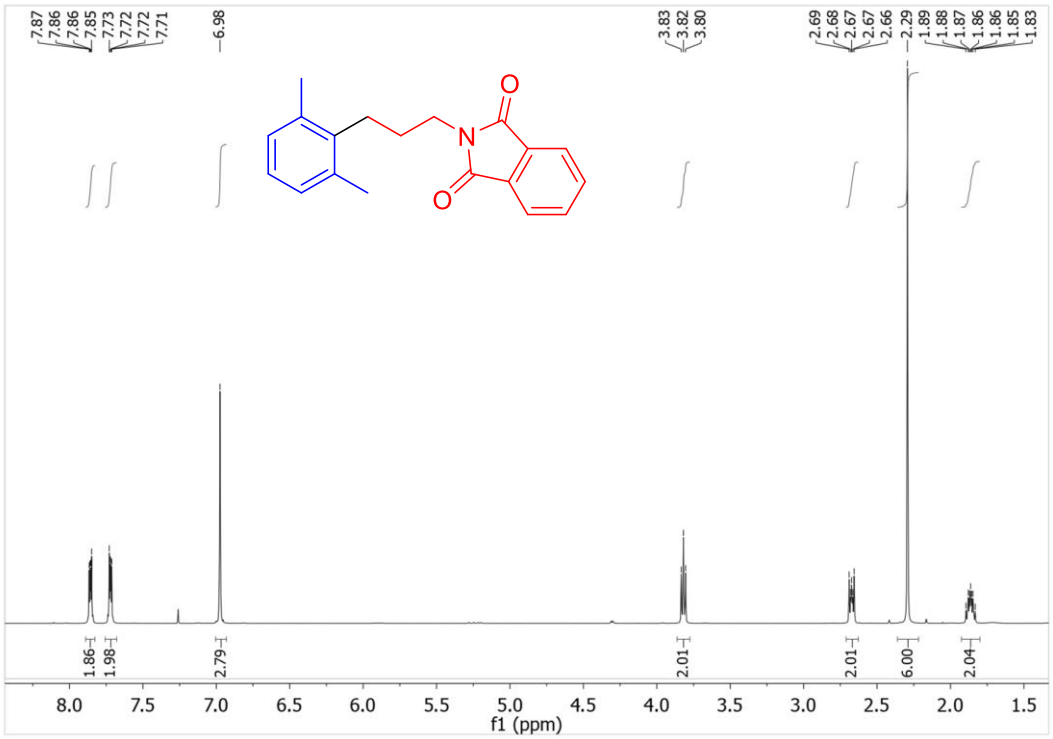


Figure S42. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 2-(3-(2,6-dimethylphenyl)propyl)isoindoline-1,3-dione, derived from substrate **4r**.

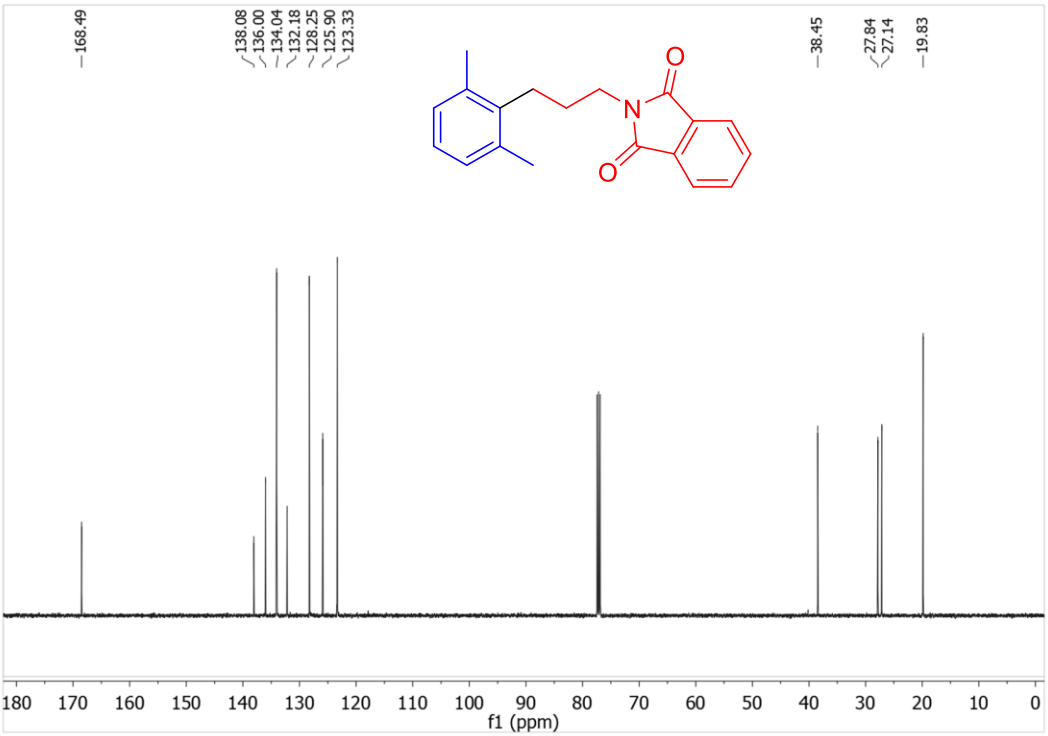


Figure S43. $^{13}C\{^{1}H\}$ NMR spectrum (151 MHz, $CDCl_3$) of 2-(3-(2,6-dimethylphenyl)propyl)isoindoline-1,3-dione, derived from substrate **4r**.

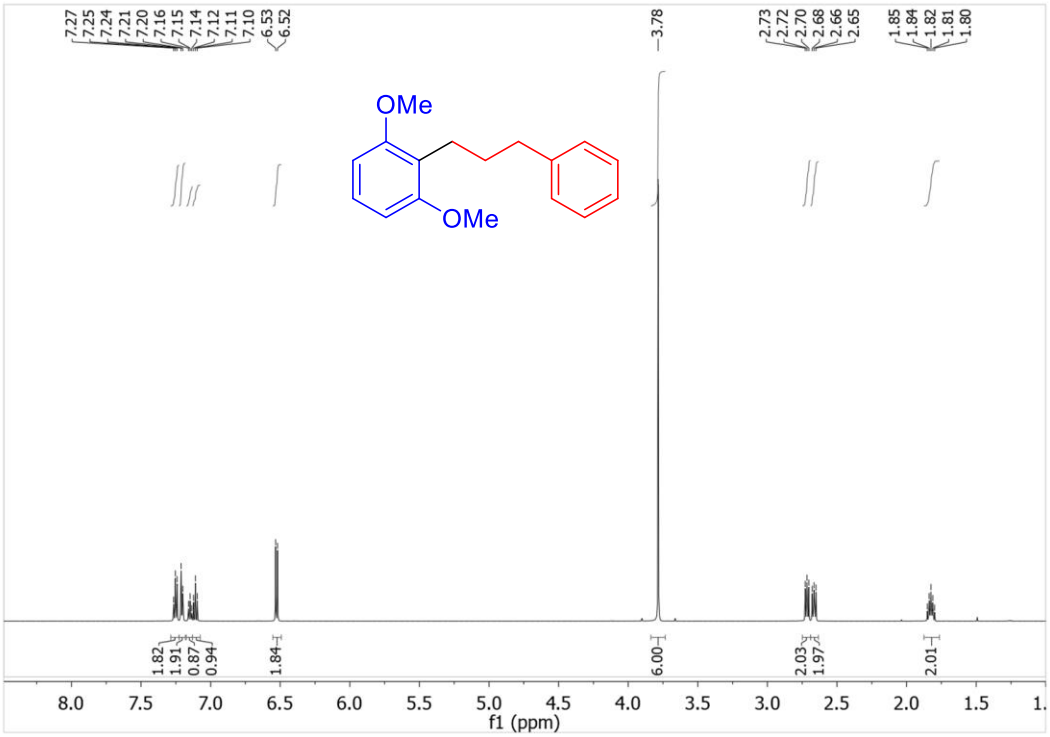


Figure S44. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 3-(3-phenylpropyl)-2,6-dimethoxybenzene, derived from substrate **4s**.

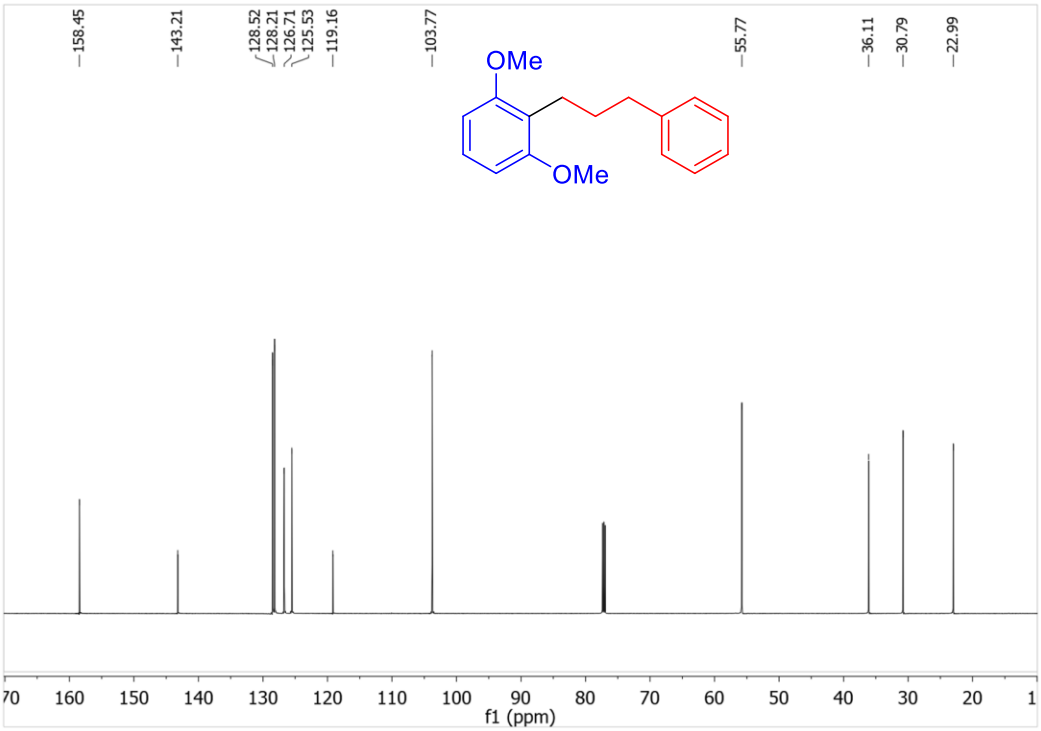


Figure S45. $^{13}C\{^{1}H\}$ NMR spectrum (151 MHz, $CDCl_3$) of 3-(3-phenylpropyl)-2,6-dimethoxybenzene, derived from substrate **4s**.

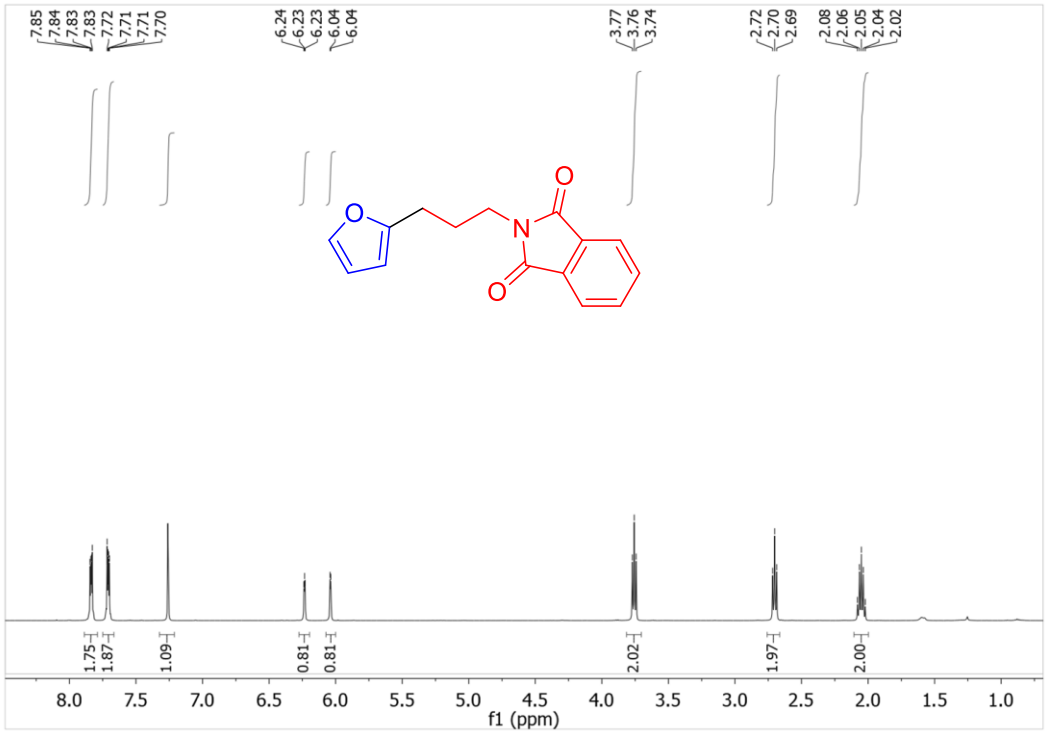


Figure S46. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 2-(3-(2-furanyl)propyl)isoindoline-1,3-dione, derived from substrate **4t**.

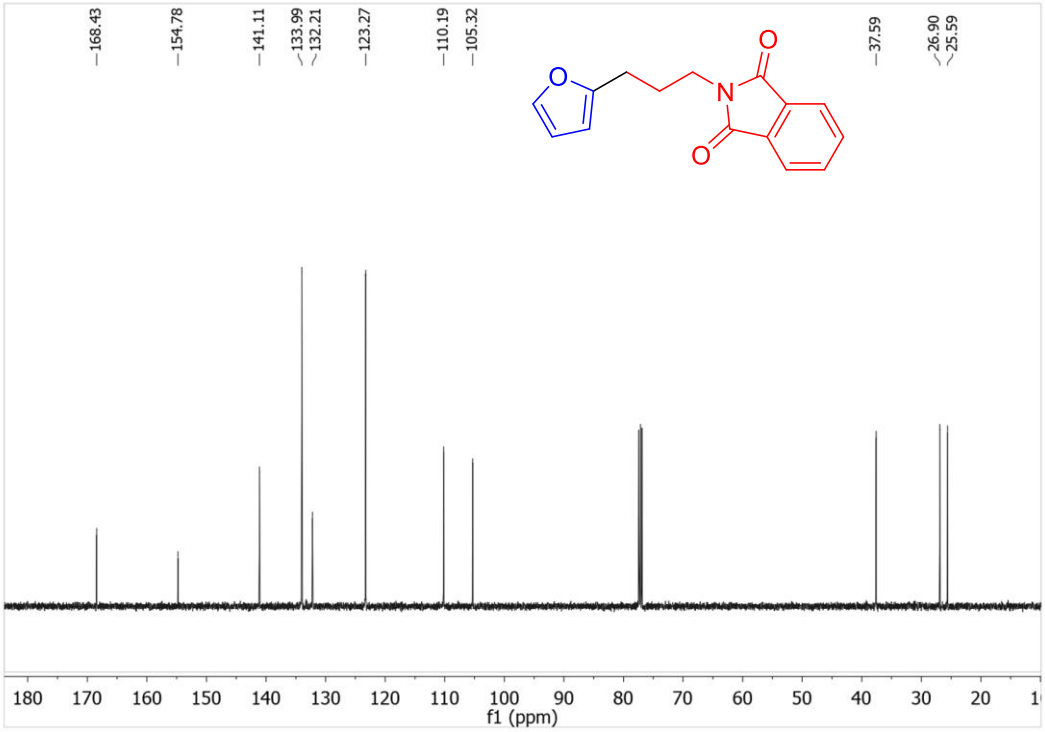


Figure S47. $^{13}C\{^{1}H\}$ NMR spectrum (151 MHz, $CDCl_3$) of 2-(3-(2-furanyl)propyl)isoindoline-1,3-dione, derived from substrate **4t**.

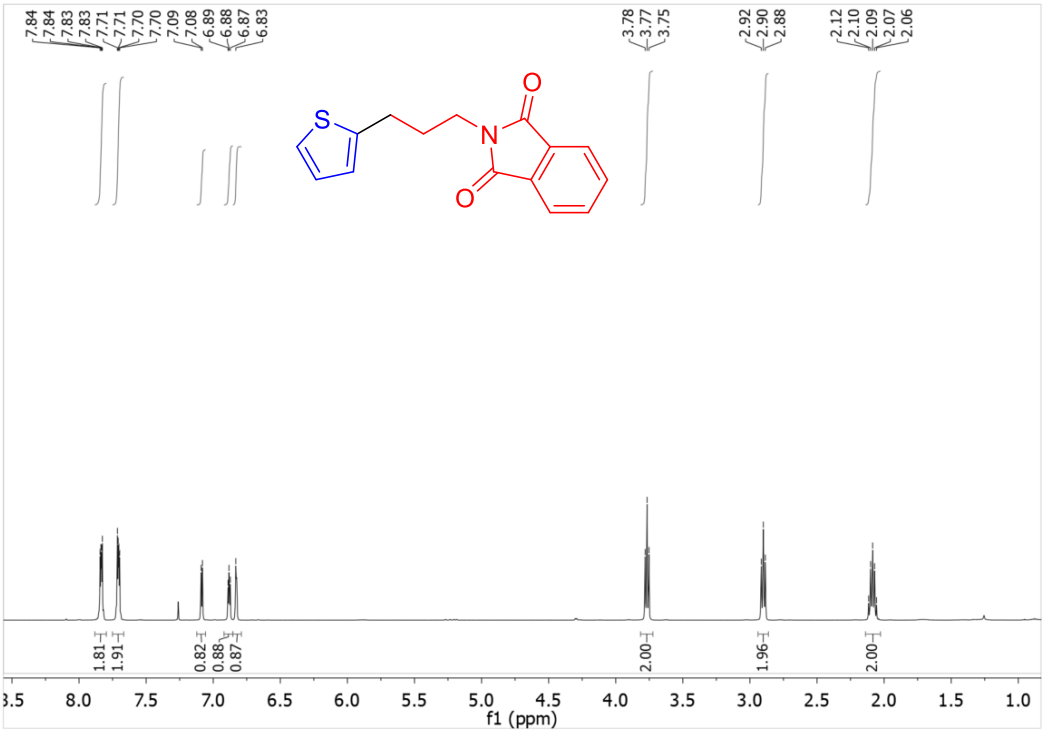


Figure S48. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 2-(3-(2-thiophenyl)propyl)isoindoline-1,3-dione, derived from substrate **4u**.

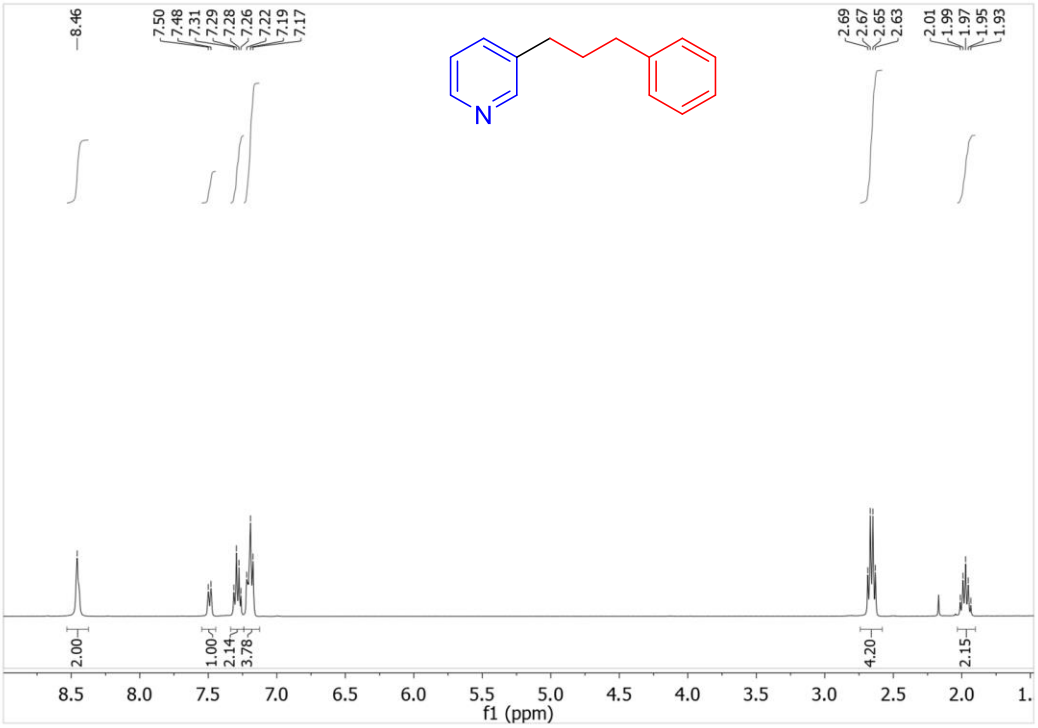


Figure S49. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 3-(3-phenylpropyl)pyridine, derived from substrate **4v**.

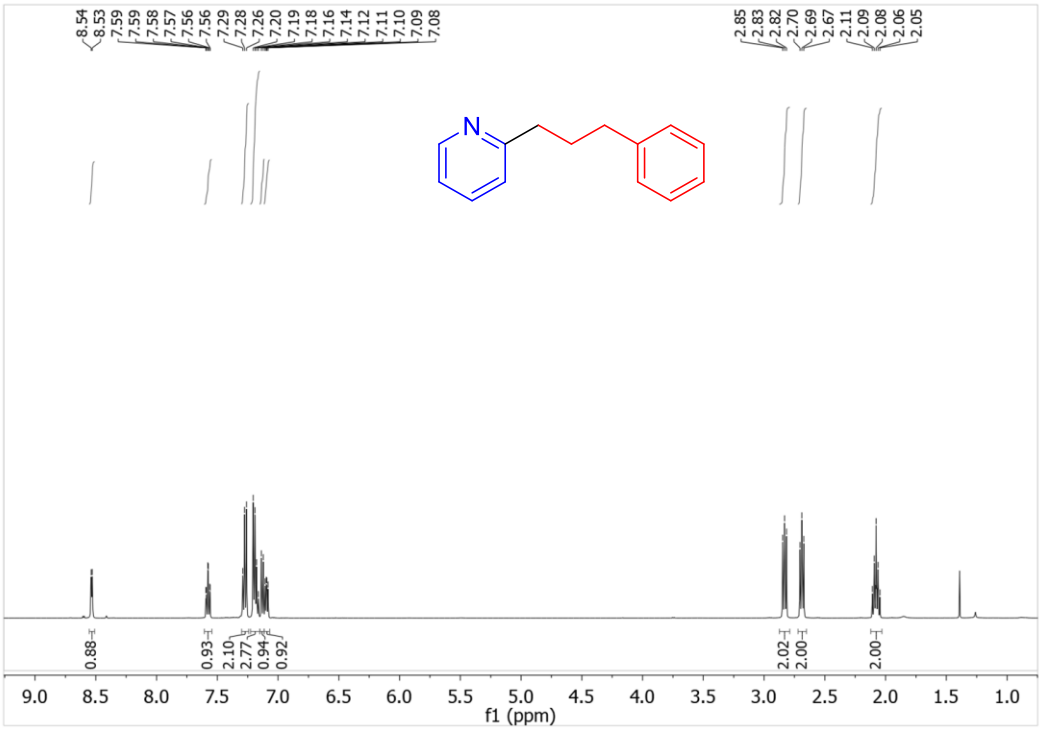


Figure S50. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 2-(3-phenylpropyl)pyridine, derived from substrate **4w**.

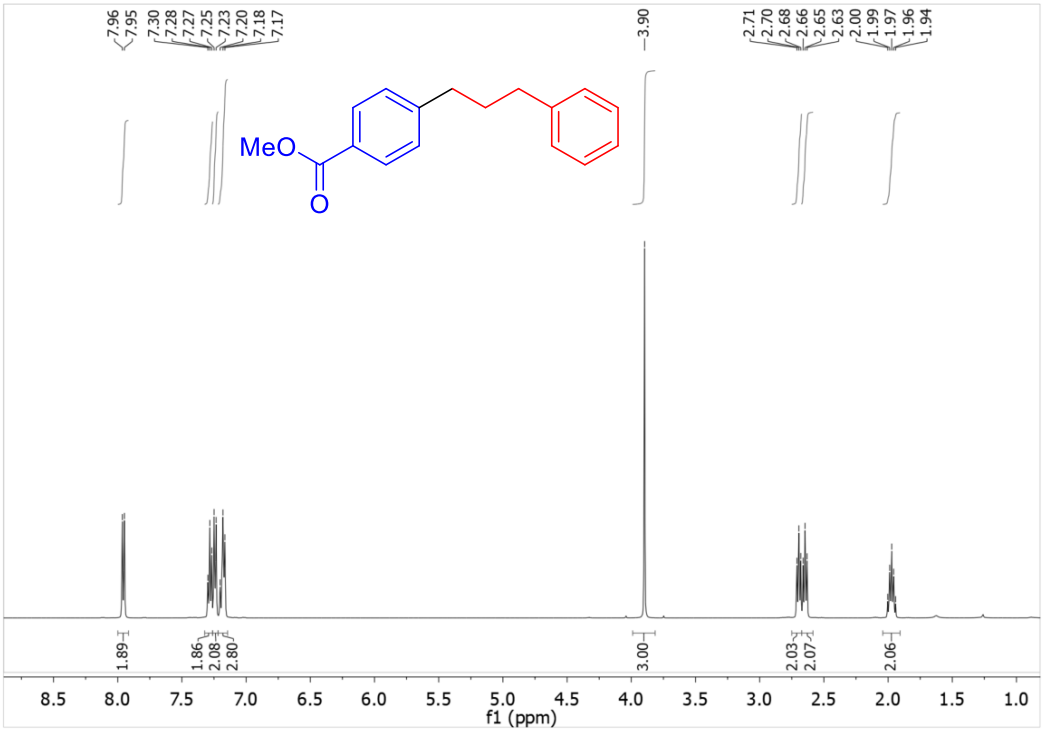


Figure S51. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4-(3-phenylpropyl)methyl-benzoate, derived from substrate **4x**.

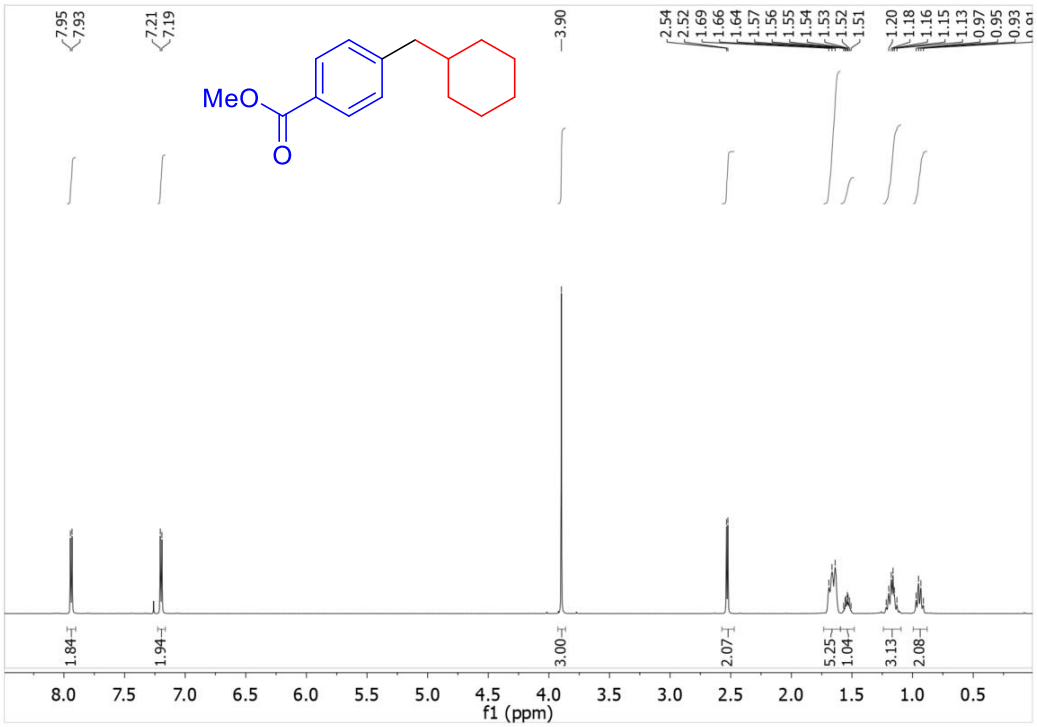


Figure S52. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of methyl 4-(cyclohexylmethyl)benzoate, derived from substrate **4y**.

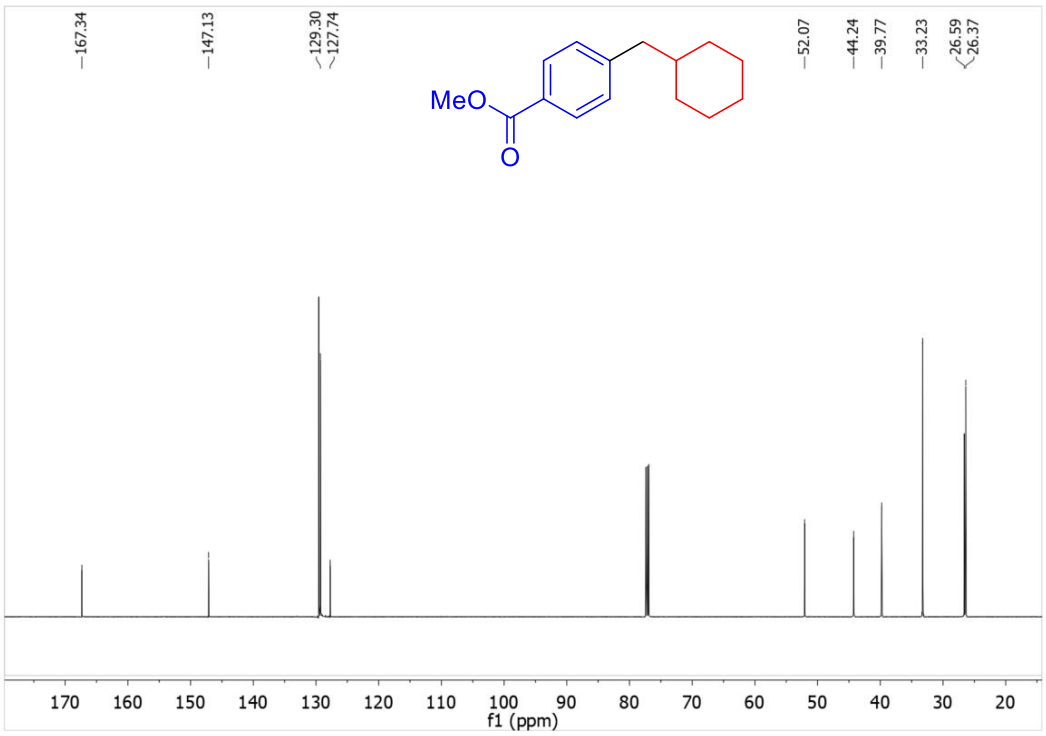


Figure S53. $^{13}C\{^{1}H\}$ NMR spectrum (151 MHz, $CDCl_3$) of methyl 4-(cyclohexylmethyl)benzoate, derived from substrate **4y**.

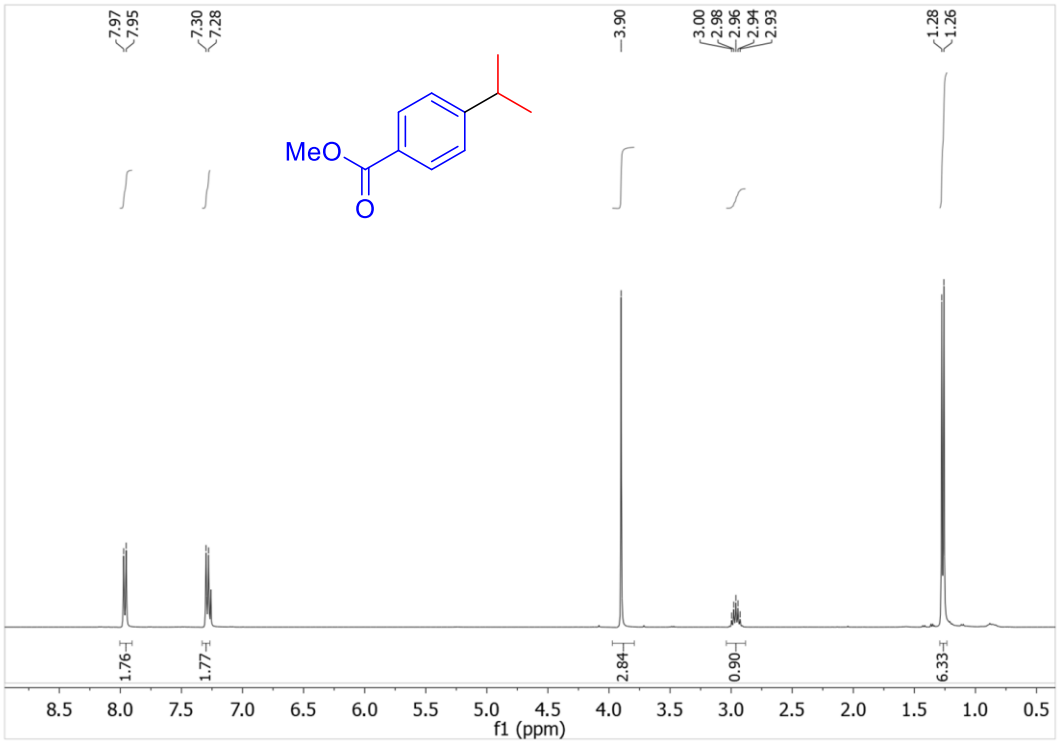


Figure S54. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of methyl 4-isopropylbenzoate, derived from substrate **4z**.

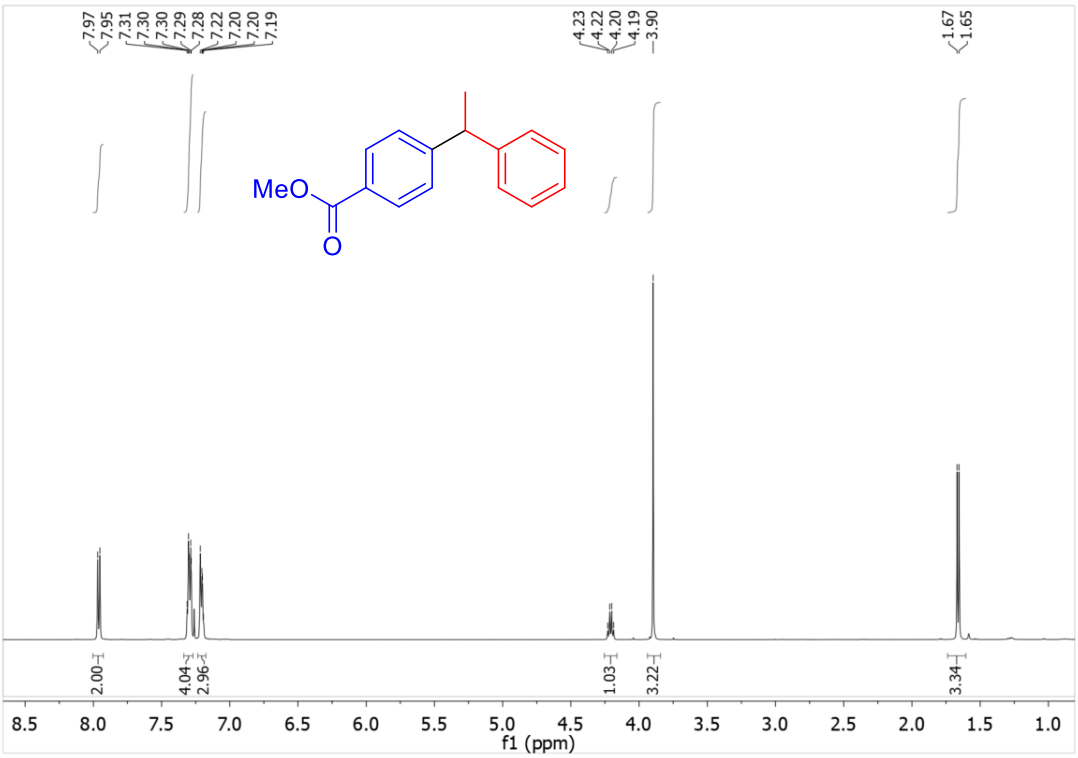


Figure S55. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of methyl 4-(1-phenylethyl)benzoate, derived from substrate **4aa**.

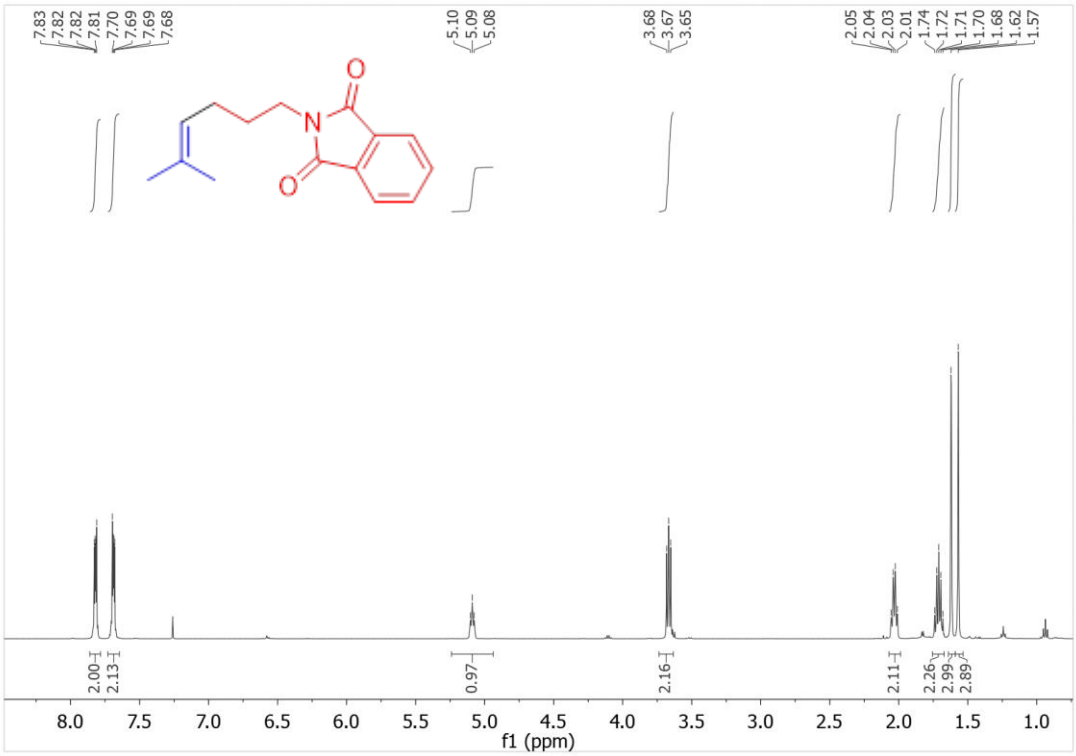


Figure S56. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 2-(5-methylhex-4-enyl)isoindoline-1,3-dione, Scheme 3. The spectrum contains trace residual ethyl acetate and hexanes from purification, which were accounted for when recording the isolated yield of the reaction.

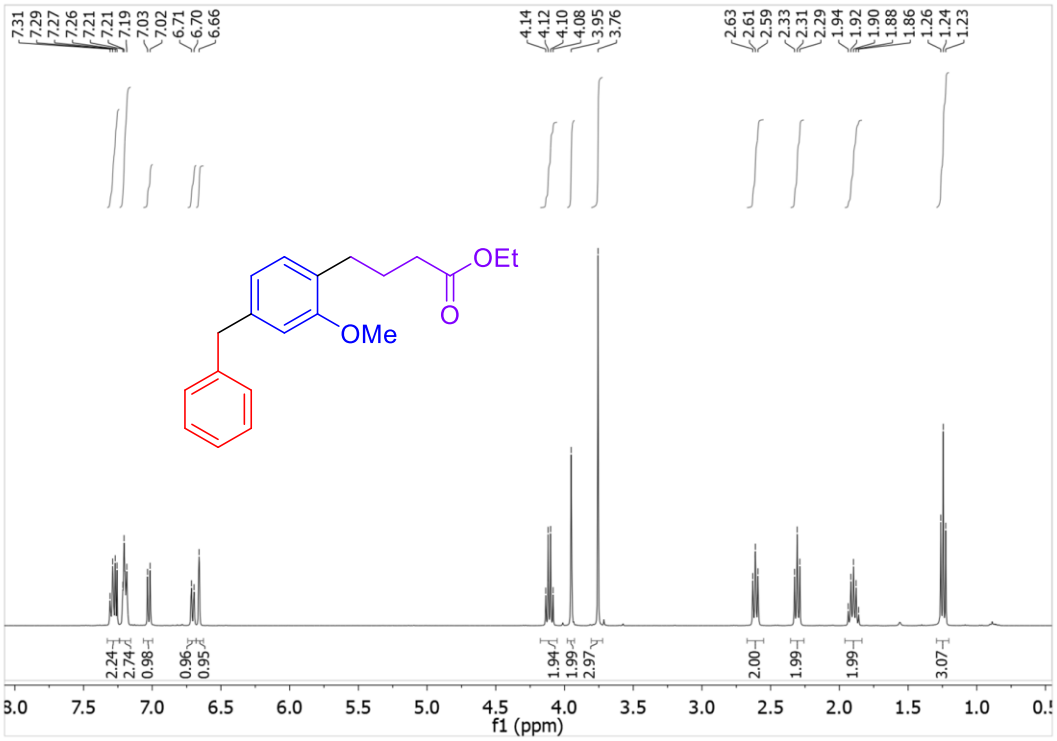


Figure S57. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ethyl 4-(4-benzyl-2-methoxyphenyl)butanoate, Table 4, Entry 1.

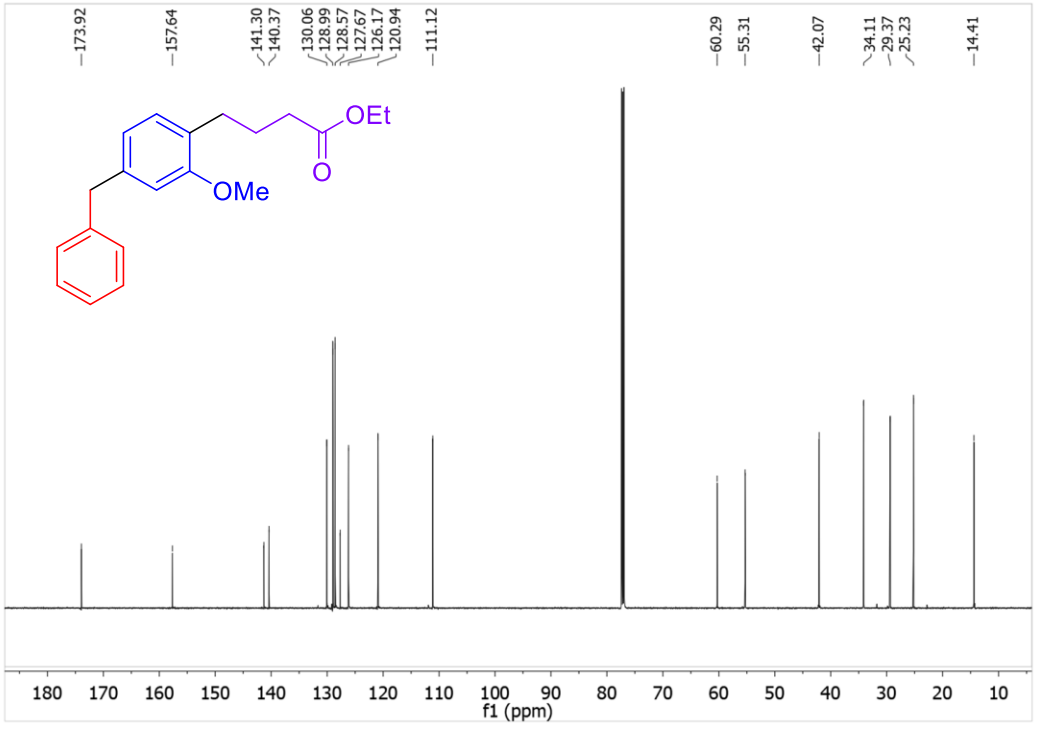


Figure S58. $^{13}C\{^{1}H\}$ NMR spectrum (151 MHz, $CDCl_3$) of ethyl 4-(4-benzyl-2-methoxyphenyl)butanoate, Table 4, Entry 1.

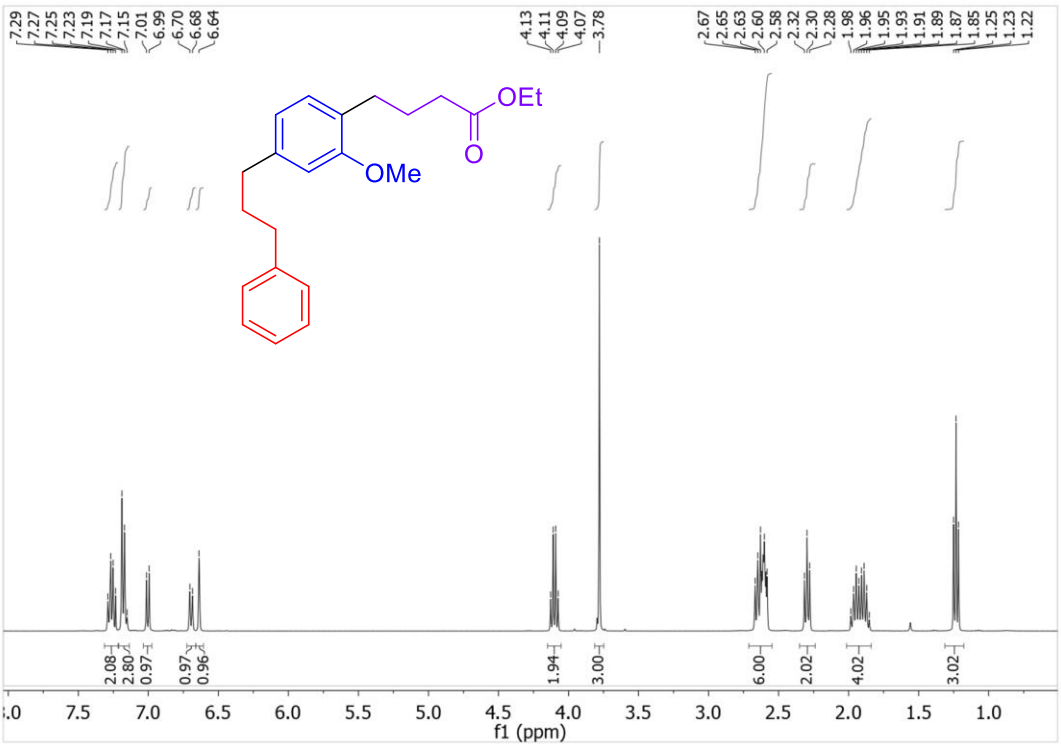


Figure S59. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ethyl 4-(3-methoxy-4-(3-phenylpropyl)phenyl)butanoate, Table 4, Entry 2.

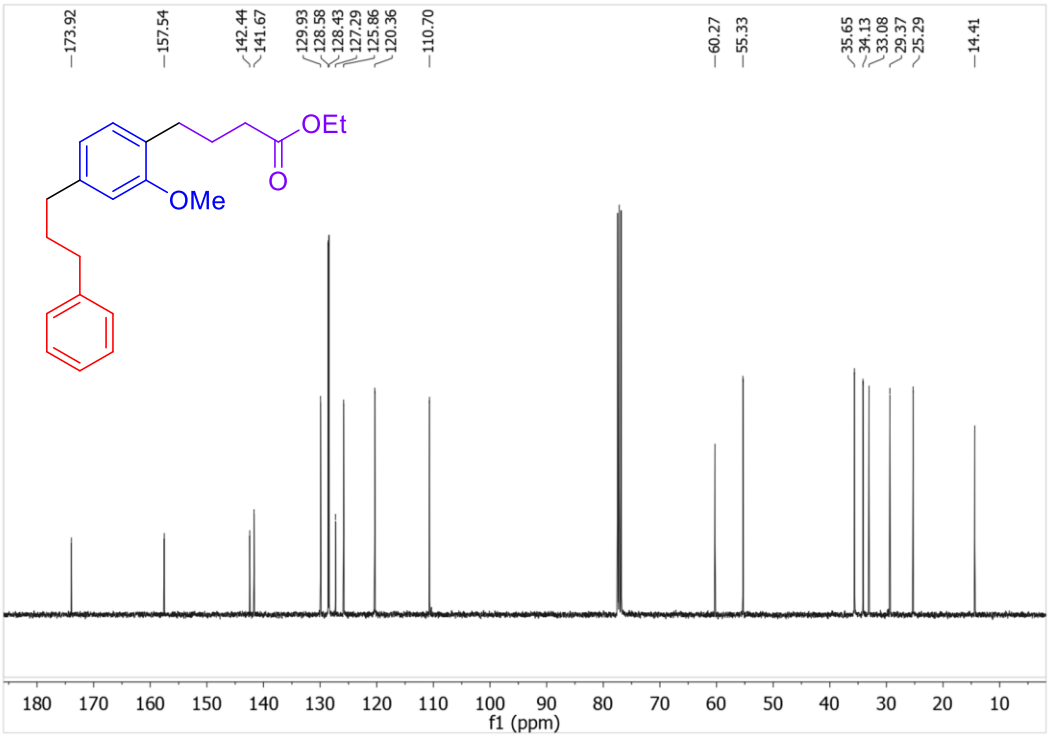


Figure S60. $^{13}C\{^{1}H\}$ NMR spectrum (151 MHz, $CDCl_3$) of ethyl 4-(3-methoxy-4-(3-phenylpropyl)phenyl)butanoate, Table 4, Entry 2.

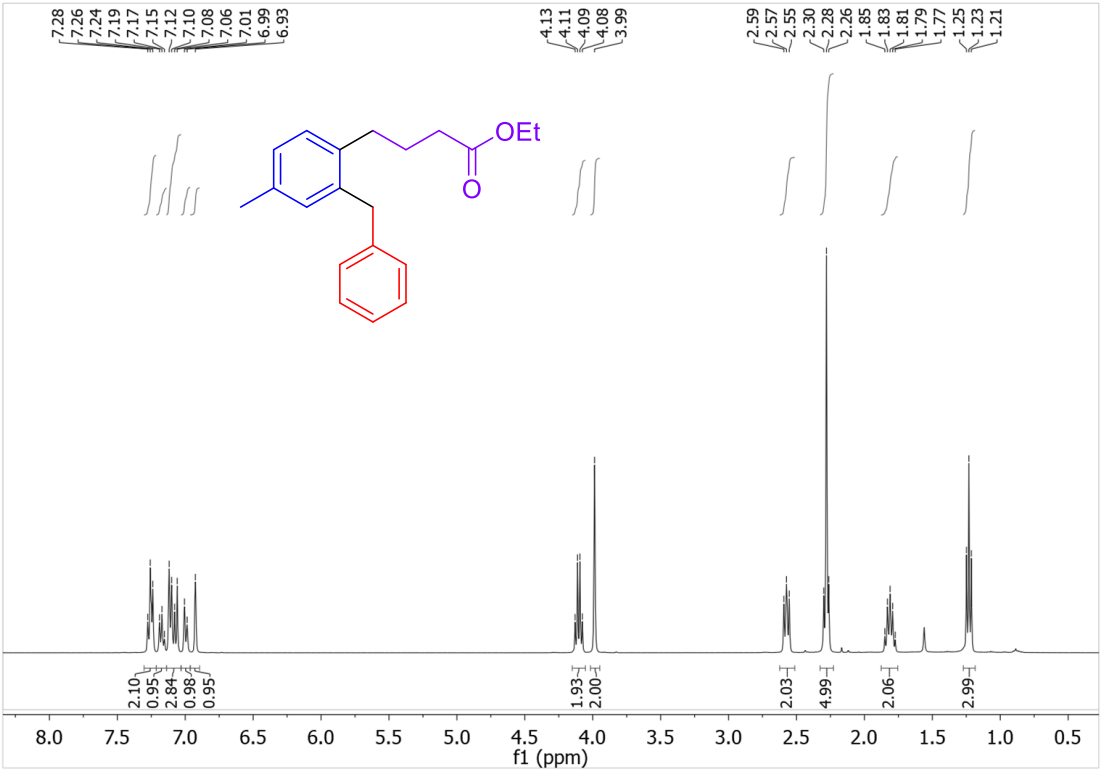


Figure S61. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ethyl 4-(2-benzyl-4-methylphenyl)butanoate, Table 4, Entry 3.

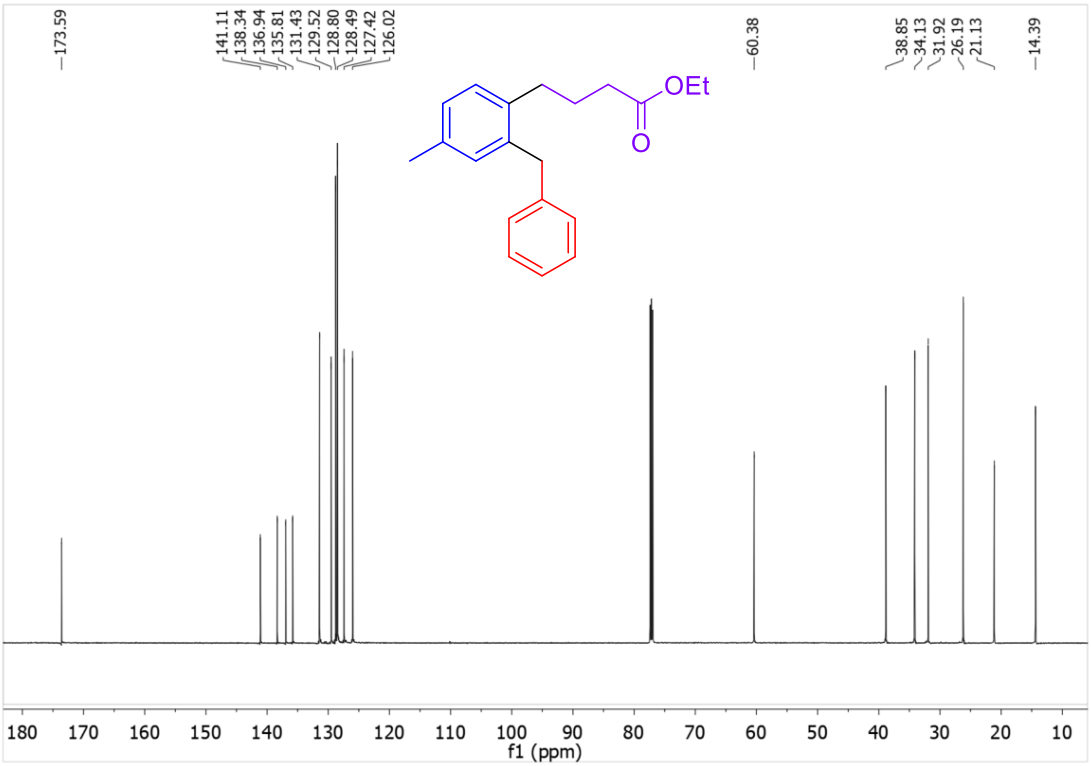


Figure S62. $^{13}C\{^{1}H\}$ NMR spectrum (151 MHz, $CDCl_3$) of ethyl 4-(2-benzyl-4-methylphenyl)butanoate, Table 4, Entry 3.

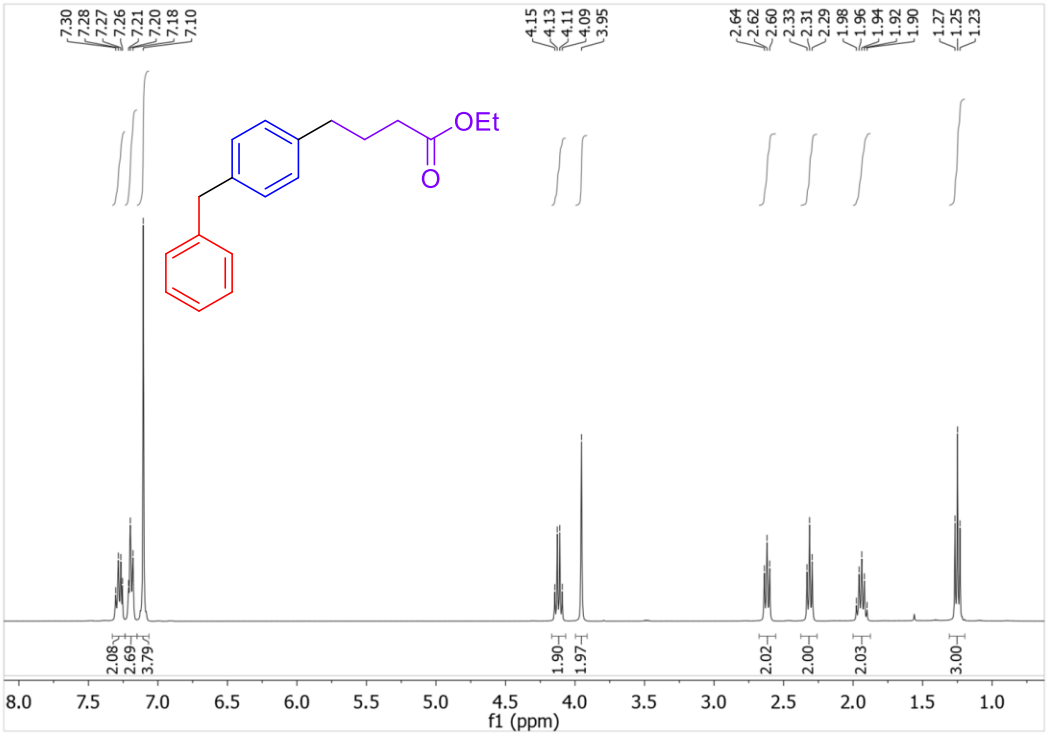


Figure S63. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ethyl 4-(4-benzylphenyl)butanoate, Table 4, Entry 4.

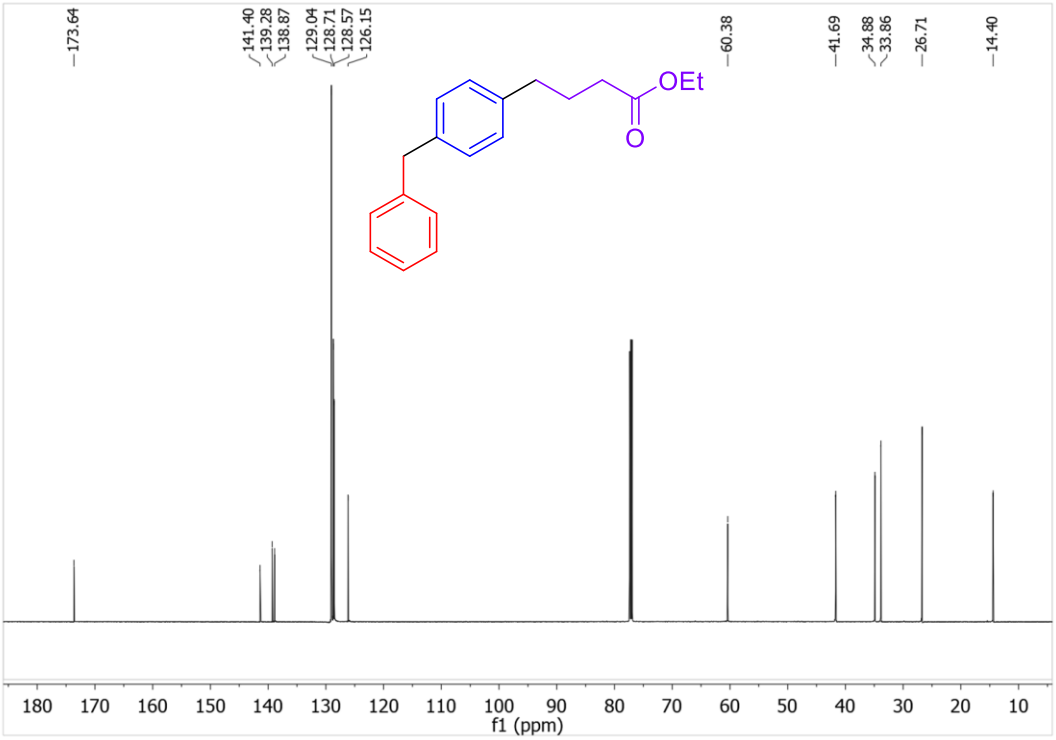


Figure S64. $^{13}C\{^{1}H\}$ NMR spectrum (151 MHz, $CDCl_3$) of ethyl 4-(4-benzylphenyl)butanoate, Table 4, Entry 4.

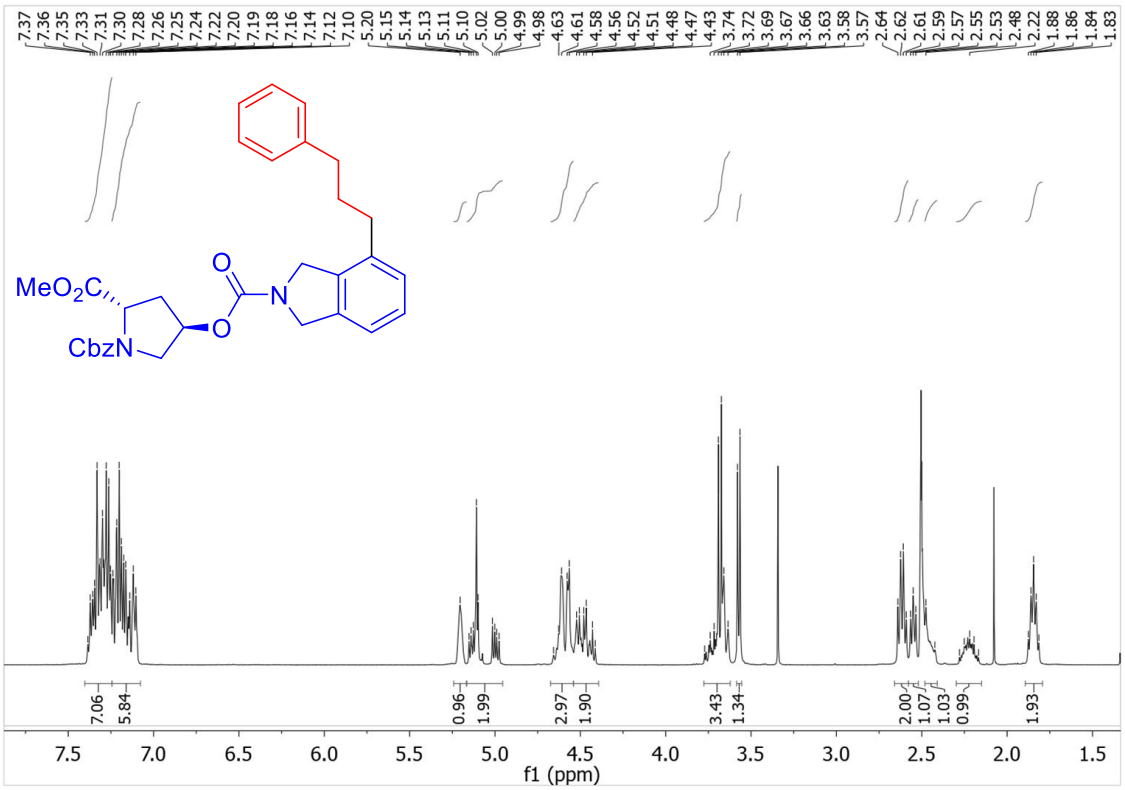


Figure S65. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of product derived from **5b**.

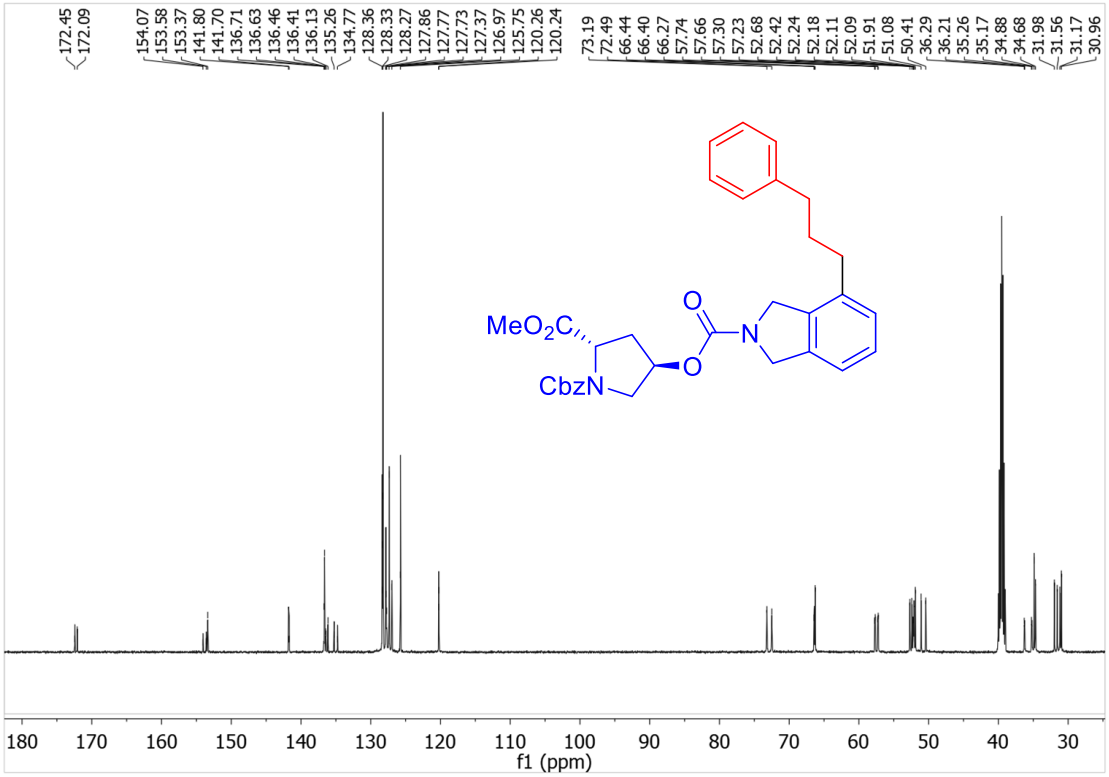


Figure S66. ^{13}C{^{1}H} NMR spectrum (151 MHz, DMSO-d_6) of product derived from **5b**.

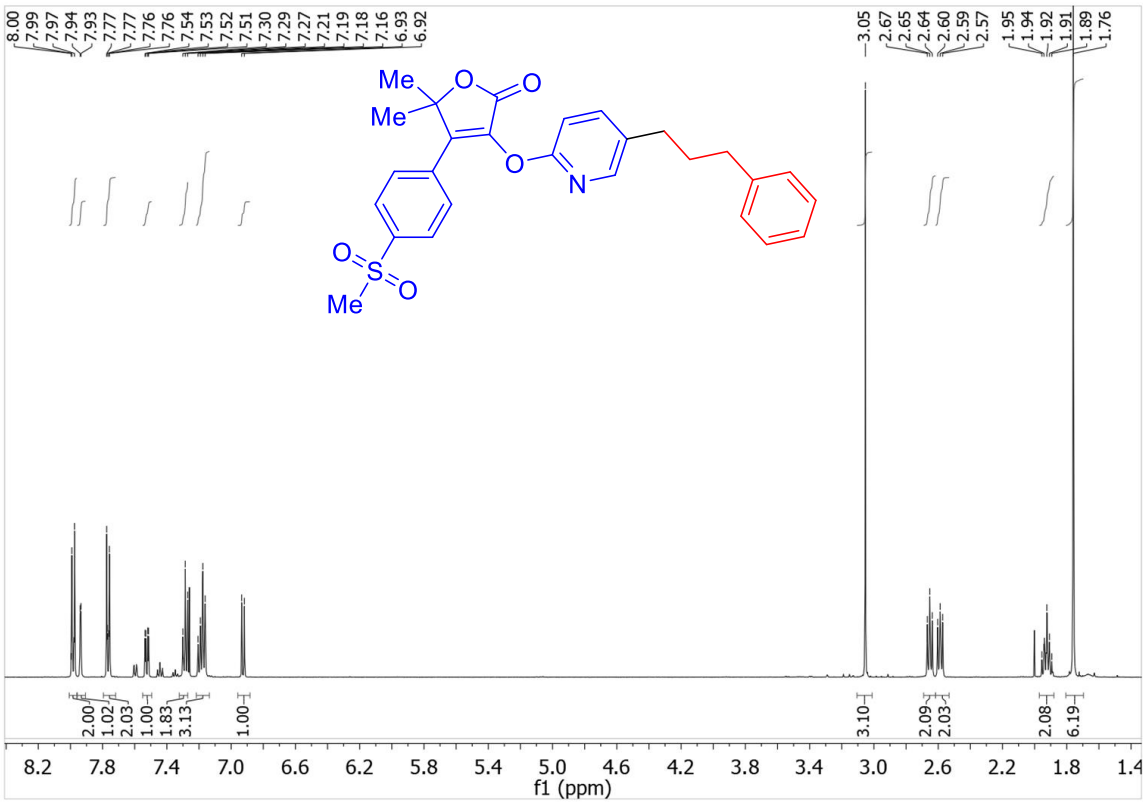


Figure S67. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of product derived from **5c**.

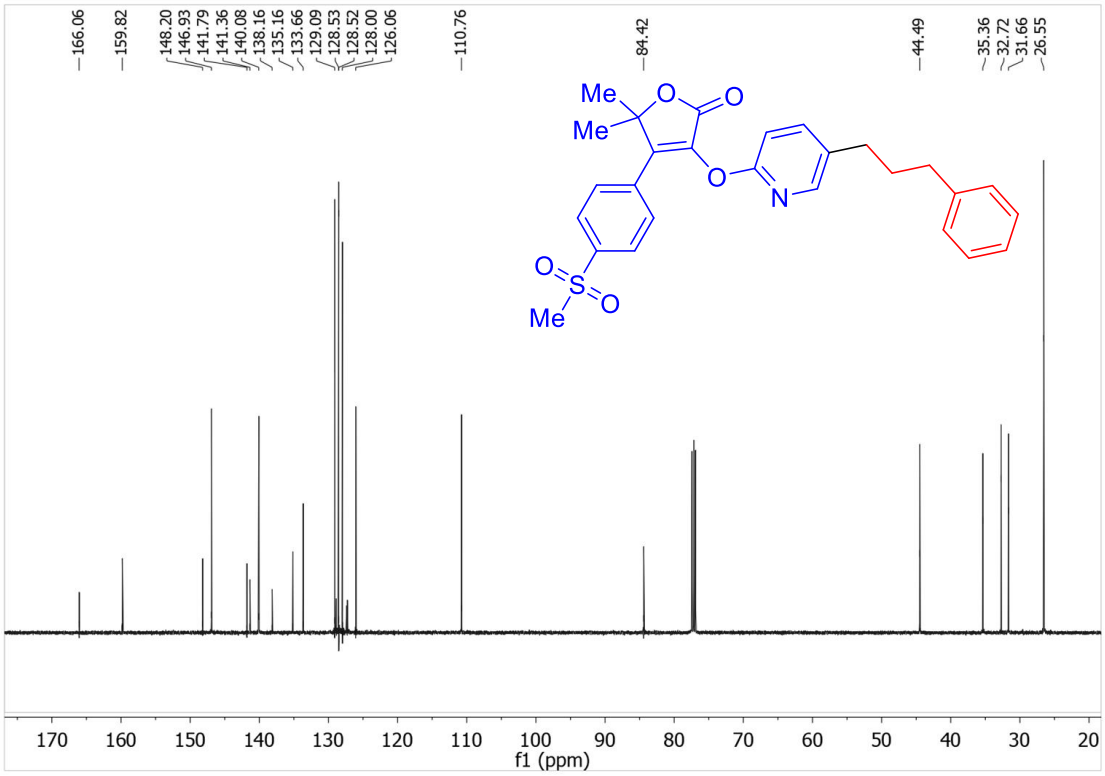


Figure S68. $^{13}C\{^{1}H\}$ NMR spectrum (151 MHz, $CDCl_3$) of product derived from **5c**.

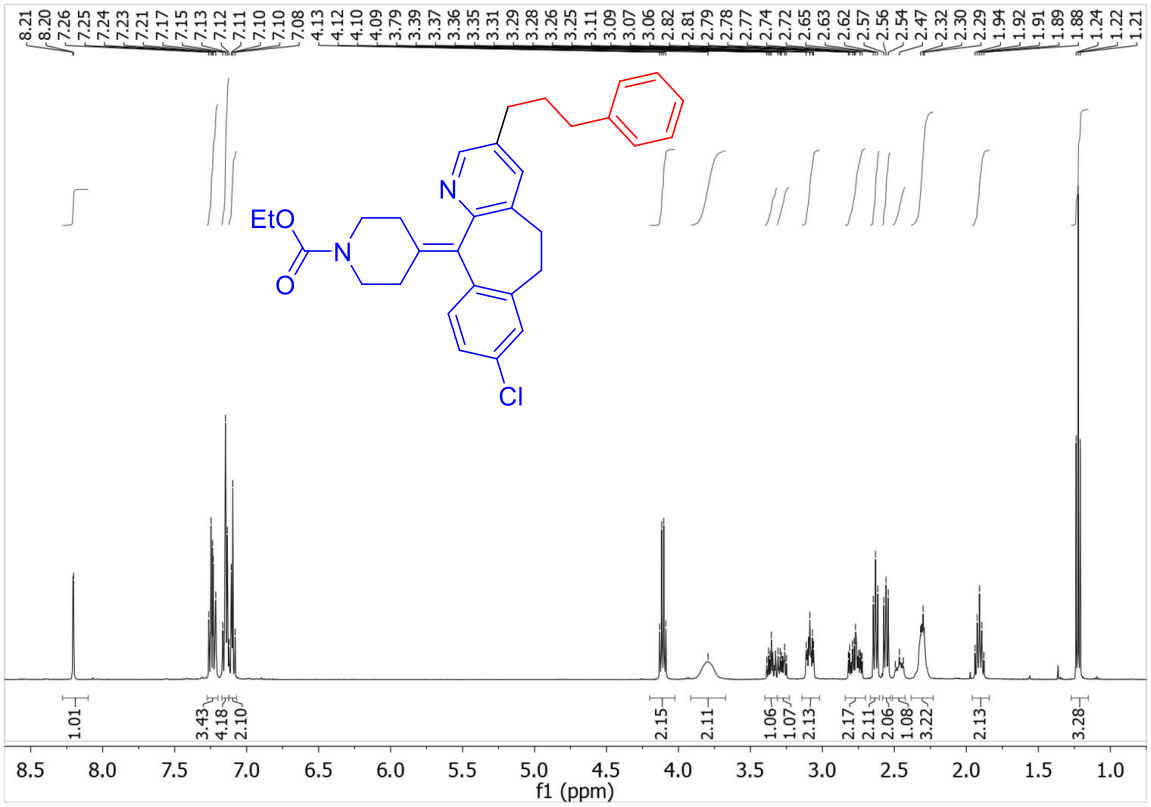


Figure S69. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of product derived from **5d**.

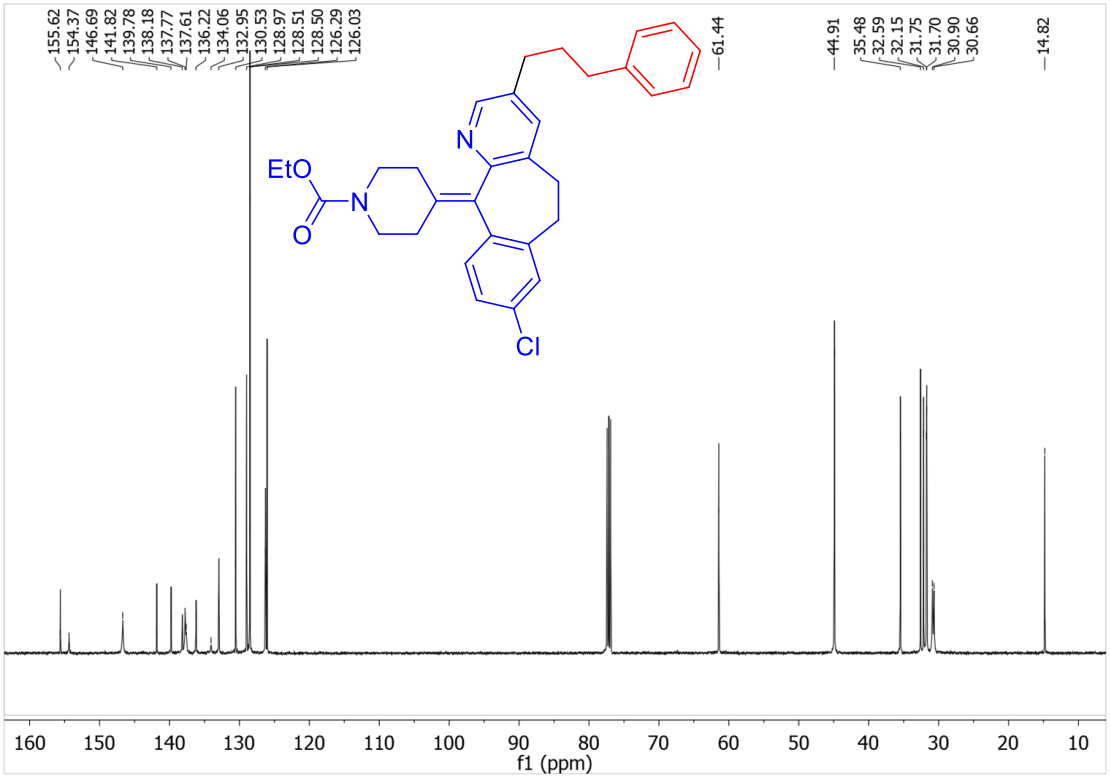


Figure S70. $^{13}C\{^{1}H\}$ NMR spectrum (151 MHz, $CDCl_3$) of product derived from **5d**.

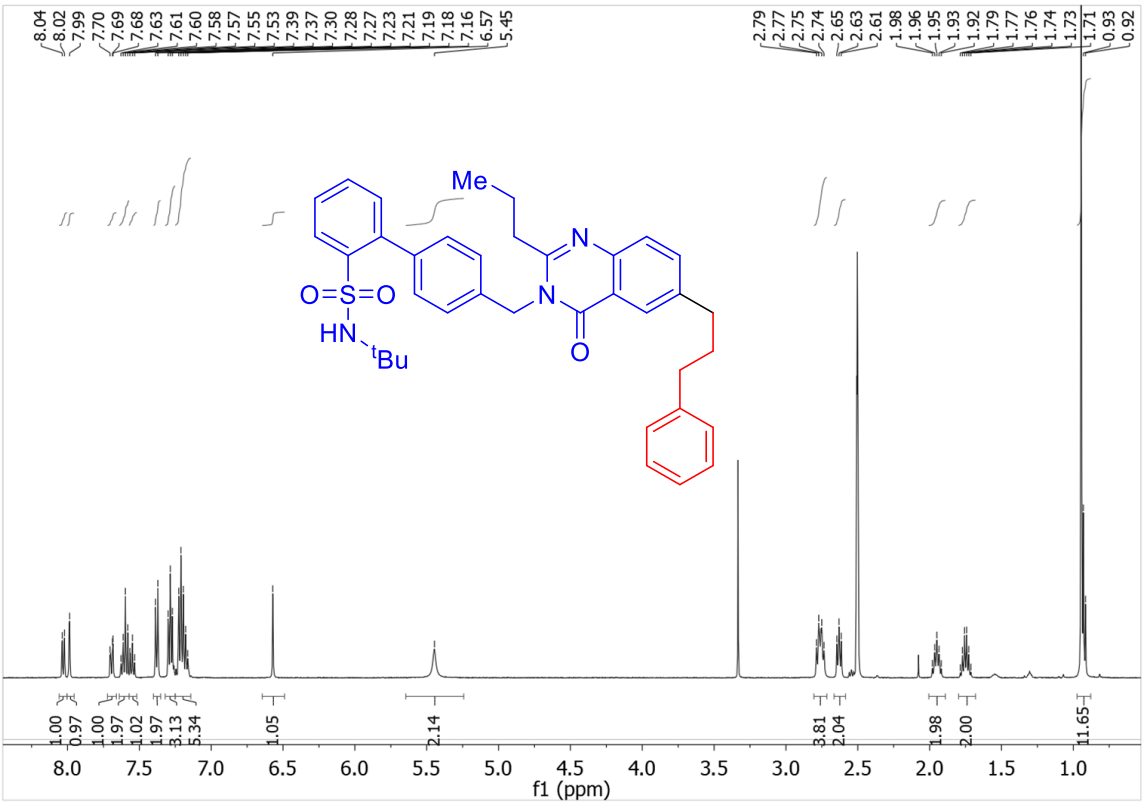


Figure S71. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of product derived from **5e**.

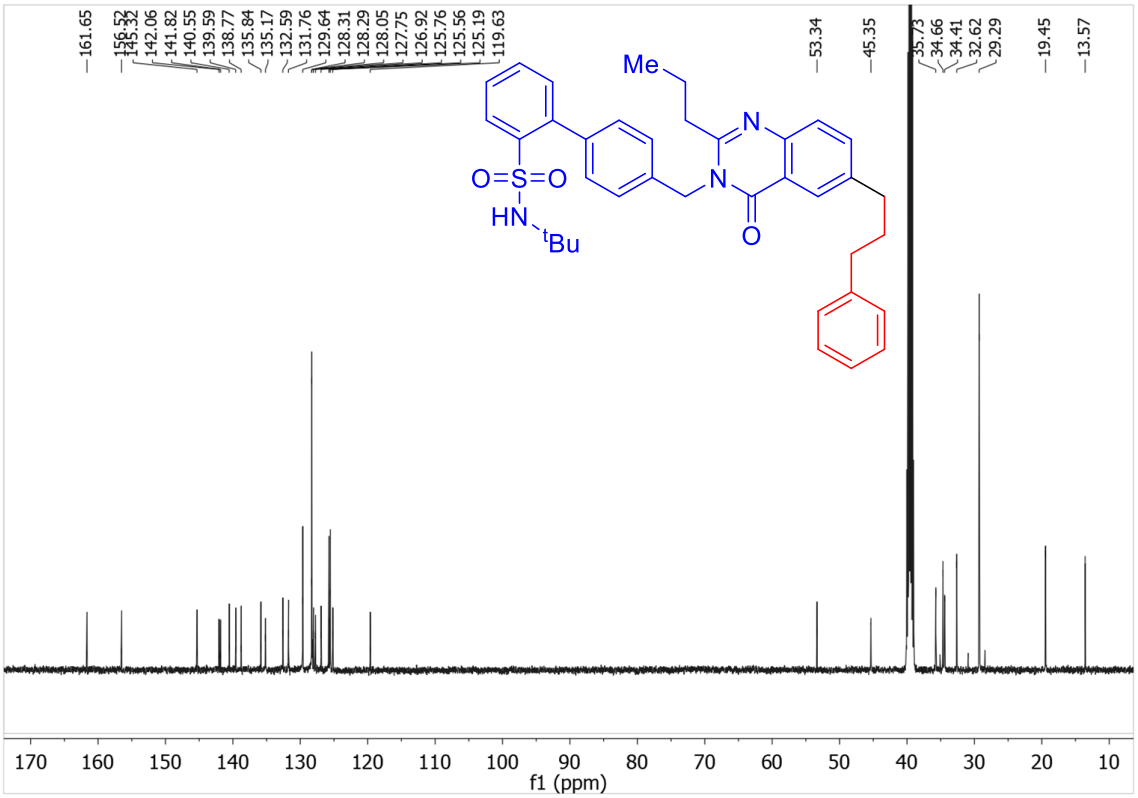


Figure S72. ^{13}C{^{1}H} NMR spectrum (151 MHz, DMSO-d_6) of **p**roduct derived from **5e**.

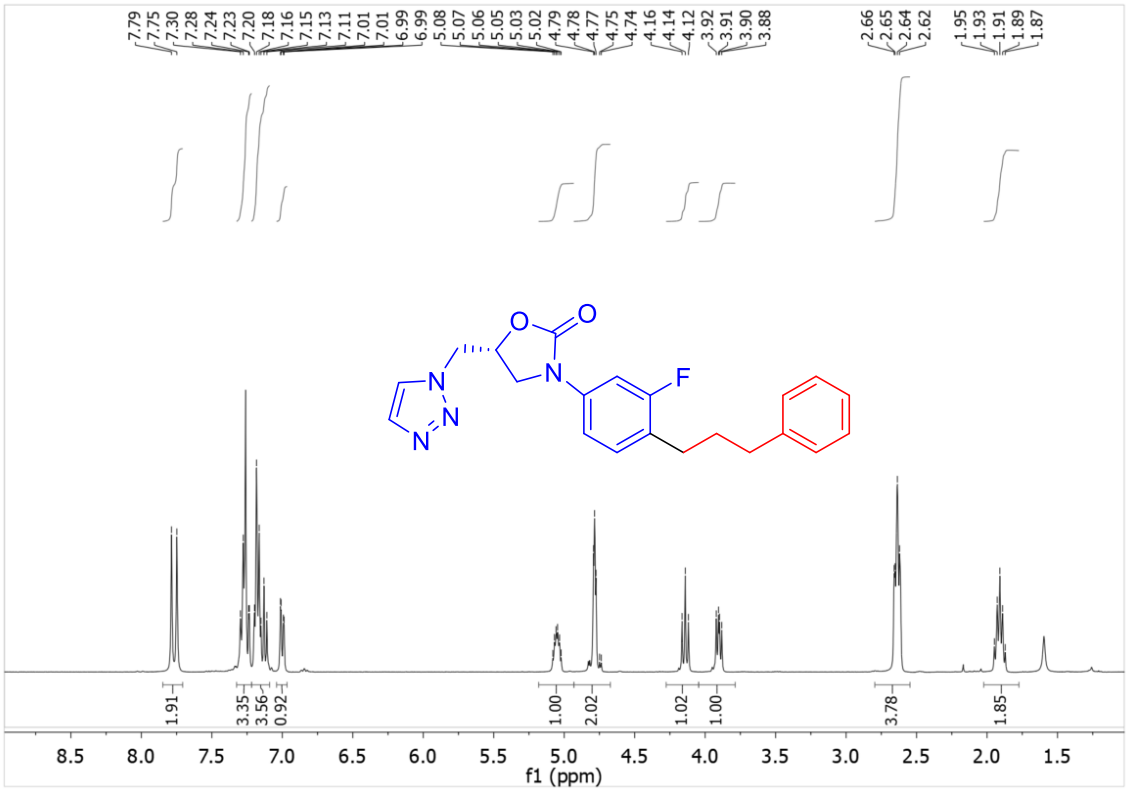


Figure S73. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of product derived from **5f**.

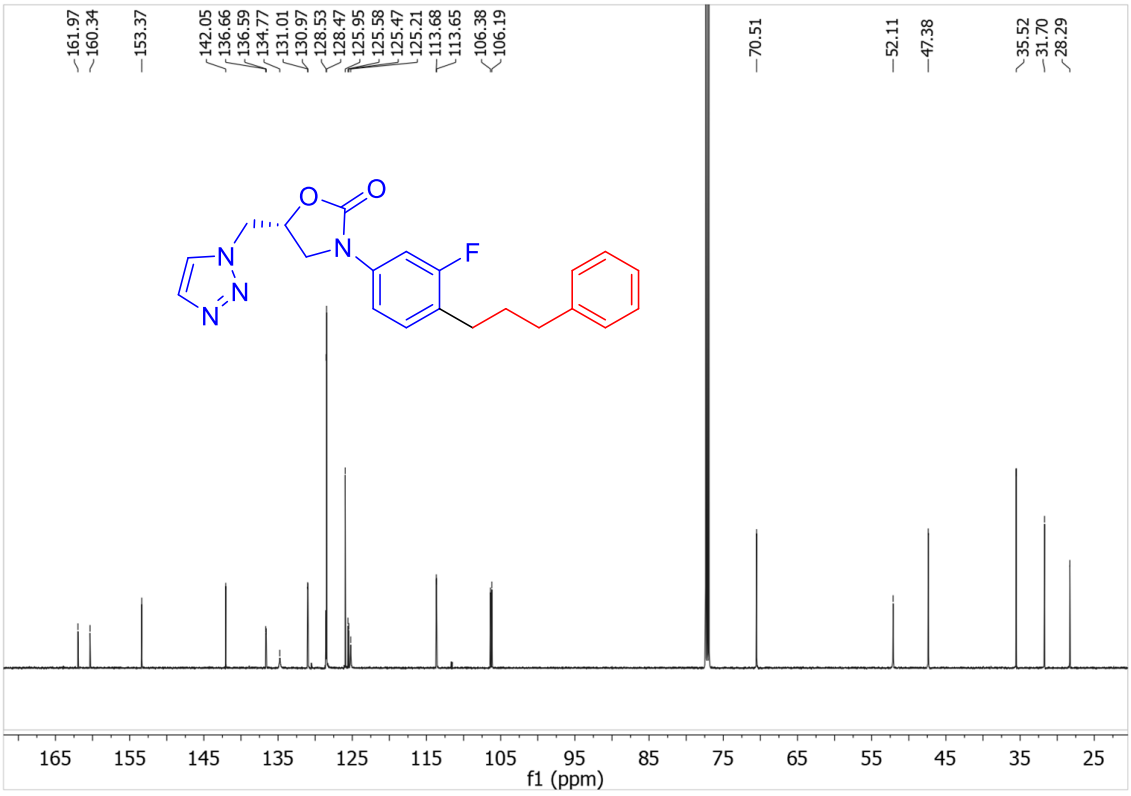


Figure S74. $^{13}C\{^{1}H\}$ NMR spectrum (151 MHz, $CDCl_3$) of product derived from **5f**.

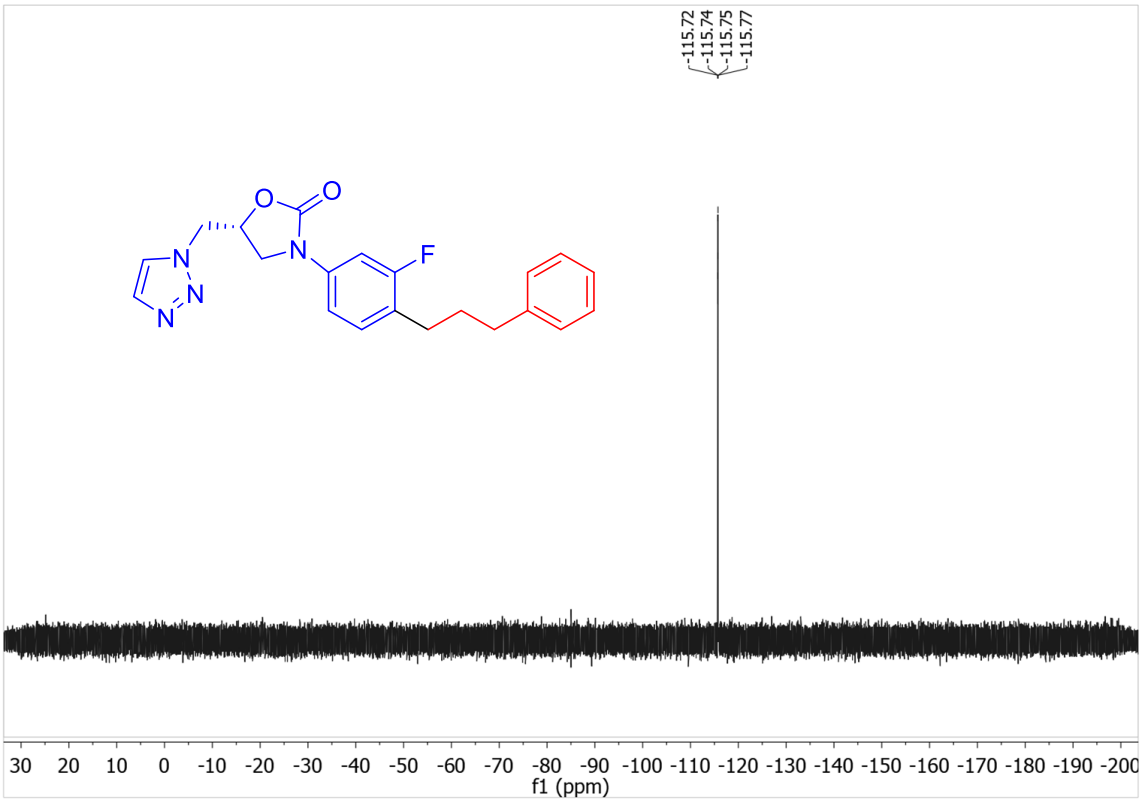


Figure S75. ^{19}F NMR spectrum (400 MHz, $CDCl_3$) of product derived from **5f**.

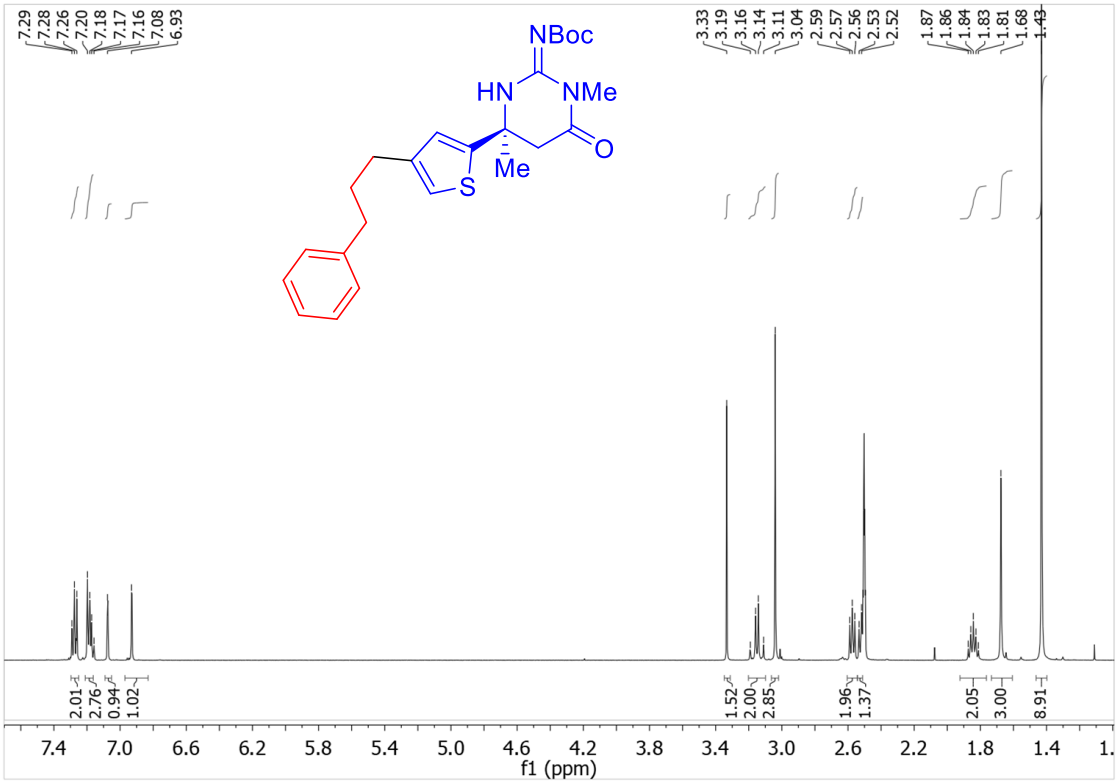


Figure S76. ^{1}H NMR spectrum (400 MHz, DMSO-d$_6$) of product derived from **5g**.

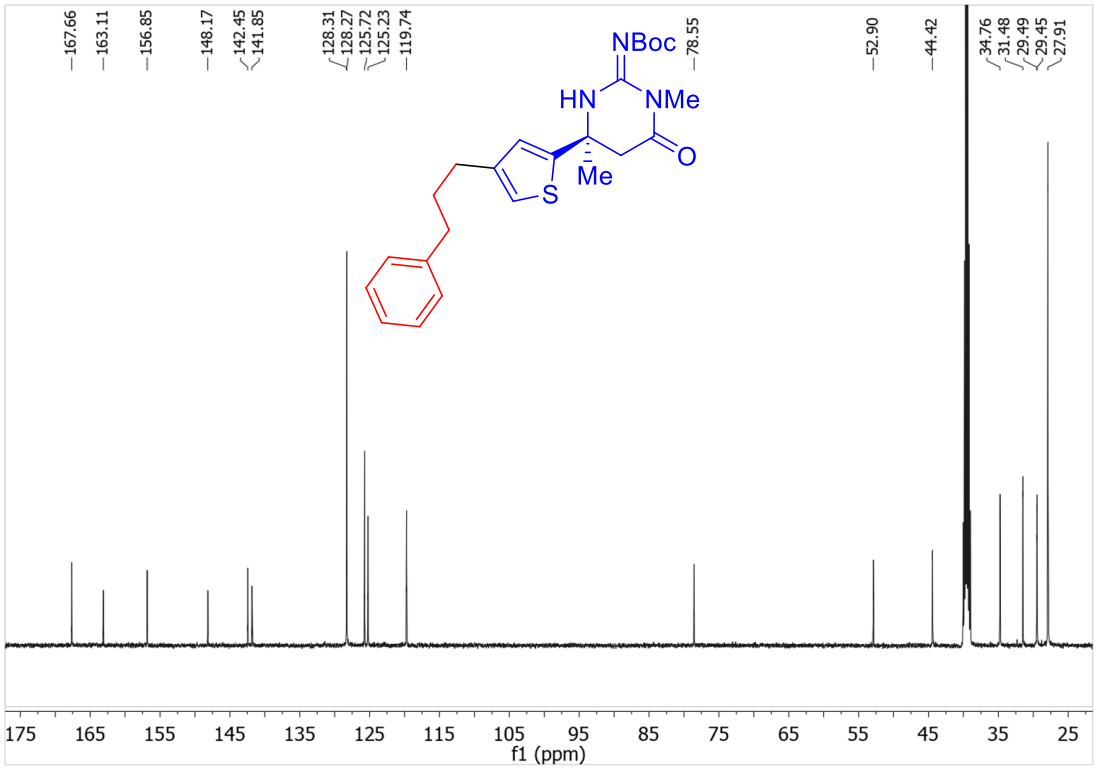


Figure S77. ^{13}C{^{1}H} NMR spectrum (151 MHz, DMSO-d$_6$) of product derived from **5g**.

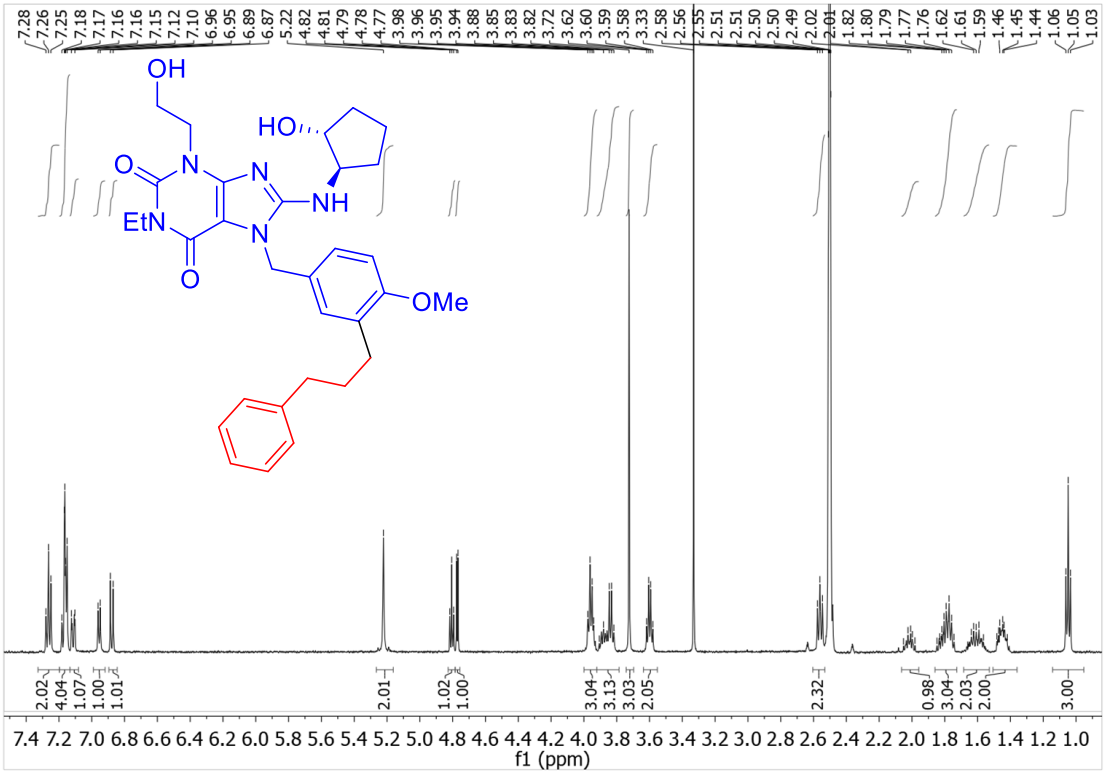


Figure S78. ^{1}H NMR spectrum (400 MHz, DMSO-d$_6$) of product derived from **5h**.

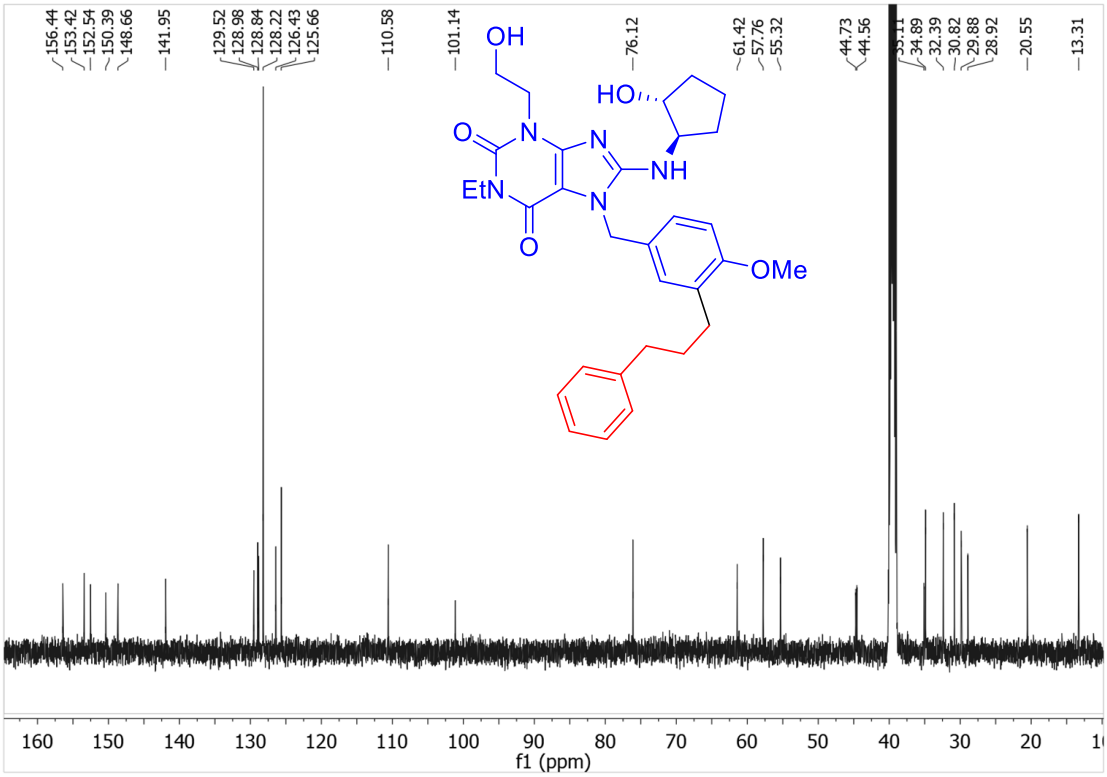


Figure S79. ^{13}C{^{1}H} NMR spectrum (151 MHz, DMSO-d$_6$) of product derived from **5h**.

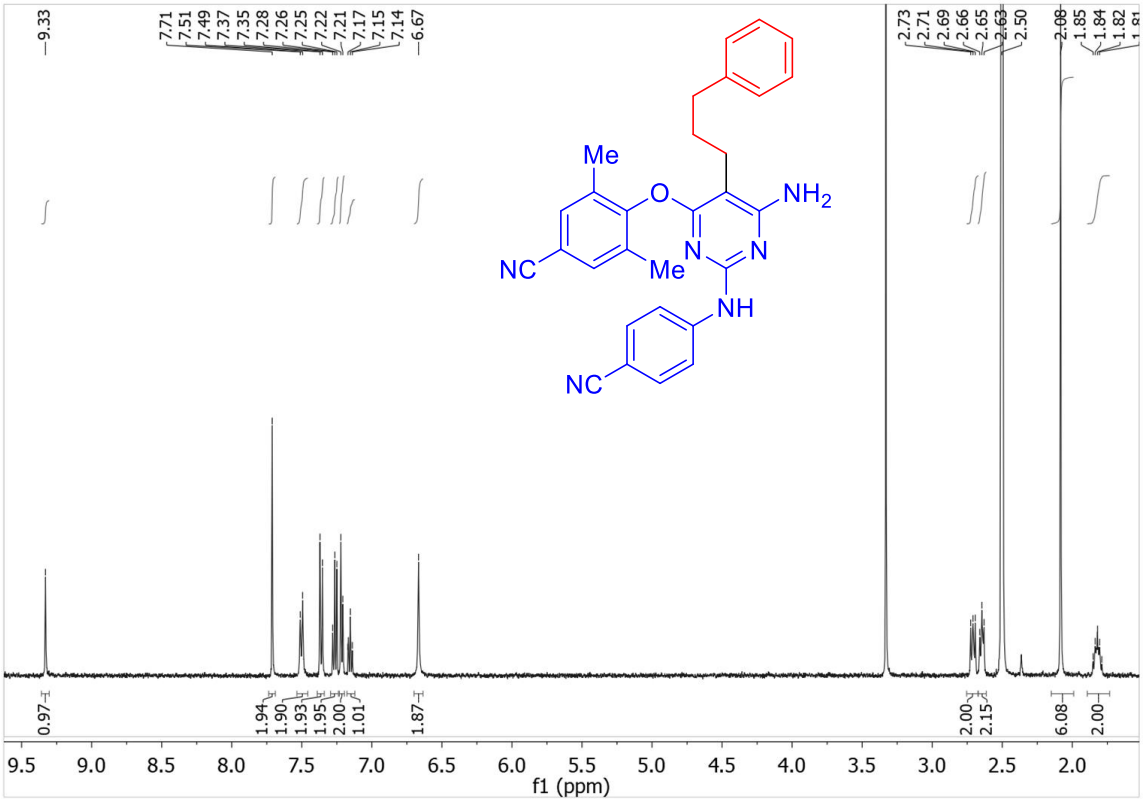


Figure S80. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of product derived from **5i**.

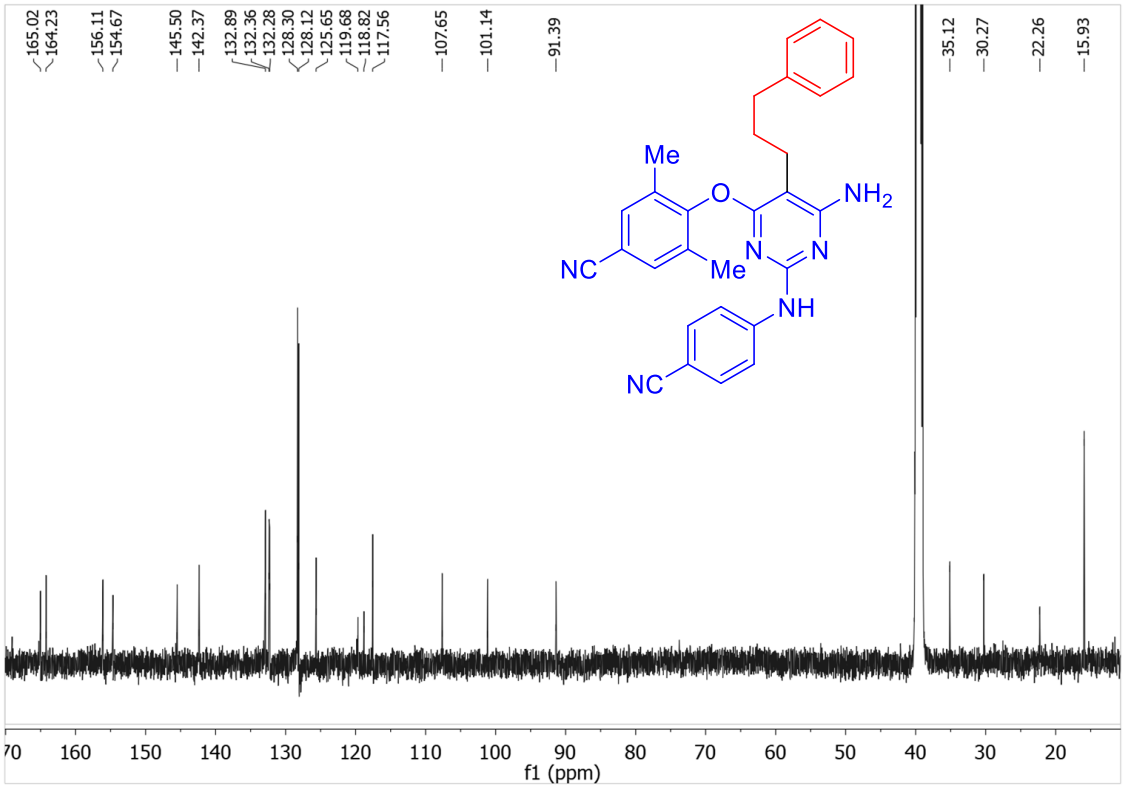


Figure S81. $^{13}C\{^{1}H\}$ NMR spectrum (151 MHz, DMSO-d_6) of product derived from **5i**.

SXXIX. UPLC Traces from HTE Experiments for Optimization of Drug-Like Aryl Halides with 1-Bromo-3-Phenylpropane

General Information:

The UPLC traces shown in this section depict the UPLC traces obtained from HTE experiments for the optimization of drug-like aryl halides with 1-bromo-3-phenylpropane (see section SXX). One UPLC trace is shown for each aryl halide, which corresponds to the conditions that were utilized to obtain ^{1}H NMR yields for the reaction (Figure 5 of manuscript). However, because the reaction with aryl halide **5i** was optimized further beyond HTE optimization, no UPLC trace is shown for this substrate. Some traces include an internal standard (biphenyl), but this introduced problems for data analysis (overlapping peaks) in the first set of HTE experiments and so was removed for subsequent experiments.

In the UPLC traces, product (Aryl-Alkyl) signals are colored in dark blue, aryl halide starting material signals are colored teal, biaryl (Aryl-Aryl) signals are colored orange, protodehalogenation (Aryl-H) signals are colored forest green, and internal standard (biphenyl) signals are colored violet (where applicable).

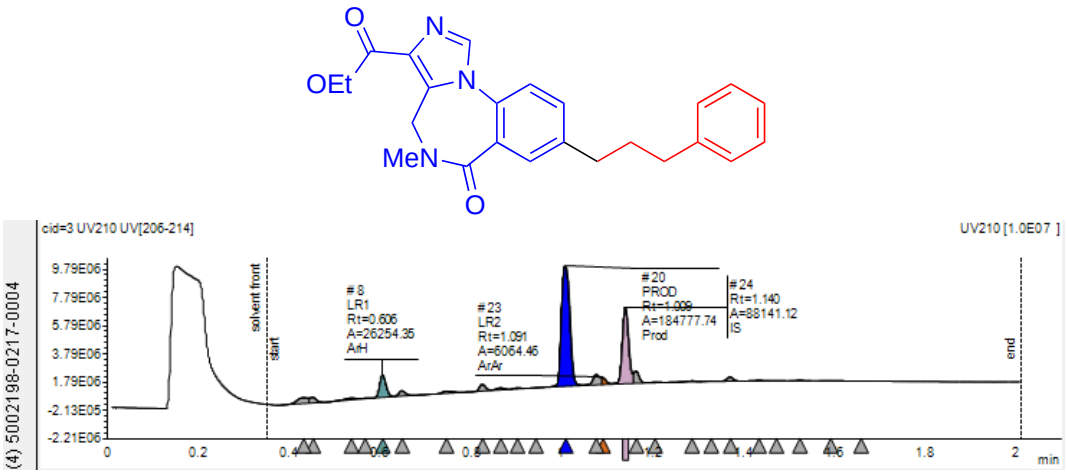


Figure S82. UPLC trace for the optimized reaction conditions of the coupling of aryl halide **5a** with 1-bromo-3-phenylpropane.

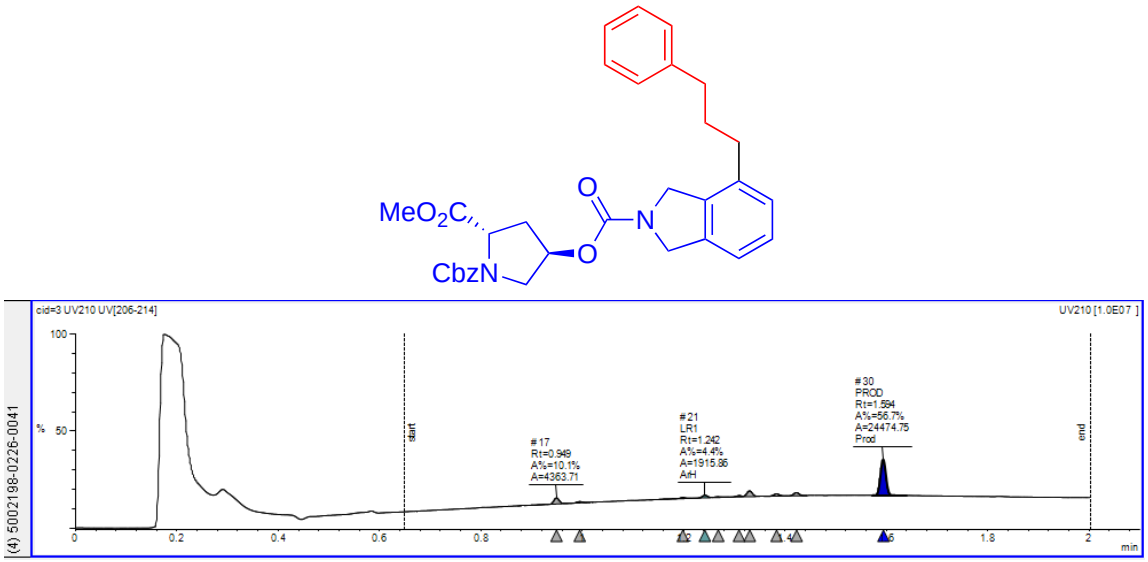


Figure S83. UPLC trace for the optimized reaction conditions of the coupling of aryl halide **5b** with 1-bromo-3-phenylpropane.

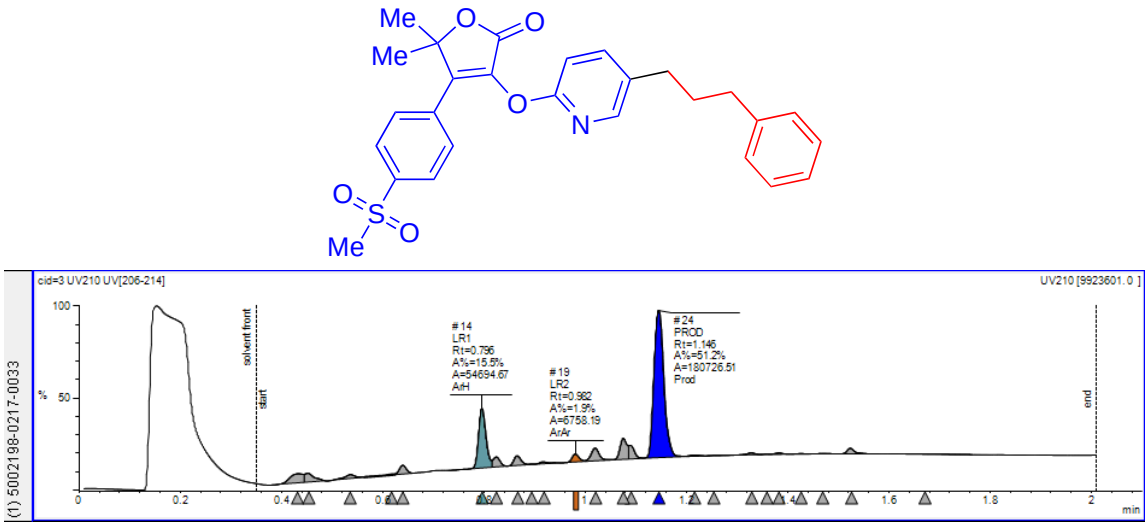


Figure S84. UPLC trace for the optimized reaction conditions of the coupling of aryl halide **5c** with 1-bromo-3-phenylpropane.

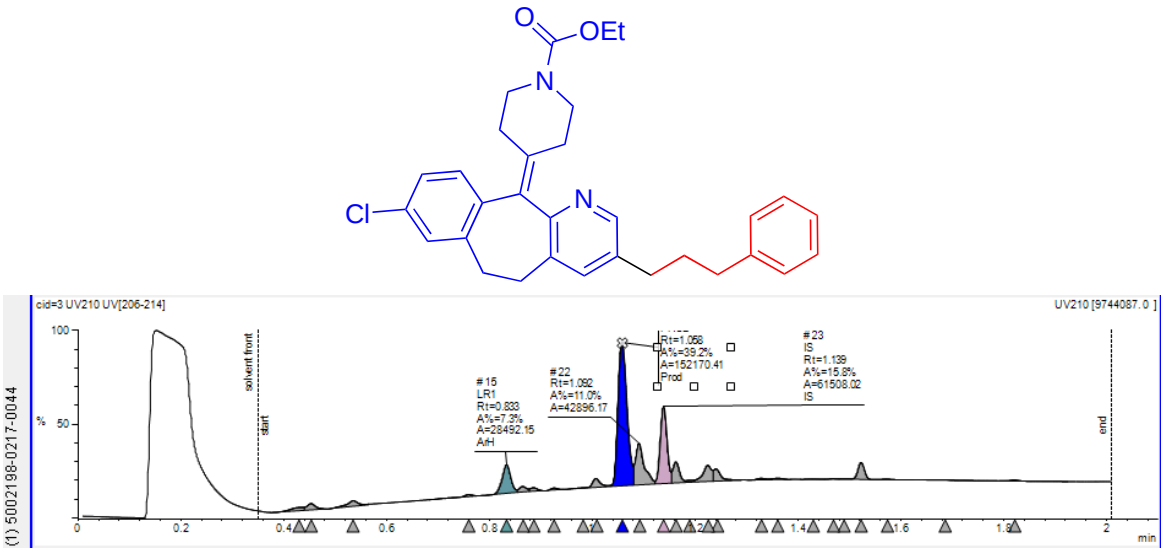


Figure S85. UPLC trace for the optimized reaction conditions of the coupling of aryl halide **5d** with 1-bromo-3-phenylpropane.

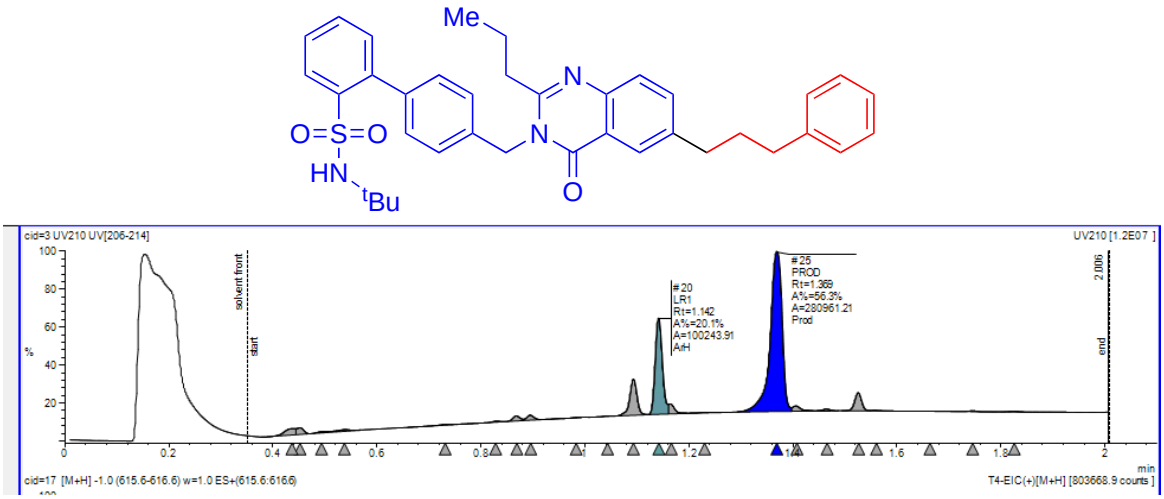


Figure S86. UPLC trace for the optimized reaction conditions of the coupling of aryl halide **5e** with 1-bromo-3-phenylpropane. Note: Aryl-Alkyl overlaps with Aryl-Iodide and Aryl-H overlaps with biphenyl internal standard in chromatograph. Low quantities of Aryl-H and Aryl-Iodide were determined by mass spectrometry ion count, consistent with the high ^{1}H NMR yield (91%) of the reaction.

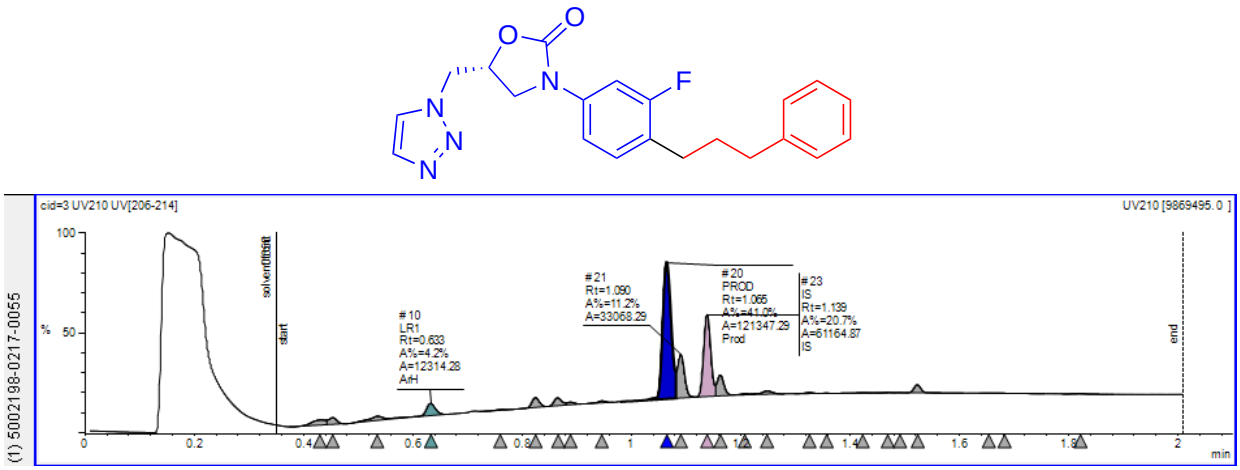


Figure S87. UPLC trace for the optimized reaction conditions of the coupling of aryl halide **5f** with 1-bromo-3-phenylpropane.

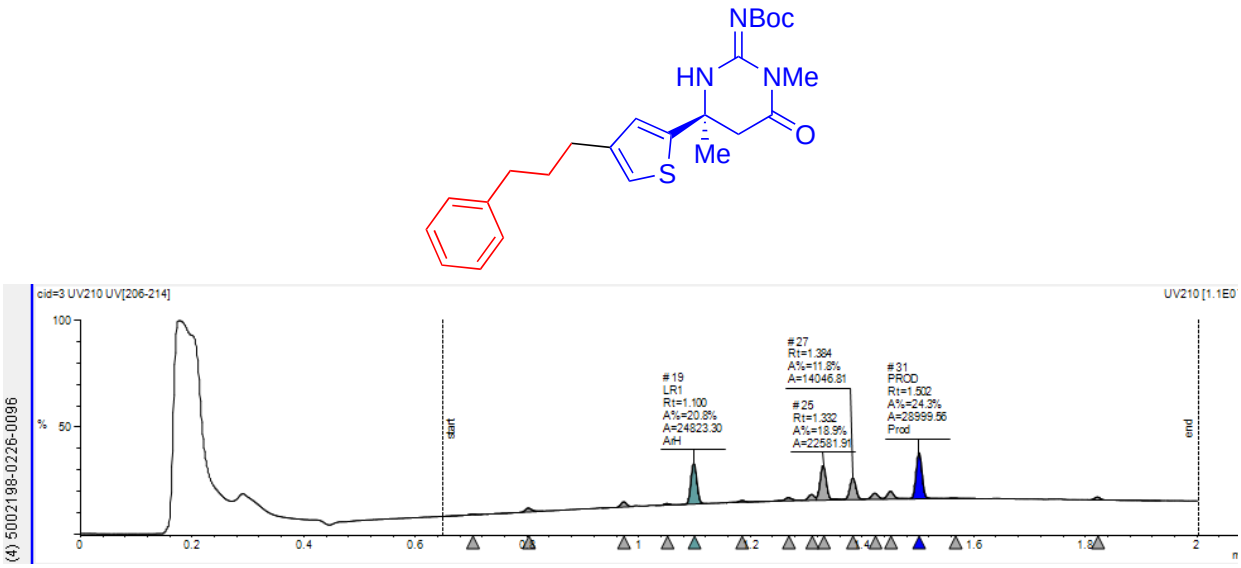


Figure S88. UPLC trace for the optimized reaction conditions of the coupling of aryl halide **5g** with 1-bromo-3-phenylpropane.

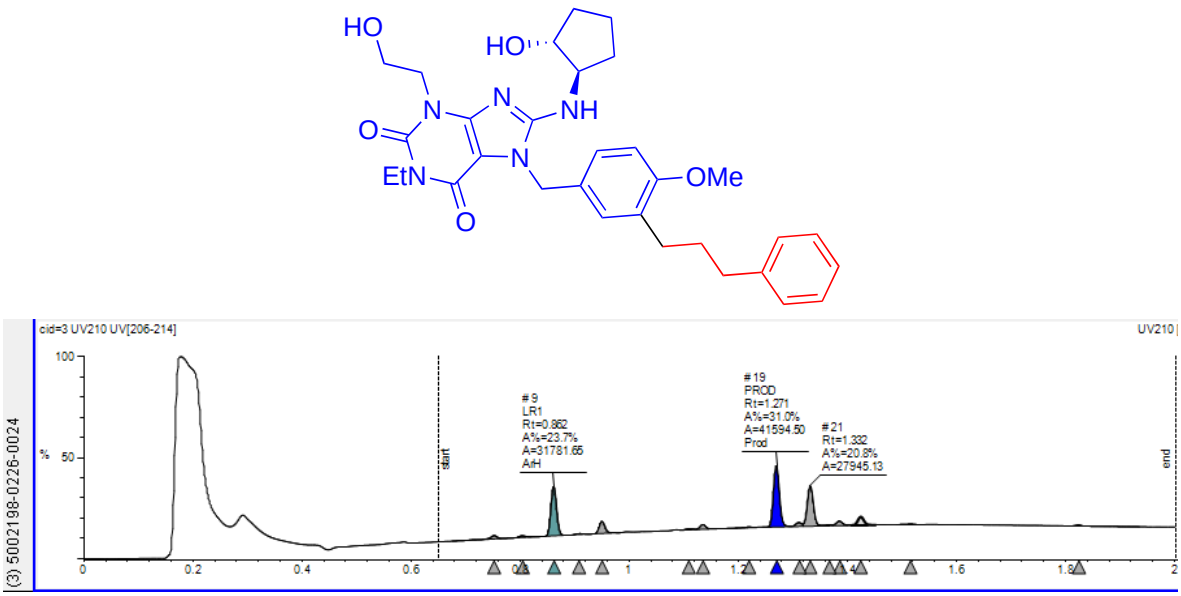


Figure S89. UPLC trace for the optimized reaction conditions of the coupling of aryl halide **5h** with 1-bromo-3-phenylpropane.

SXXX. UPLC Traces from HTE Experiments for Parallel Library Synthesis Using Substrate 5f

General Information:

The UPLC traces shown in this section depict the UPLC traces obtained from HTE experiments for the parallel library synthesis of substrate **5f** (see section SXXII).

In the UPLC traces, product (Aryl-Alkyl) signals are colored in dark blue, aryl halide starting material signals are colored teal, biaryl (Aryl-Aryl) signals are colored forest green, protodehalogenation (Aryl-H) signals are colored red.

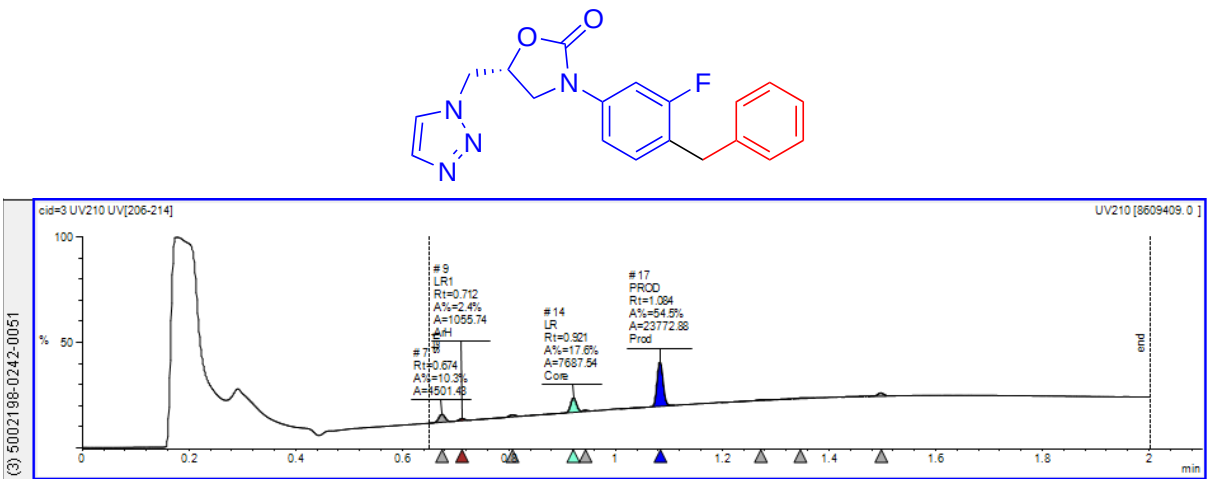


Figure S90. UPLC trace the cross-electrophile coupling of **5f** with substrate **6a**.

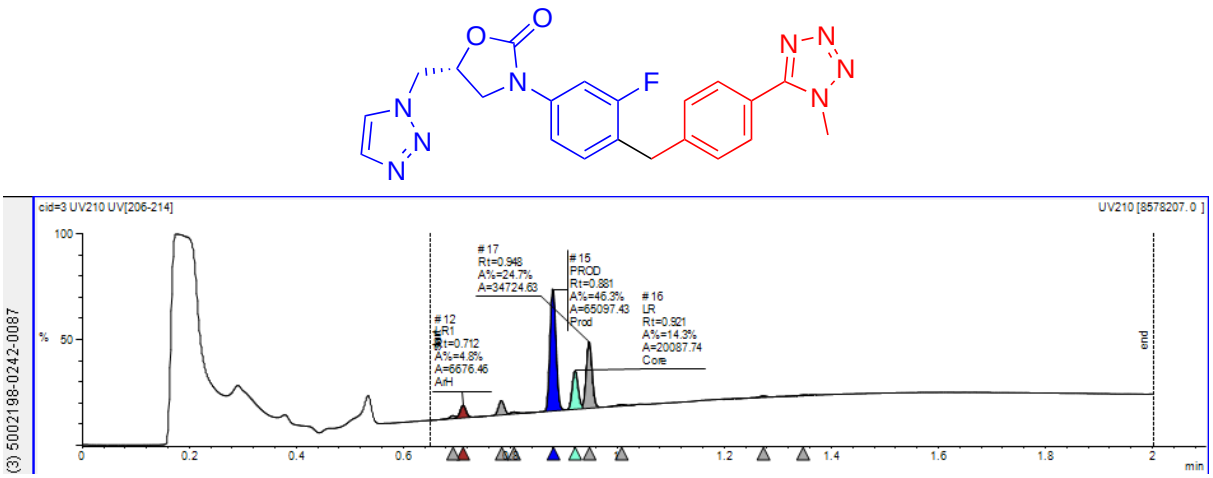


Figure S91. UPLC trace the cross-electrophile coupling of **5f** with substrate **6b**.

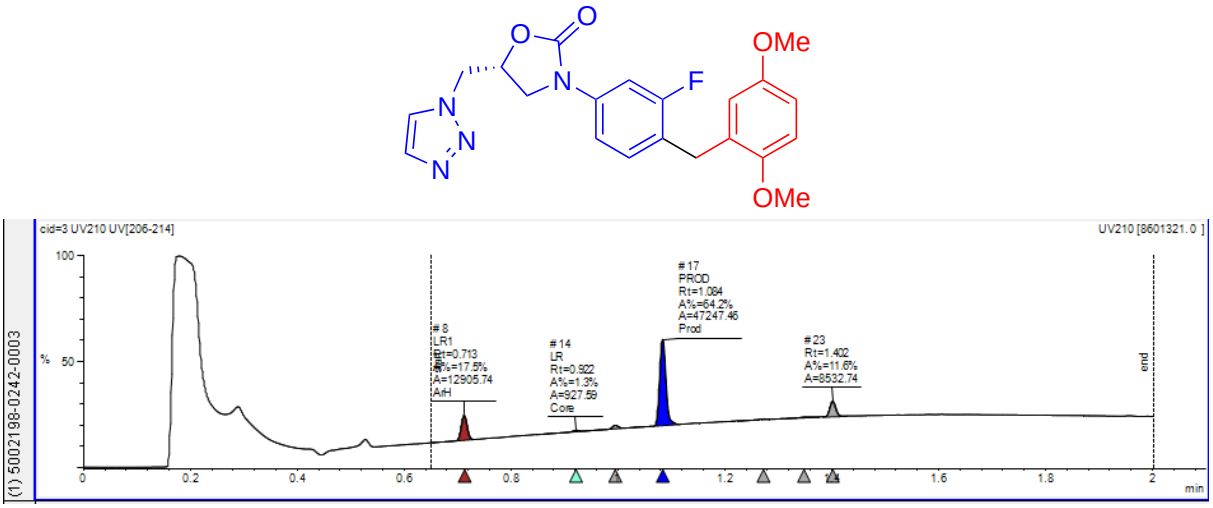


Figure S92. UPLC trace the cross-electrophile coupling of **5f** with substrate **6c**.

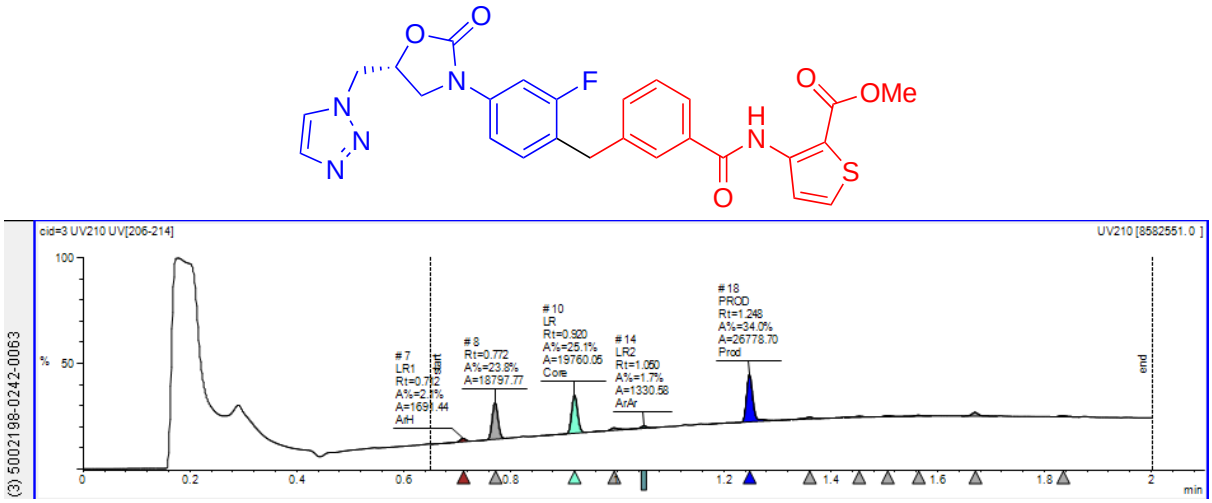


Figure S93. UPLC trace the cross-electrophile coupling of **5f** with substrate **6d**.

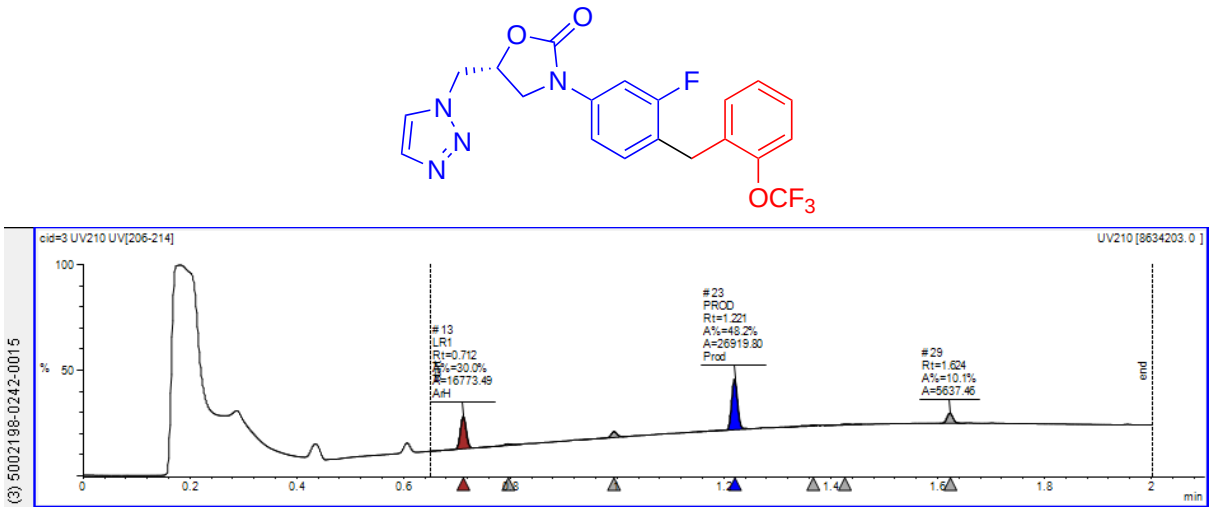


Figure S94. UPLC trace the cross-electrophile coupling of **5f** with substrate **6e**.

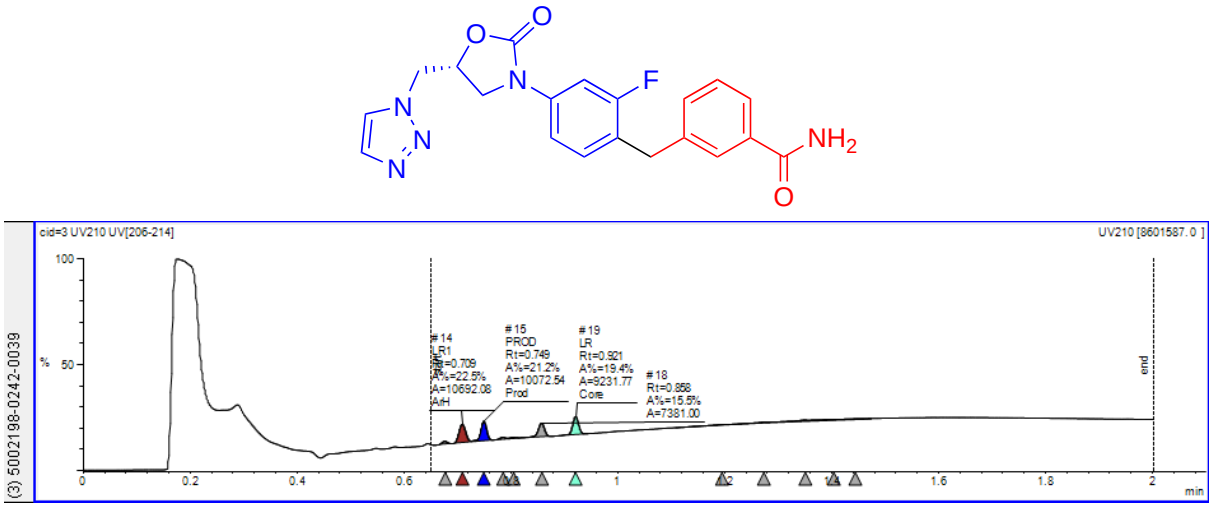


Figure S95. UPLC trace the cross-electrophile coupling of **5f** with substrate **6f**.

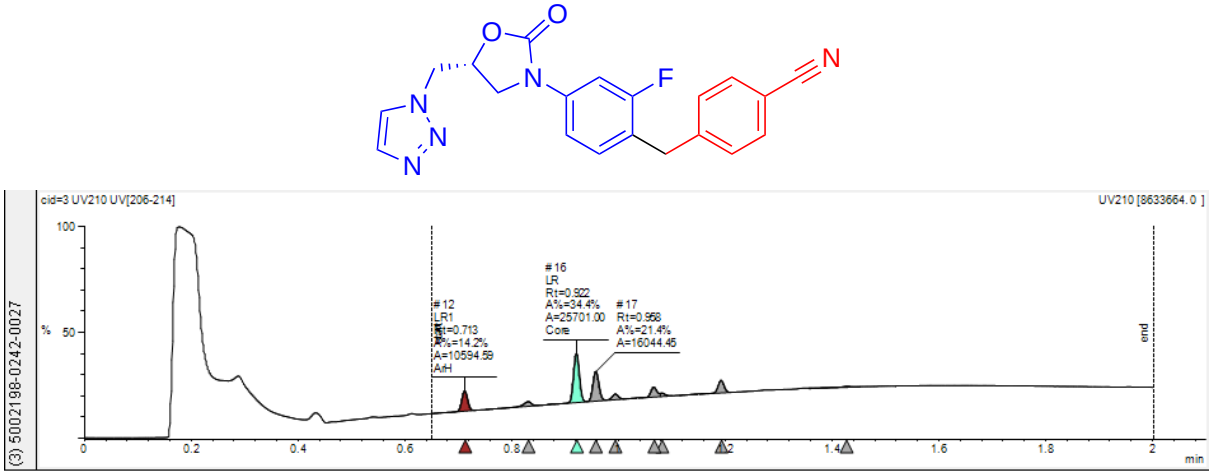


Figure S96. UPLC trace the cross-electrophile coupling of **5f** with substrate **6g**.

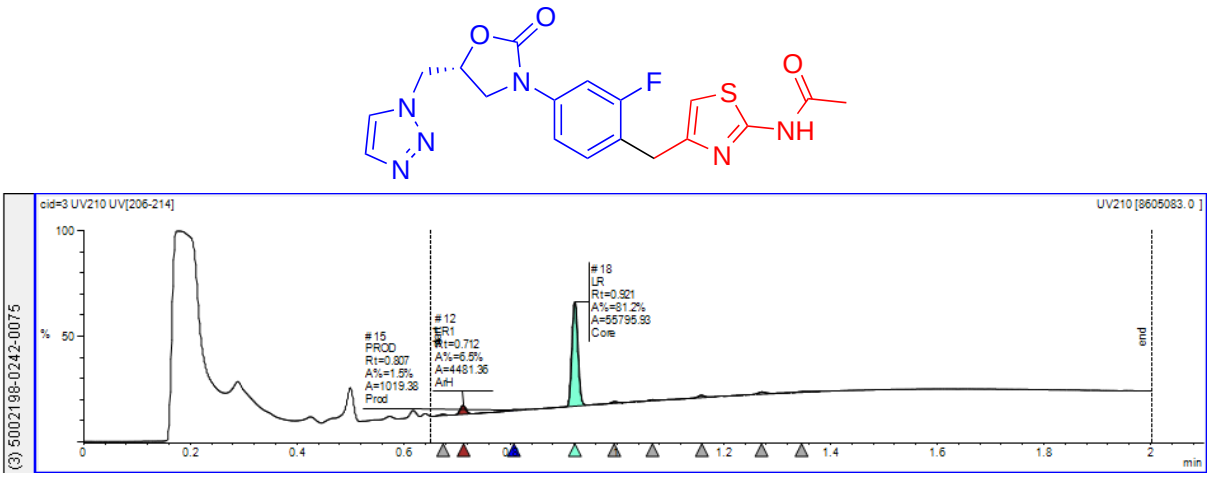


Figure S97. UPLC trace the cross-electrophile coupling of **5f** with substrate **6h**.

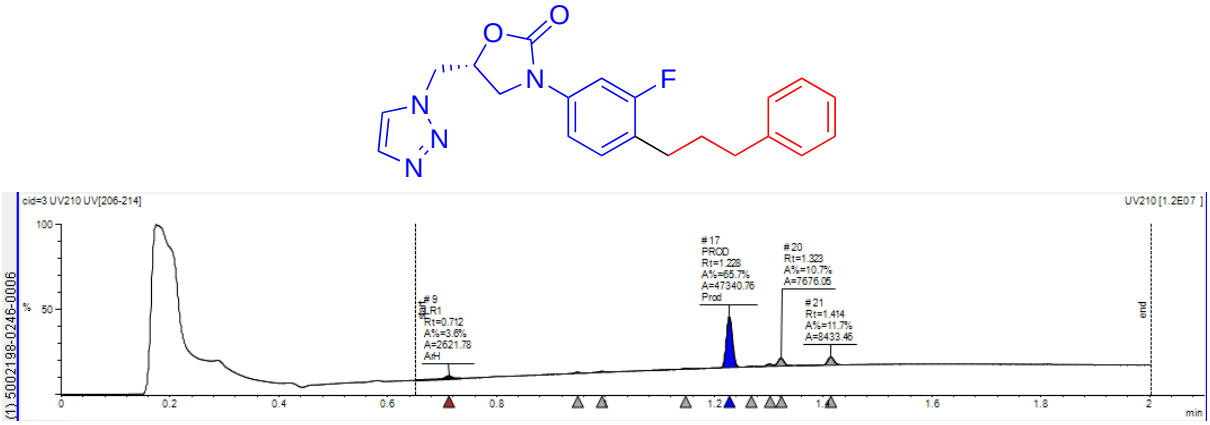


Figure S98. UPLC trace the cross-electrophile coupling of **5f** with substrate **6i**.

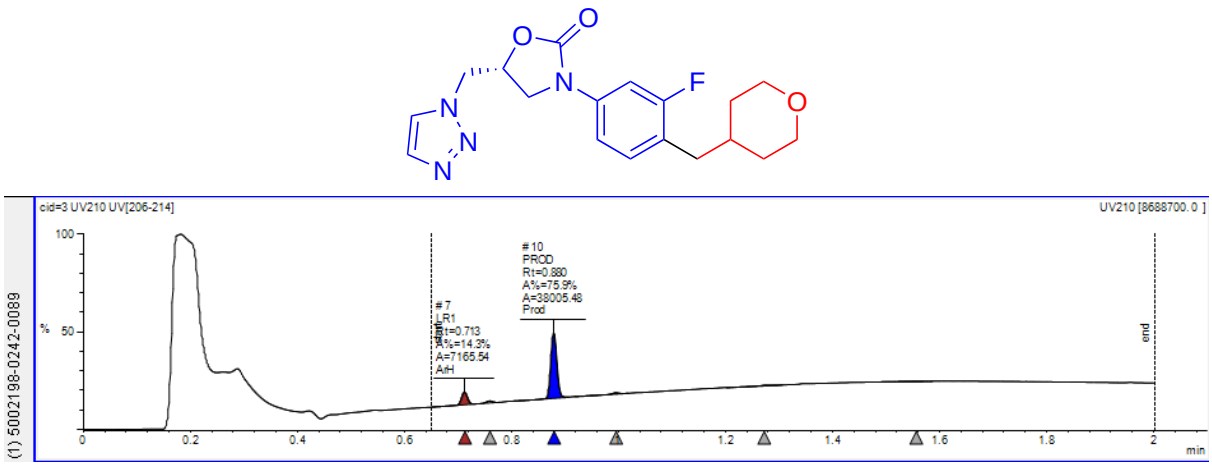


Figure S99. UPLC trace the cross-electrophile coupling of **5f** with substrate **6**j.

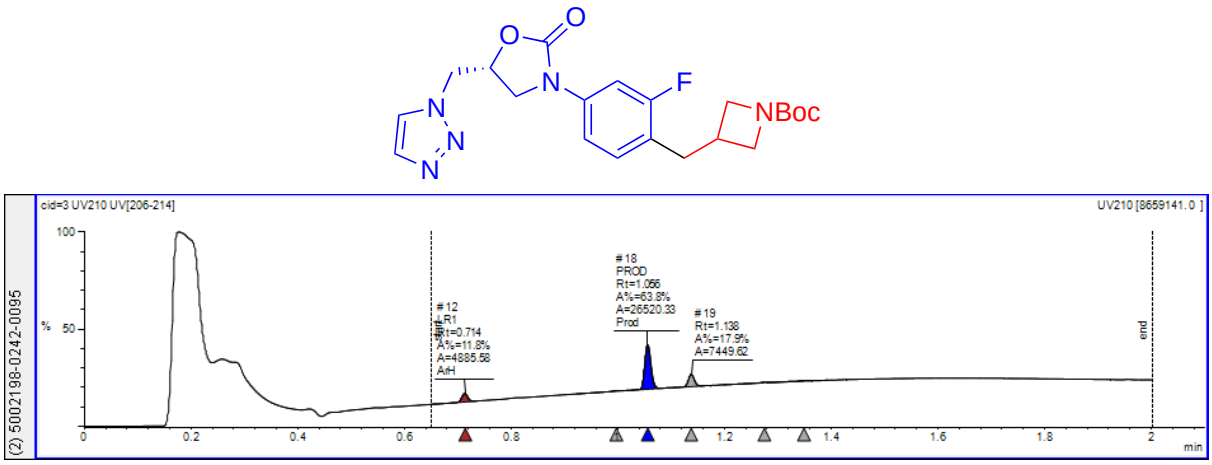


Figure S100. UPLC trace the cross-electrophile coupling of **5f** with substrate **6k**.

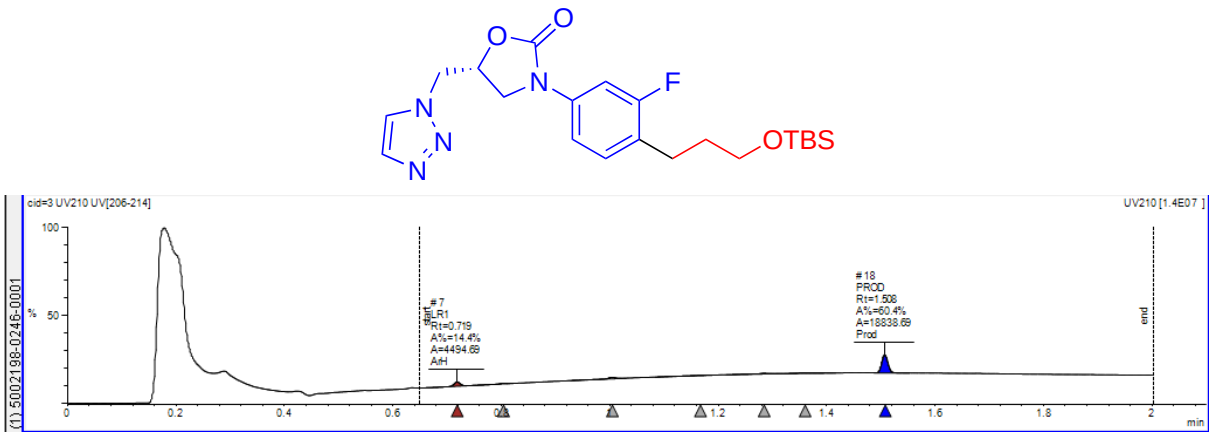


Figure S101. UPLC trace the cross-electrophile coupling of **5f** with substrate **6l**.

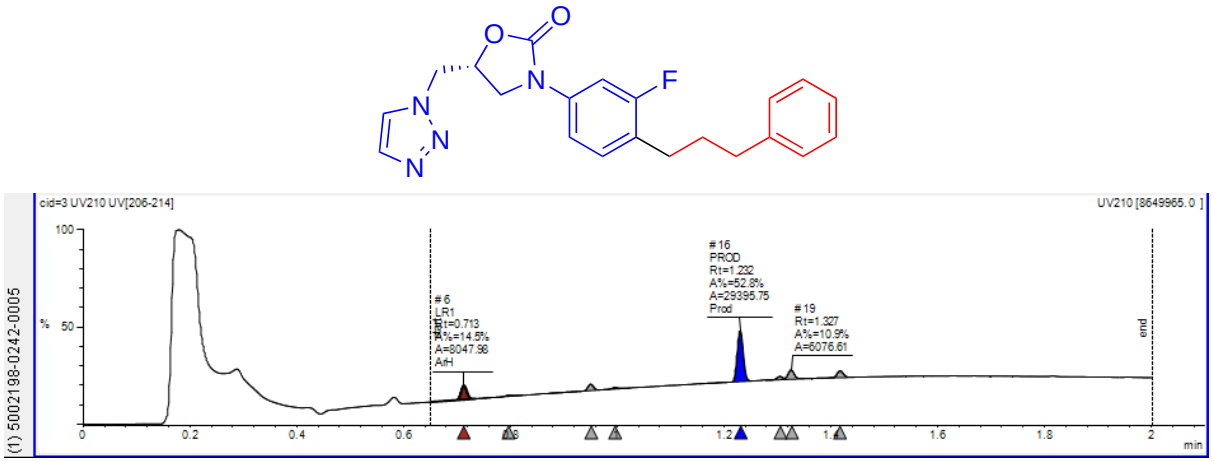


Figure S102. UPLC trace the cross-electrophile coupling of **5f** with substrate **6m**.

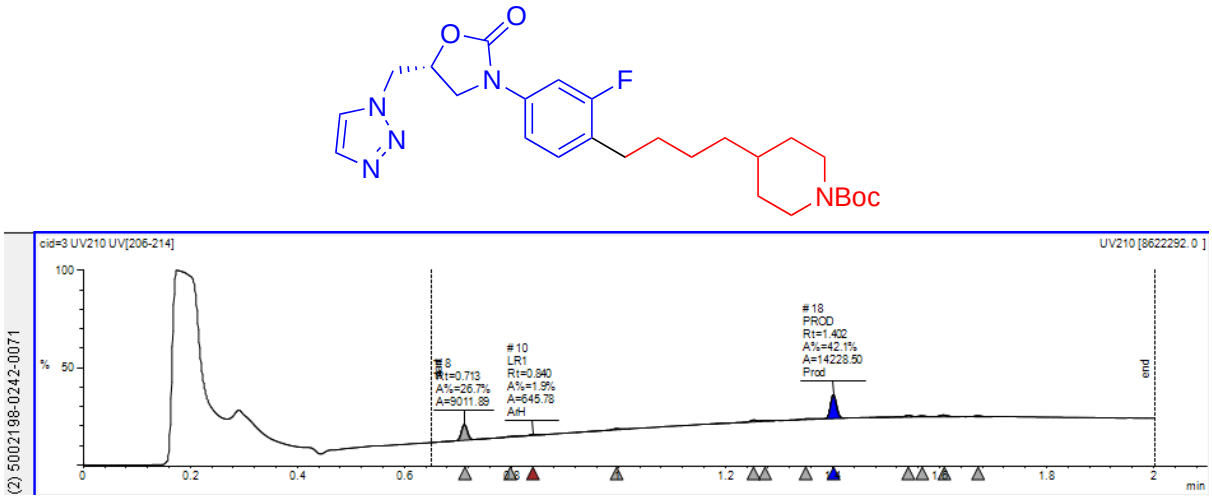


Figure S103. UPLC trace the cross-electrophile coupling of **5f** with substrate **6n**.

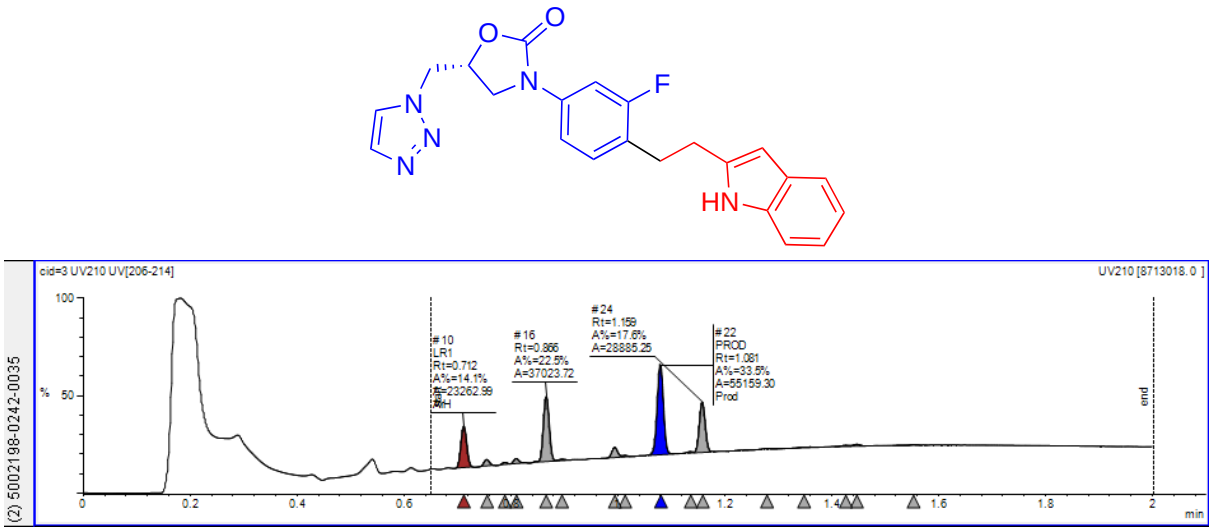


Figure S104. UPLC trace the cross-electrophile coupling of **5f** with substrate **6o**.

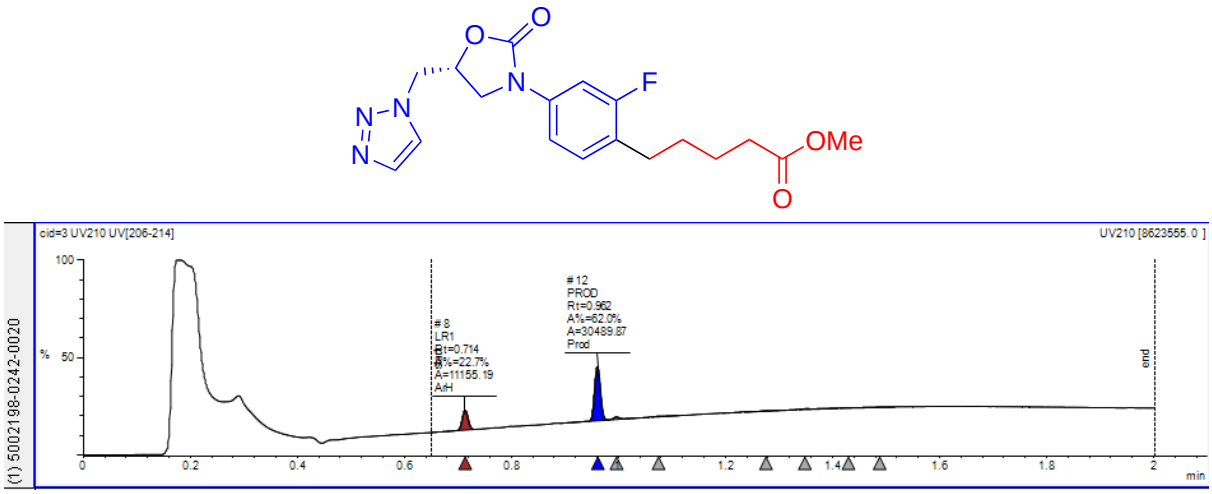


Figure S105. UPLC trace the cross-electrophile coupling of **5f** with substrate **6p**.

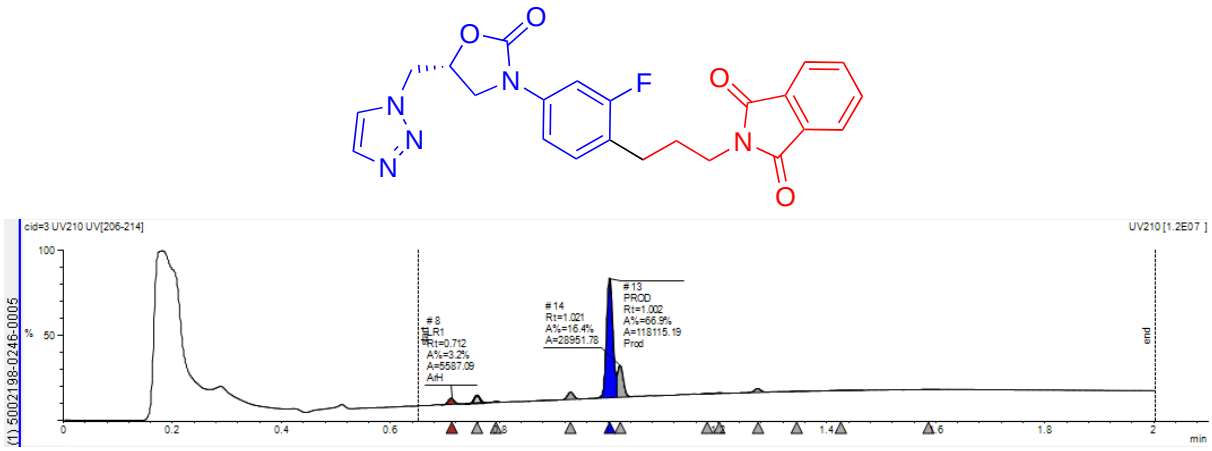
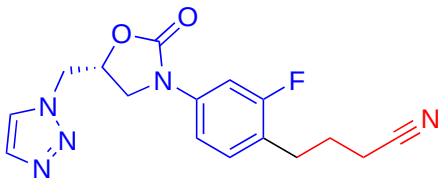


Figure S106. UPLC trace the cross-electrophile coupling of **5f** with substrate **6q**.



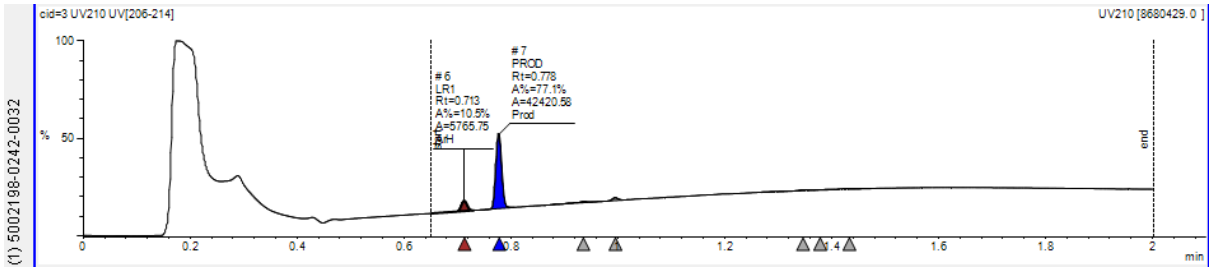
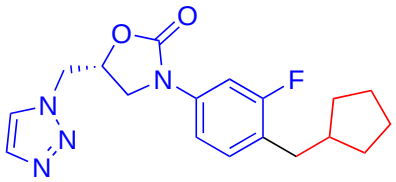


Figure S107. UPLC trace the cross-electrophile coupling of **5f** with substrate **6r**.



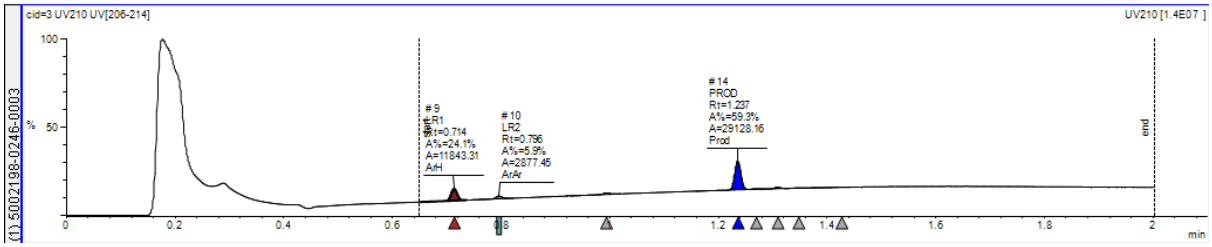
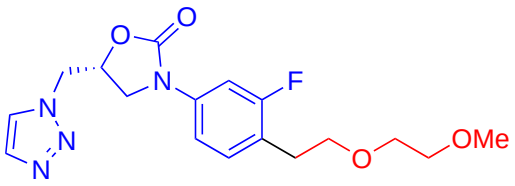


Figure S108. UPLC trace the cross-electrophile coupling of **5f** with substrate **6s**.



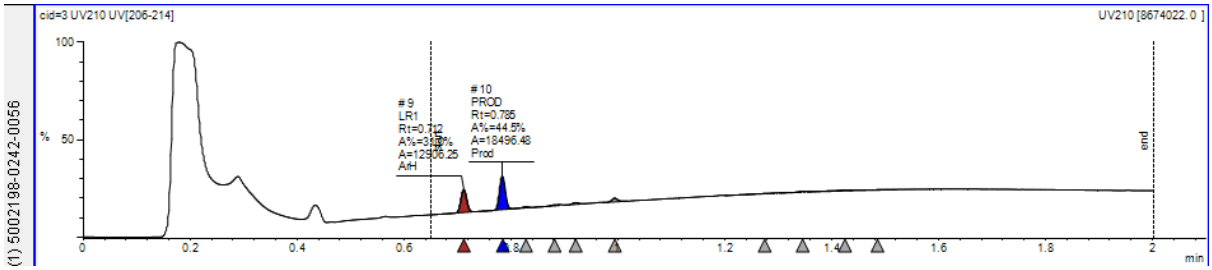
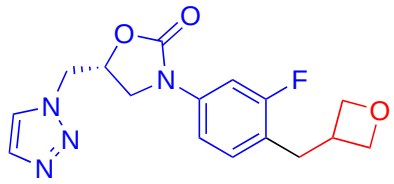


Figure S109. UPLC trace the cross-electrophile coupling of **5f** with substrate **6t**.



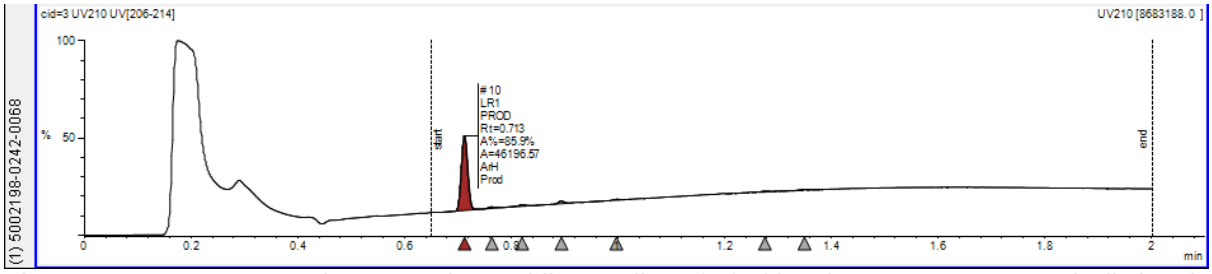


Figure S110. UPLC trace the cross-electrophile coupling of **5f** with substrate **6u**. Note: Aryl-Alkyl and Aryl-H overlap.

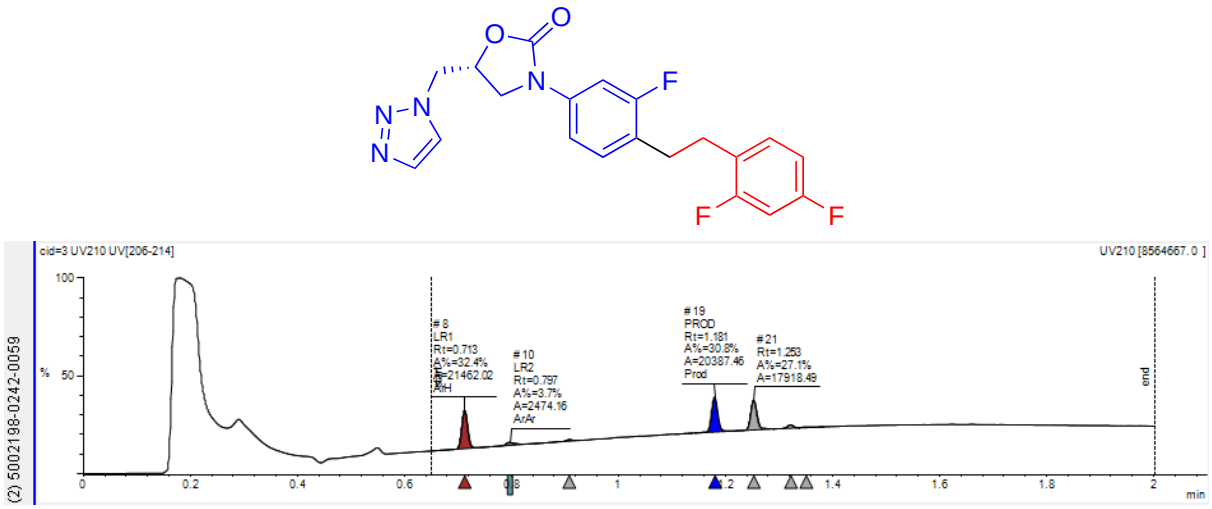


Figure S111. UPLC trace the cross-electrophile coupling of **5f** with substrate **6v**.

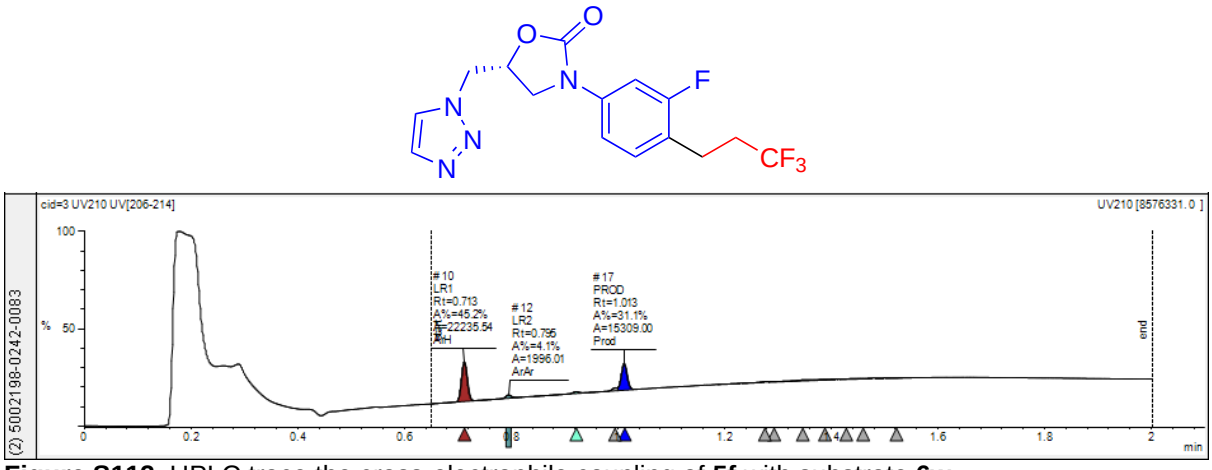


Figure S112. UPLC trace the cross-electrophile coupling of **5f** with substrate **6w**.

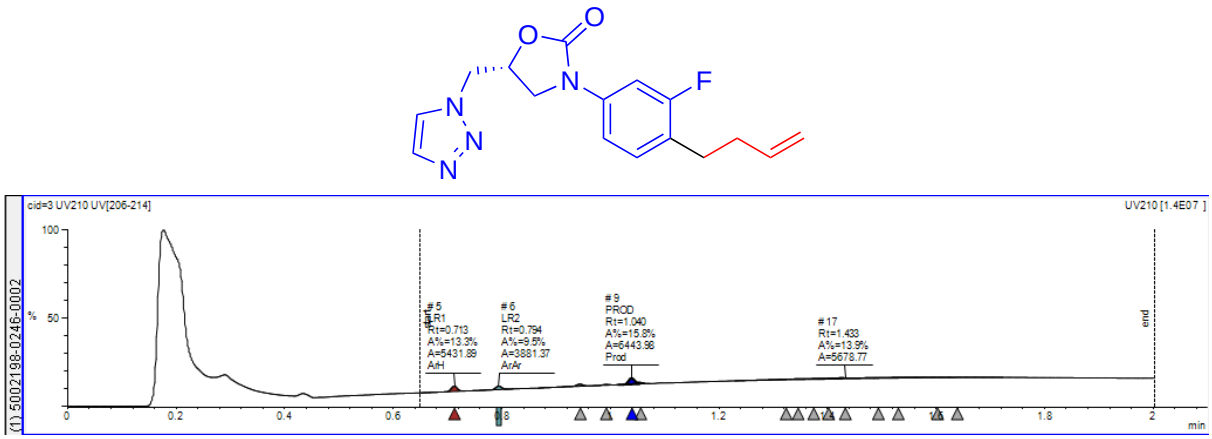


Figure S113. UPLC trace the cross-electrophile coupling of **5f** with substrate **6x**.

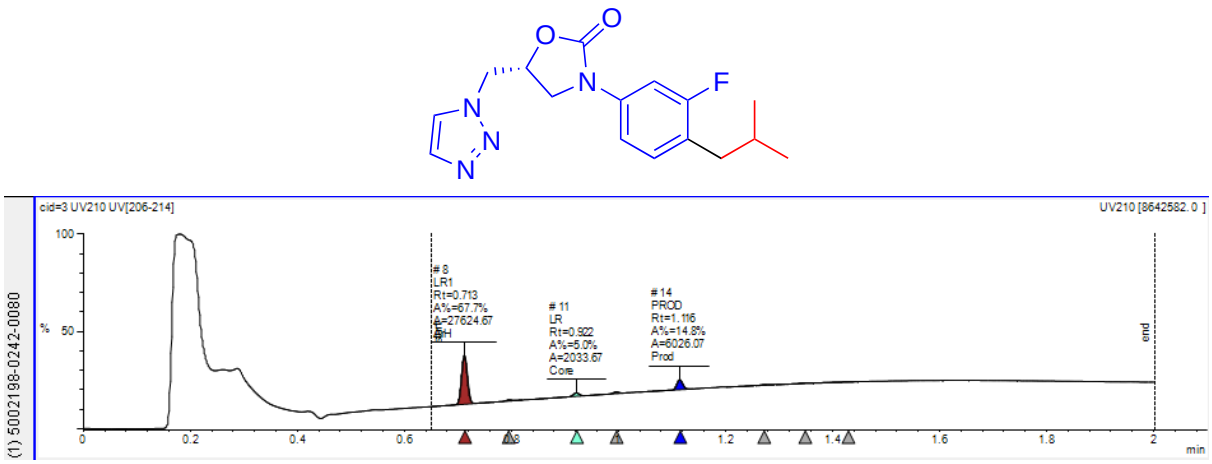


Figure S114. UPLC trace the cross-electrophile coupling of **5f** with substrate **6y**.

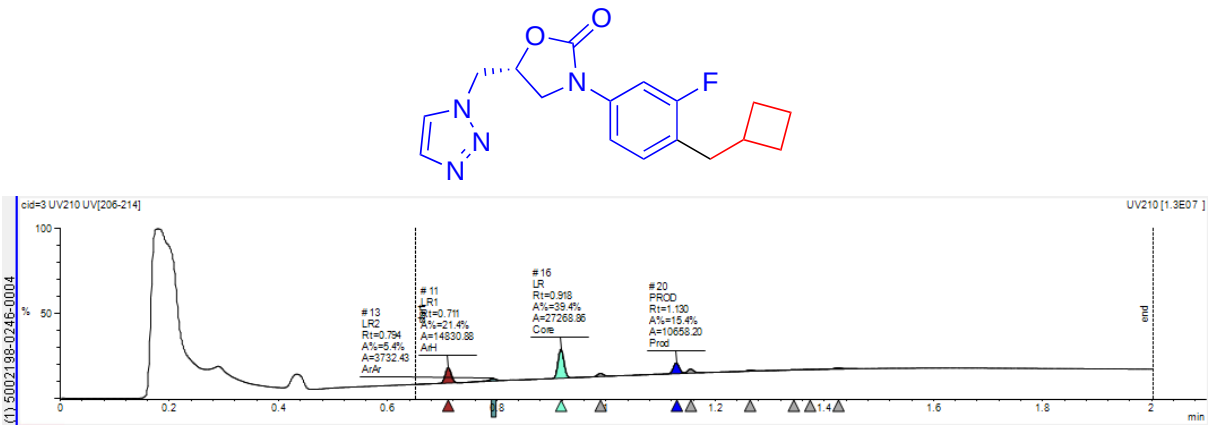


Figure S115. UPLC trace the cross-electrophile coupling of **5f** with substrate **6z**.

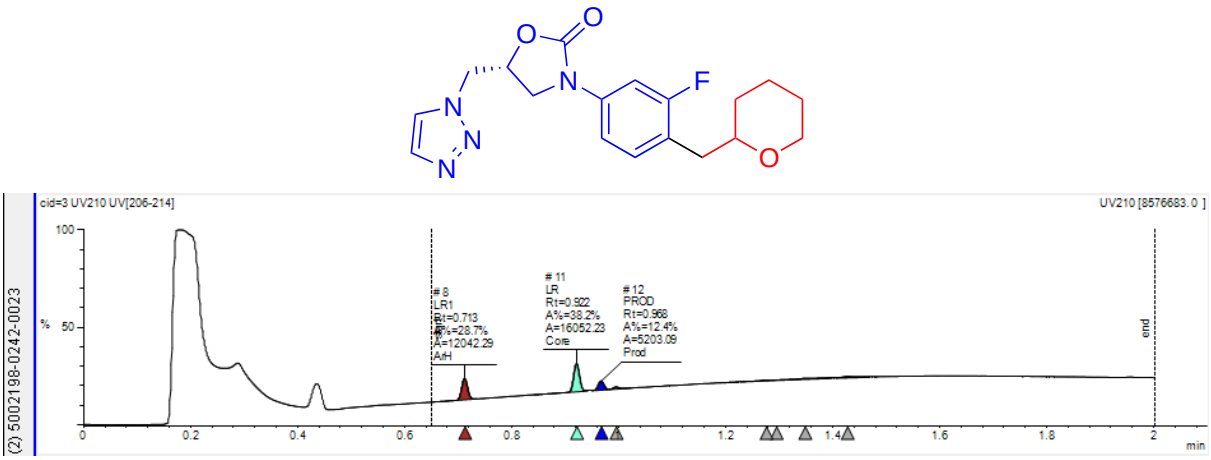


Figure S116. UPLC trace the cross-electrophile coupling of **5f** with substrate **6aa**.

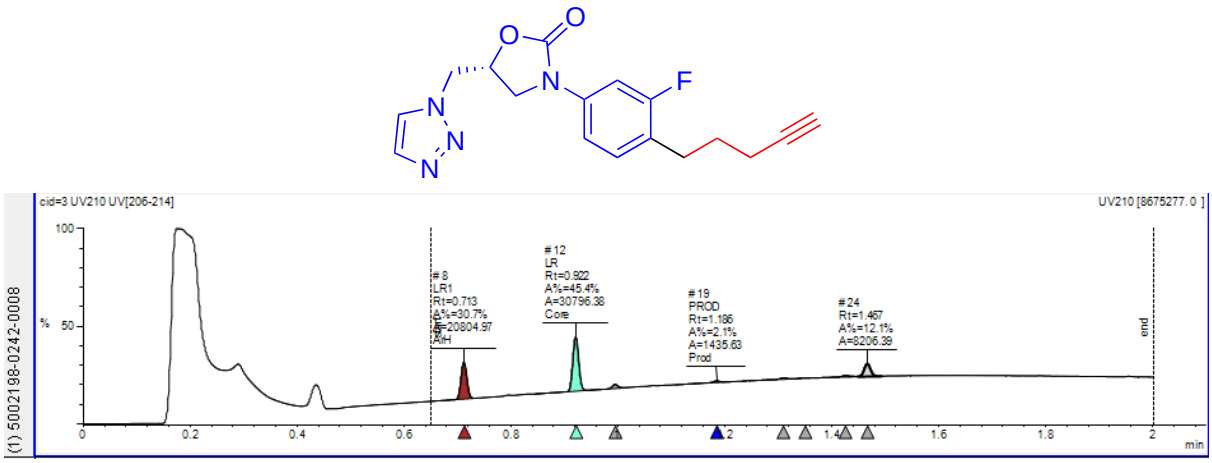


Figure S117. UPLC trace the cross-electrophile coupling of **5f** with substrate **6ab**.

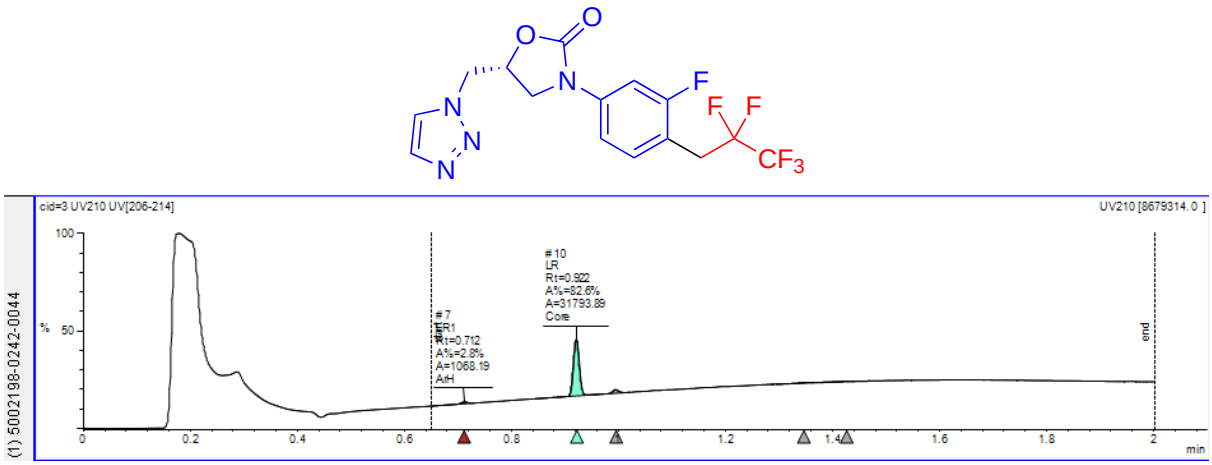


Figure S118. UPLC trace the cross-electrophile coupling of **5f** with substrate **6ac**.

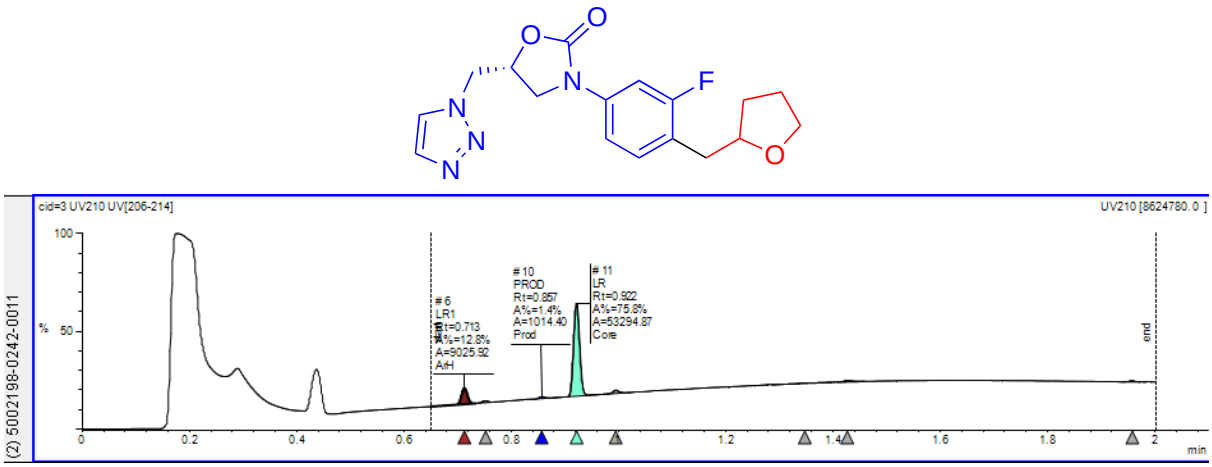


Figure S119. UPLC trace the cross-electrophile coupling of **5f** with substrate **6ad**.

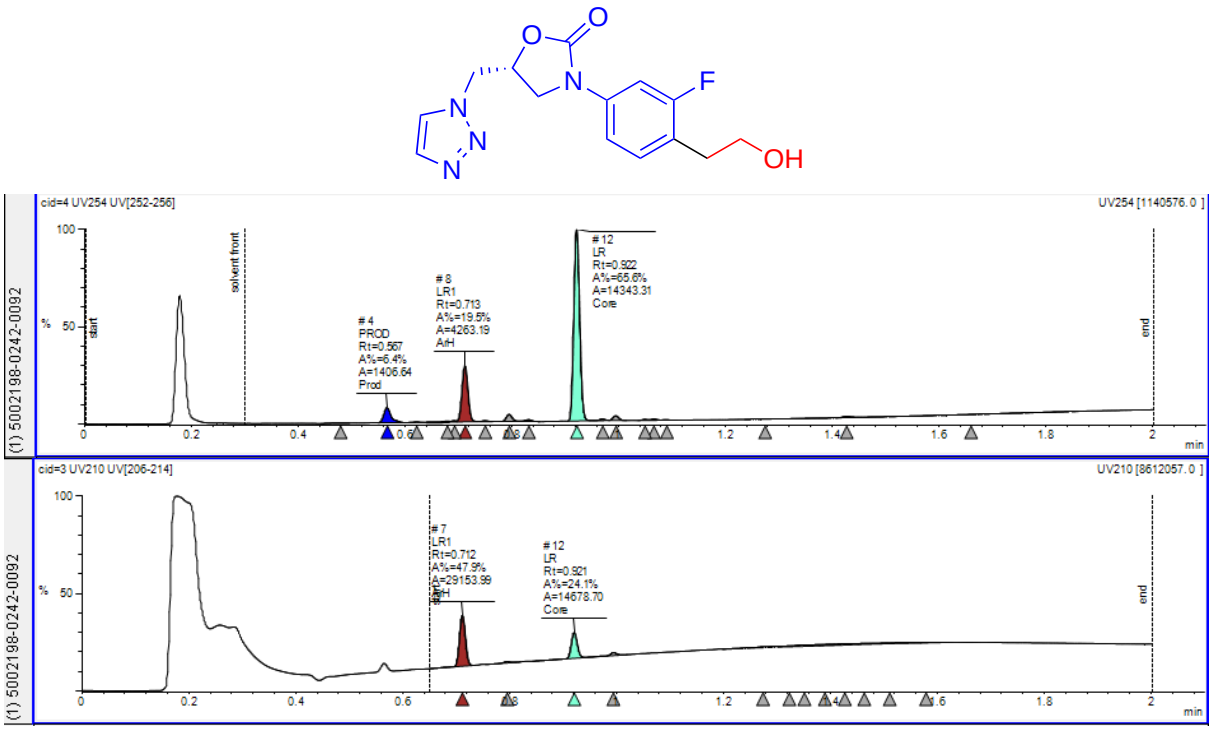


Figure S120. UPLC trace the cross-electrophile coupling of **5f** with substrate **6ae**. (Top) Trace at UV 254 nm. (Bottom) Trace at UV 210 nm.

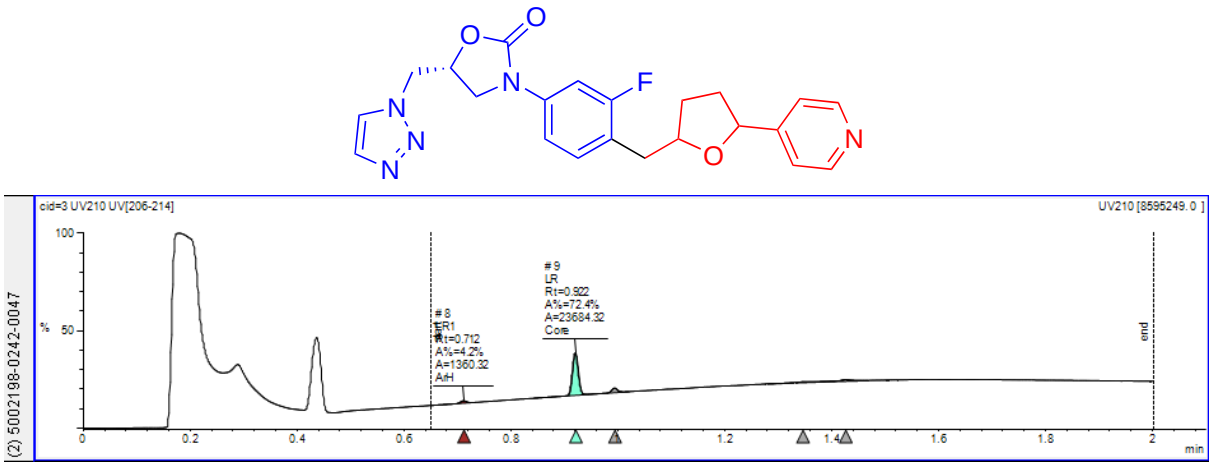


Figure S121. UPLC trace the cross-electrophile coupling of **5f** with substrate **6af**.

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