Supporting Information

Sterically Controlled Isodesmic Late-Stage C–H Iodination of Arenes

Mirxan Farizyan,[a] Rita de Jesus,[a,b,‡] Jyotirmoy Dey,[a,b,‡] Manuel van Gemmeren[a,b,*]

[a]Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, Corrensstraße 40, 48149 Münster, Germany

[b]Otto-Diels-Institut für Organische Chemie, Christian-Albrechts-Universität zu Kiel, Otto-Hahn-Platz 4, 24118 Kiel, Germany

‡ These authors contributed equally to this work

* mvangemmeren@oc.uni-kiel.de

Contents

1 General Experimental Methods

Solvents, Reagents and Techniques

Unless otherwise noted, all reactions were carried out in oven-dried glassware. Reaction temperatures are reported as the temperature of the metal block surrounding the vessel.

The following solvents were dried by distillation over the drying agents indicated in parentheses: HFIP (activated 3Å molecular sieves), toluene (CaH_2). Additional anhydrous solvents (<50 ppm water) were purchased from Acros Organics, Sigma-Aldrich, or Carl Roth and stored over molecular sieves under an argon atmosphere. For optimal yields of the reported iodination reaction the quality of the HFIP was found to be essential. There is a substantial detrimental influence of water on this reaction and thus HFIP was freshly distilled and utilized within days during the course of this project. A strong and homogeneous stirring was also found to be crucial for the optimal yield and reaction vessels were generally placed on the inner circle of the metal block. Ag_2O should be powdered and should be in good quality for successfulness of the reaction.

Commercially available chemicals were obtained from ABCR, Acros Organics, Aldrich Chemical Co., Alfa Aesar, Combi-Blocks, Carbolution, Fluorochem, and TCI Europe and used as received unless otherwise stated. The Ag_2O was obtained from Carbolution and stored in a glove box. Batches for short term use were extracted as required.

Chromatography

Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 aluminum plates (Merck). Visualization was achieved by exposure to ultraviolet light (254 nm, 366 nm) and/or by staining. For staining the TLC plates were dipped into a solution of $KMnO_4$ (1 g $KMnO_4$, 6 g K_2CO_3 and 0.1 g KOH in 100 mL H_2O) and developed with a heat gun if necessary. Flash column chromatography was performed on silica gel (35-70 μm mesh, 60A, Acros) with a positive argon overpressure. For purification of the iodination product, the column must be performed quickly to avoid detrimental effects of diffusion on the separation.

Nuclear Magnetic Resonance (NMR) Spectroscopy

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded at room temperature on a Bruker Avance II 300 MHz, Bruker Avance II 400 MHz, Agilent DD2 500 or Agilent DD2 600 spectrometer. Chemical shifts (δ) of ^{1}H and ^{13}C NMR spectra are given in ppm relative to tetramethylsilane (TMS) using the residual solvent peaks for calibration ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm).[1] ^{19}F NMR spectra are not externally calibrated and chemical shifts are given relative to the proton residual solvent peaks according to the unified chemical shift scale.[2] Chemical shifts are generally reported with two (^{1}H) or one (all other nuclei) digits after the decimal point. NMR-data are reported as follows: chemical shift (multiplicity [s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, m = multiplet, br = broad], coupling constants (*J*, Hz) and integration). For the spectra of regioisomeric mixtures, signals clearly assigned to a particular regioisomer are labelled with a superscript at the integration. The number of protons in such cases refers to the number of protons of the respective isomer. The absence of such an index indicates that the signals of all observed regioisomers overlap, the integration given corresponds to the number of protons in each isomer. The ^{13}C NMR spectra of mixtures are reported as observed. Due to the low signal intensity and potentially an overlap of signals, the number of signals can deviate from the hypothetical value, however, the signals of the major components are clearly recognizable in all cases and correspond to the literature values whenever the respective compounds are literature known. All spectra were processed using the MestReNova program.

Mass Spectrometry (MS)

High resolution mass spectra (HRMS) were recorded on a Bruker Daltonics MicroTof or on a Thermo-Fisher Scientific Orbitrap LTQ XL spectrometer using electrospray ionization (ESI) and on a Exactive GC Orbitrap using electron impact ionization (EI).

Infrared Spectroscopy (IR)

Infrared spectra were recorded neat on a Shimadzu FTIR 8400S or a Varian Associates FTIR 3100 Excalibur spectrometer. The wave numbers (ν) of recorded IR-signals are quoted in cm^{-1}.

Gas Chromatography with Flame Ionization Detection (GC-FID)

GC-FID analyses were performed using an Agilent Technologies 7890B setup equipped with an HP5 column (30 m, 0.32mm × 0.25 μm).

Gas Chromatography coupled with Mass Spectrometry (GC-MS)

GC-MS spectra were recorded on an Agilent Technologies 7890A GC-system with an Agilent 5975C VL MSD or an Agilent 5975 inert Mass Selective Detector (EI) and an HP-5MS column (30 m, 0.32mm × 0.25 μm).

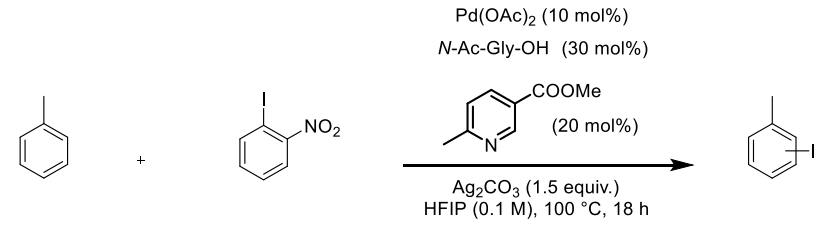
2 Optimization of the Reaction Conditions

General procedure for the reactions carried out during optimization (General procedure A):

An oven dried 10 mL Schlenk tube was charged with a Pd-source, an amino acid-derived ligand, a pyridine ligand, a Ag-source, substrate (0.10 mmol), an iodine source and HFIP. The reaction mixture was then placed into the inside circle of a preheated aluminum block with a tightly fitting recess on a magnetic stirrer and stirred (1000 rpm stirring speed) at the indicated temperature until completion of the reaction.

After completion of the reaction, the reaction mixture was allowed to cool to room temperature. A stock solution of 1,3,5-trimethylbenzene in ethyl acetate was added and the reaction mixture was further diluted with ethyl acetate (2 mL). After making the solution homogeneous, an aliquot (500 µL) of the resulting solution was filtered over a short silica column using ethyl acetate as the eluent and the resulting sample was subjected to GC-FID analysis. All yields and ratios given during the optimization studies were determined by GC-FID analysis of the crude reaction mixture using 1,3,5-trimethylbenzene as the internal standard.

Scheme S1: Preliminary control experiments using toluene (**1c**).

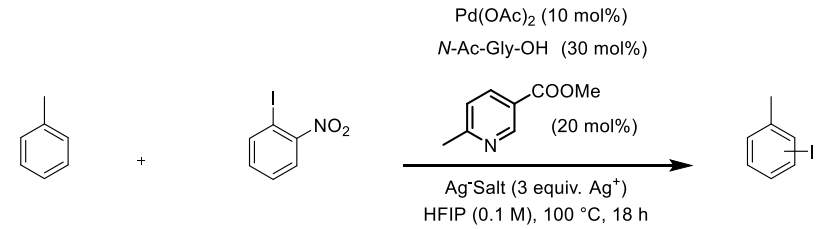


(0.1 mmol) (2.0 equiv.)

Entry	Deviation	Conv.*/%	Yield*/%	o:m:p*
1	none	77	32	0:69:31
2	no Ag_2CO_3	1	11	0:67:33
3	no Pyr-Ligand	70	18	0:61:39
4	no *N*-Ac-Gly-OH	2	5	0:65:35
5	no $Pd(OAc)_2$		-	
6	no catalyst		-	

* GC-FID determination using TMB as internal standard

Scheme S2: Preliminary silver salt screening.



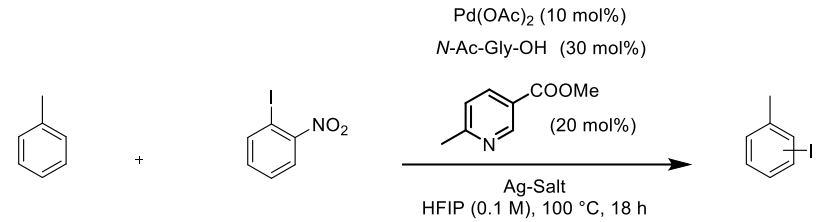
(0.1 mmol) (2.0 equiv.)

Entry	Ag-Salt	Conv.*/%	Yield*/%	o:m:p
1	Ag_2CO_3 (ref)	75	36	-:69:31
2	AgOAc	74	38	-:68:32
3	Ag_2O	-3	2	-:65:35
4	AgF	78	14	-:67:33
5	$AgNO_3$	80	43	-:71:29
6	AgTFA	13	16	-:61:39
7	$AgBF_4$	-11	2	-:96:4
8	$AgCO_2Ph$	-2	5	-:72:28
9	Ag_3PO_4	17	19	-:70:30

* GC-FID determination using TMB as internal standard

Note: The silver salt presumably acts as a Lewis acid, e.g. aiding the oxidative addition and/or reductive elimination steps. A further potential role is as a halide scavenger for the iodide freed in the side reaction (biaryl formation) to prevent catalyst poisoning. These roles can be achieved with catalytic amounts of silver ions, which agrees well with the results obtained in the following tables.

Scheme S3: Screening of AgOAc amount.

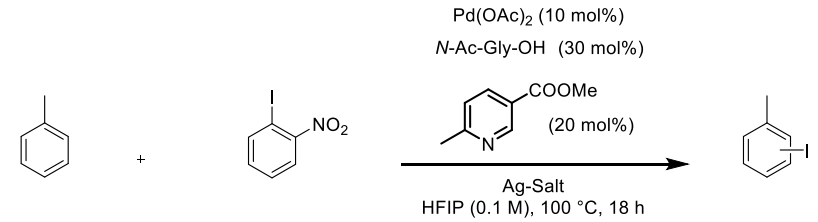


(0.1 mmol) (2.0 equiv.)

Entry	AgOAc (equiv.)	Conv.*/%	Yield*/%	o:m:p
1	4.0	81	30	1:67:32
2	3.5	80	32	1:67:32
3	3.0	78	35	1:67:32
4	2.5	77	37	1:67:32
5	2.0	82	36	1:66:33
6	1.5	77	38	1:67:32
7	1.0	79	39	1:66:33
8	0.5	71	42	1:67:32

* GC-FID determination using TMB as internal standard

Scheme S4: Screening of $AgNO_3$ amount.

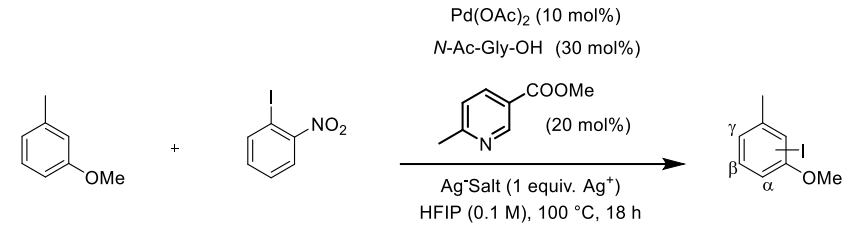


(0.1 mmol) (2.0 equiv.)

Entry	$AgNO_3$ (equiv.)	Conv.*/%	Yield*/%	o:m:p
9	4.0	84	51	2:67:31
10	3.5	80	52	2:67:31
11	3.0	80	46	3:68:30
12	2.5	85	55	2:67:31
13	2.0	81	44	3:67:30
14	1.5	78	47	4:69:29
15	1.0	74	50	4:67:29
16	0.5	72	53	3:67:30

* GC-FID determination using TMB as internal standard

Scheme S5: Screening of silver salts using *m*-cresol methyl ether (**1a**).

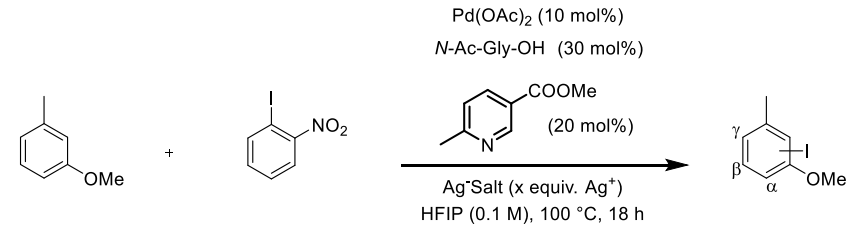


(0.1 mmol) (2.0 equiv.)

Entry	Ag-Salt	Conv.*/%	Yield*/%	α:β:γ
1	Ag_2CO_3	47	26	13:84:3
2	AgOAc	51	28	13:84:3
3	AgF	52	17	23:72:5
4	$AgNO_3$	69	19	14:82:4
5	AgTFA	27	10	51:43:6
6	Ag_3PO_4	11	6	17:78:5
7	$AgNO_3$ (0.5 equiv., ref)	65	16	13:84:3

* GC-FID determination using mesitylene as internal standard

Scheme S6: Screening of Ag_2CO_3 amount.

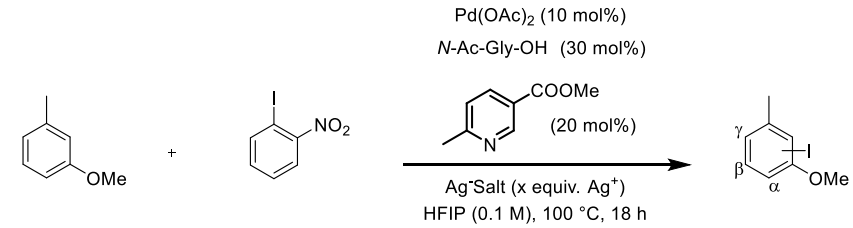


(0.1 mmol) (2.0 equiv.)

Entry	Ag_2CO_3 (equiv.)	Conv.*/%	Yield*/%	α:β:γ
1	1.0	50	24	13:84:3
2	0.25	45	29	12:85:3
3	0.15	39	26	12:85:3
4	0.05	25	18	12:86:3

* GC-FID determination using mesitylene as internal standard

Scheme S7: Screening of AgOAc amount.

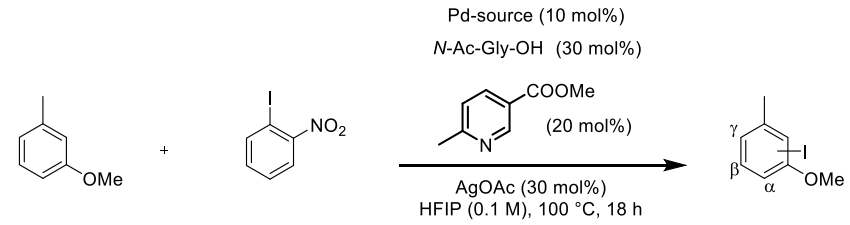


(0.1 mmol) (2.0 equiv.)

Entry	AgOAc (equiv.)	Conv.*/%	Yield*/%	α:β:γ
5	2.0	52	29	13:84:3
6	0.5	50	30	13:84:3
7	0.3	43	28	13:84:3
8	0.1	30	21	12:86:3

* GC-FID determination using mesitylene as internal standard

Scheme S8: Screening of Pd source.

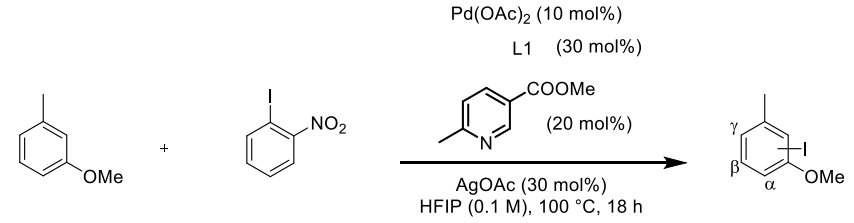


(0.1 mmol) (2.0 equiv.)

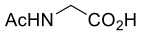
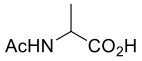
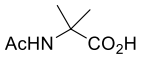
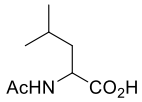
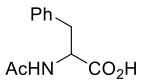
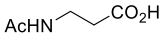
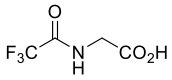
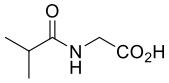
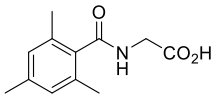
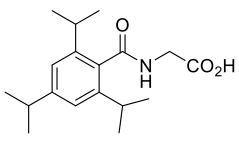
Entry	Pd-source	Conv.*/%	Yield*/%	α:β:γ
1	Pd(OAc)2	38	26	13:84:3
2	$Pd(TFA)_2$	39	30	14:83:3
3	$Pd(OPiv)_2$	18	11	14:83:3
4	$Pd(acac)_2$	5	3	14:86:0
5	$Pd(MeCN)_2Cl_2$	30	23	12:85:3
6	$PdCl_2$	22	18	12:85:3
7	$Pd(PPh_3)_4$	1	0	-
8	$Pd(PPh_3)_2Cl_2$	1	0	-
9	$Pd_2(allyl)_2Cl_2$	10	2	0:75:25
10	$Pd(COD)Cl_2$	7	0	-
11	$Pd(Ph\text{-}CN)_2Cl_2$	18	14	11:86:3

* GC-FID determination using mesitylene as internal standard

Scheme S9: Screening of bidentate ligands (L1).

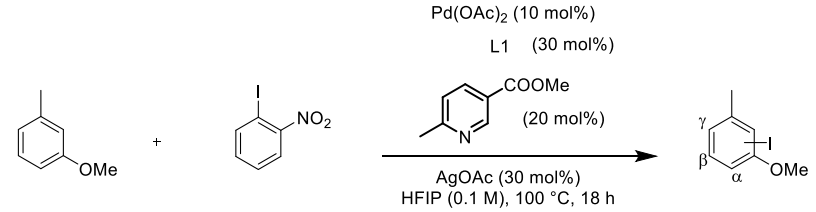


(0.1 mmol) (2.0 equiv.)

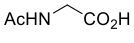
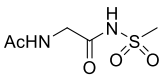
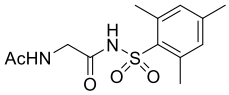
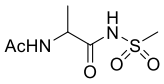
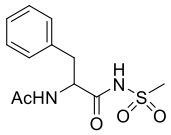
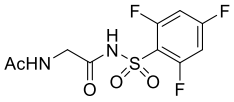
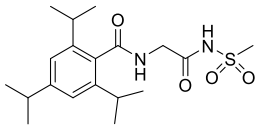
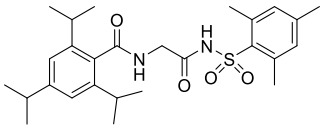
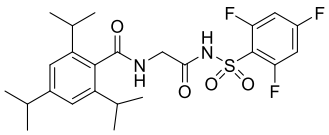
Entry	L1	Conv.*/%	Yield*/%	α:β:γ
1		39	26	13:84:3
2		27	15	13:83:4
3		0	0	-
4		38	25	13:83:4
5		19	11	10:87:3
6		23	13	36:52:12
7		21	13	39:48:13
8		33	20	15:82:4
9		17	9	14:82:4
10		12	6	13:87:0

* GC-FID determination using mesitylene as internal standard

Scheme S10: Screening of bidentate ligands (L1).

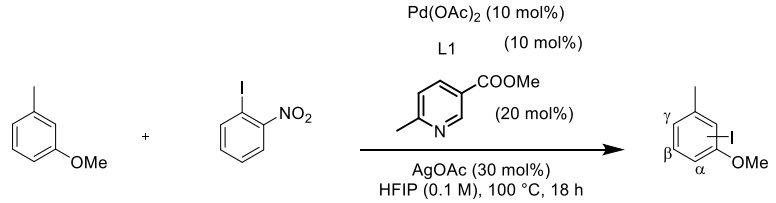


(0.1 mmol) (2.0 equiv.)

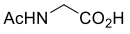
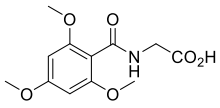
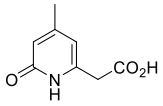
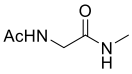
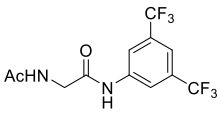
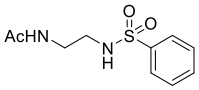
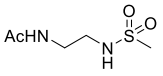
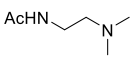
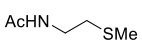
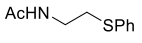
Entry	L1	Conv.*/%	Yield*/%	α:β:γ
1		37	24	13:84:3
2		13	5	14:86:0
3		10	3	14:86:0
4		8	4	14:86:0
5		9	3	12:88:0
6		13	6	15:85:0
7		6	1	-
8		6	traces	-
9		6	1	-

* GC-FID determination using mesitylene as internal standard

Scheme S11: Screening of bidentate ligands (L1) with lower loading.

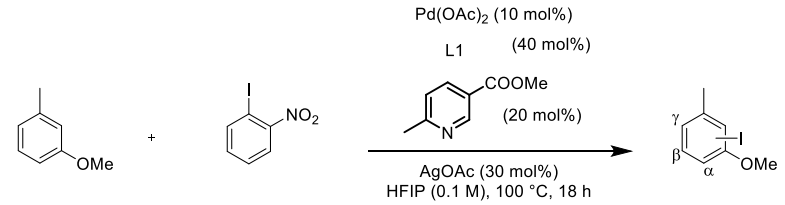


(0.1 mmol) (2.0 equiv.)

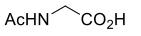
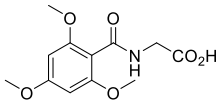
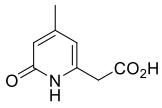
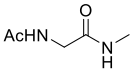
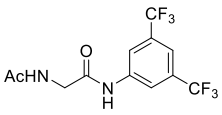
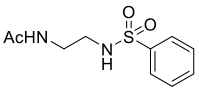
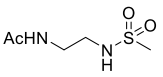
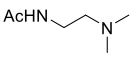
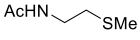
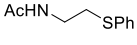
Entry	L1	Conv.*/%	Yield*/%	α:β:γ
1		43	29	14:82:4
2		31	22	15:83:3
3		6	2	17:83:0
4		16	9	25:14:62
5		17	9	18:27:55
6		10	4	50:27:23
7		9	5	54:22:24
8		8	4	22:70:8
9		9	2	12:51:37
10		18	4	13:60:27

* GC-FID determination using mesitylene as internal standard

Scheme S12: Rescreening of bidentate ligands (L1) with higher loading.

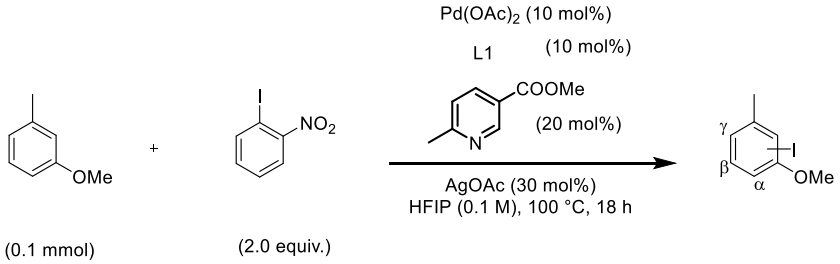


(0.1 mmol) (2.0 equiv.)

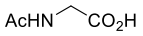
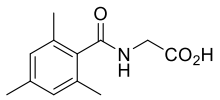
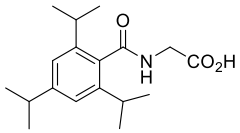
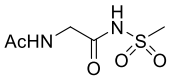
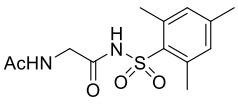
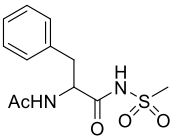
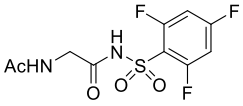
Entry	L1	Conv.*/%	Yield*/%	α:β:γ
1		40	26	13:84:3
2		15	7	28:72:0
3		0	0	-
4		16	8	61:16:22
5		20	9	14:39:46
6		4	2	41:38:21
7		9	3	46:32:22
8		4	1	15:85:0
9		7	1	0:44:56
10		6	2	0:51:49

* GC-FID determination using mesitylene as internal standard

Scheme S13: Rescreening of bidentate ligands (L1) with lower loading.

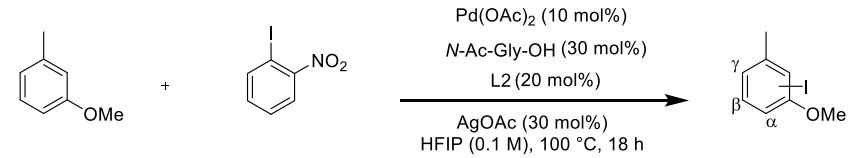


(0.1 mmol) (2.0 equiv.)

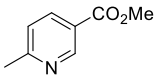
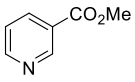
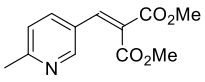
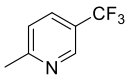
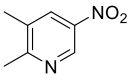
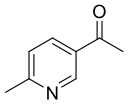
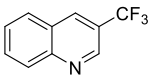
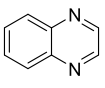
Entry	L1	Conv.*/%	Yield*/%	α:β:γ
1		45	31	14:82:4
2		26	15	18:77:6
3		23	15	19:75:6
4		16	8	15:81:4
5		13	7	16:80:4
6		16	8	15:81:4
7		18	9	15:81:4

* GC-FID determination using mesitylene as internal standard

Scheme S14: Screening of monodentate ligands (L2).

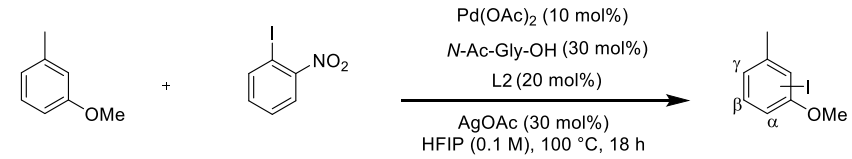


(0.1 mmol) (2.0 equiv.)

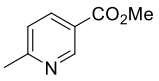
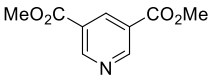
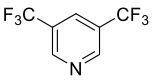
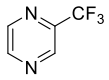
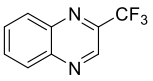
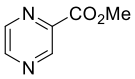
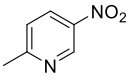
Entry	L2	Conv.*/%	Yield*/%	α:β:γ
1		38	25	13:84:3
2		27	17	16:80:5
3		39	26	12:85:3
4		39	24	14:83:3
5		49	30	13:84:3
6		53	30	12:85:3
7		41	28	12:84:3
8		56	28	12:85:3
9		44	28	10:87:3
10		46	29	10:87:3

* GC-FID determination using mesitylene as internal standard

Scheme S15: Screening of monodentate ligands (L2).

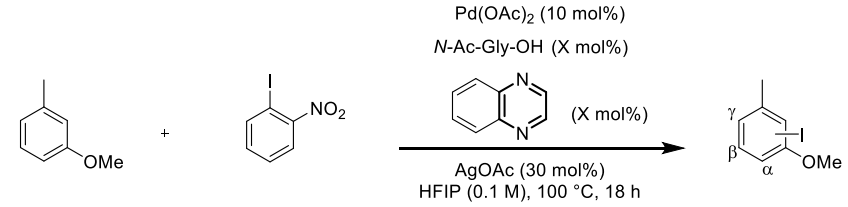


(0.1 mmol) (2.0 equiv.)

Entry	L2	Conv.*/%	Yield*/%	α:β:γ
1		43	28	13:84:3
2		48	29	11:86:3
3		60	34	13:83:4
4		66	35	15:80:5
5		59	34	14:82:4
6		60	33	13:83:4
7		58	33	15:82:3

* GC-FID determination using mesitylene as internal standard.

Scheme S16: Screening of ligand ratios.

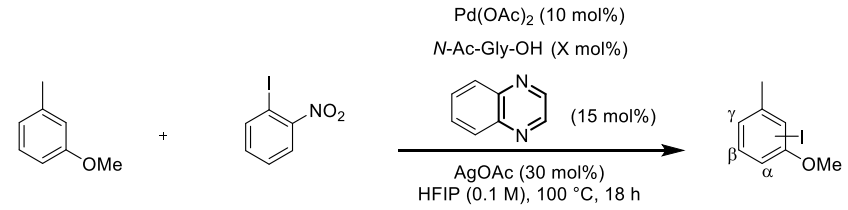


(0.1 mmol) (2.0 equiv.)

Entry	Quinoxaline (mol%)	*N*-Ac-Gly-OH (mol%)	Conv.*/%	Yield*/%	α:β:γ
1	10	20	57	36	15:81:4
2	10	30	54	33	13:83:4
3	10	40	59	36	13:83:3
4	10	50	57	38	13:84:3
5	20	20	52	32	11:86:3
6	20	30	48	31	11:86:3
7	20	40	49	31	10:87:3
8	20	50	47	30	10:87:3

* GC-FID determination using mesitylene as internal standard

Scheme S17: Screening of *N*-Acetylglycine amount.

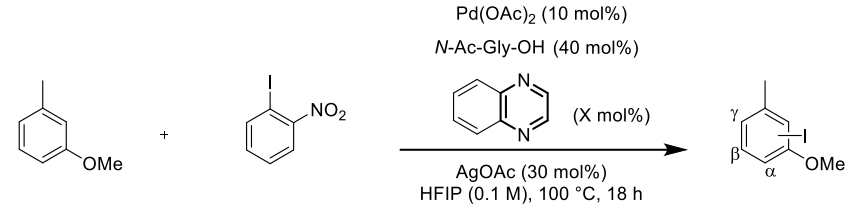


(0.1 mmol) (2.0 equiv.)

Entry	*N*-Ac-Gly-OH (mol%)	Conv.*/%	Yield*/%	α:β:γ
1	20	55	35	12:84:3
2	30	54	33	12:85:3
3	40	53	34	11:86:3
4	50	53	33	11:87:3

* GC-FID determination using mesitylene as internal standard

Scheme S18: Screening of Quinoxaline amount.

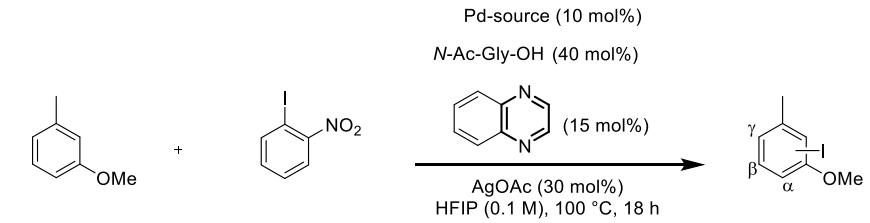


(0.1 mmol) (2.0 equiv.)

Entry	Quinoxaline (mol%)	Conv.*/%	Yield*/%	α:β:γ
1	10	56	35	13:84:3
2	12	56	34	12:85:3
3	15	53	34	11:86:3
4	18	49	30	10:87:3
5	20	49	30	10:87:3

* GC-FID determination using mesitylene as internal standard

Scheme S19: Re-screening of Pd source.

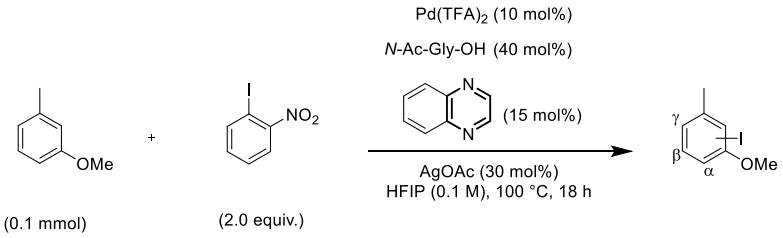


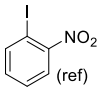
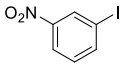
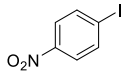
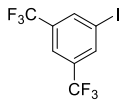
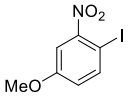
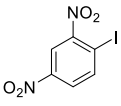
(0.1 mmol) (2.0 equiv.)

Entry	Pd-source	Conv.*/%	Yield*/%	α:β:γ
1	$Pd(OAc)_2$	53	34	11:86:3
2	$Pd(TFA)_2$	62	42	11:86:3
3	$Pd(MeCN)_2Cl_2$	43	32	13:83:4

* GC-FID determination using mesitylene as internal standard

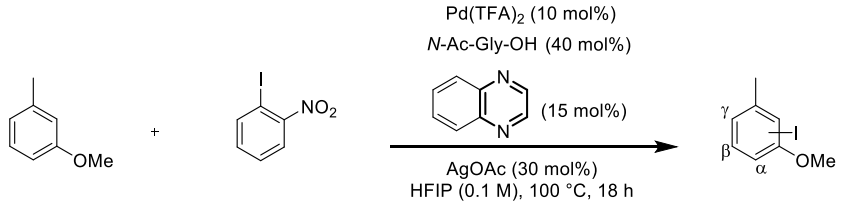
Scheme S20: Screening of iodine sources.



Entry	Iodine-Reagent	Conv.*/%	Yield*/%	α:β:γ
1	 (ref)	58	41	11:86:3
2			n.d	
3			traces	-
4			n.d.	
5		48	21	66:22:12
6		39	34	0:0:100
7		35	21	41:50:10
8			n.d.	
9		70	41	23:71:6
10		68	44	18:77:4
11		20	7	9:85:6
12		14	2	-

* GC-FID determination using mesitylene as internal standard

Scheme S21: Screening of iodine source amount.

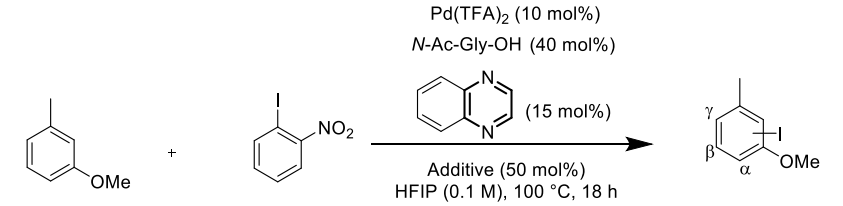


(0.1 mmol) (X equiv.)

Entry	Equiv. I-Reagent	Conv.*/%	Yield*/%	α:β:γ
1	1.1	49	31	10:88:3
2	1.3	53	36	10:87:3
3	1.5	55	37	10:87:3
4	1.7	58	40	11:87:3
5	2.0	60	43	11:86:3
6	2.3	63	44	11:85:3
7	2.5	68	47	14:82:4
8	3.0	69	50	14:82:4

* GC-FID determination using mesitylene as internal standard

Scheme S22: Screening of additives with AgOAc.

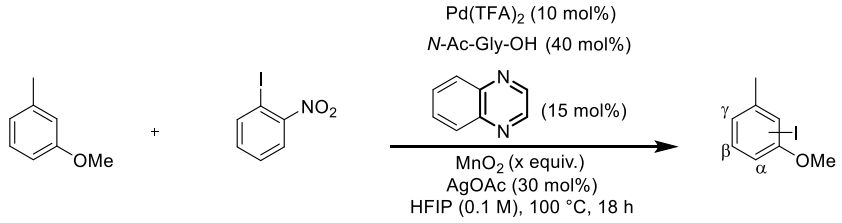


(0.1 mmol) (2.0 equiv.)

Entry	Additive(s) with 30 mol% AgOAc	Conv.*/%	Yield*/%	α:β:γ
1	CuOAc (0.5 equiv.)	51	41	15:80:5
2	$Cu(OAc)_2$ (0.5 equiv.)	49	36	14:82:4
3	$Cu(acac)_2$ (0.5 equiv.)	6	4	13:66:22
4	Oxone (0.5 equiv.)	33	22	39:47:14
5	$CsCO_3$ (0.5 equiv.)	36	21	14:82:4
6	KTFA (0.5 equiv.)	58	43	12:85:3
7	KTFA (0.5 equiv.) + $Cu(OAc)_2$ (1.0 equiv.)	44	33	18:77:5
8	MnO_2 (0.6 equiv.)	65	48	11:86:3

* GC-FID determination using mesitylene as internal standard

Scheme S23: Screening of MnO_2 amount.

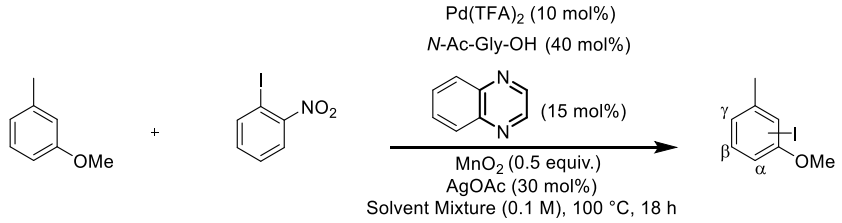


(0.1 mmol) (2.0 equiv.)

Entry	Equiv. MnO_2	Conv.*/%	Yield*/%	α:β:γ
1	0 (ref)	60	43	11:86:3
2	0.25	62	45	11:86:3
3	0.5	64	48	11:86:3
4	0.75	60	43	11:86:3
5	1.0	55	39	10:87:3
6	1.5	62	42	11:86:3
7	2.0	63	43	12:85:3
8	3.0	58	40	11:86:3

* GC-FID determination using mesitylene as internal standard

Scheme S24: Screening of solvent mixtures with HFIP.

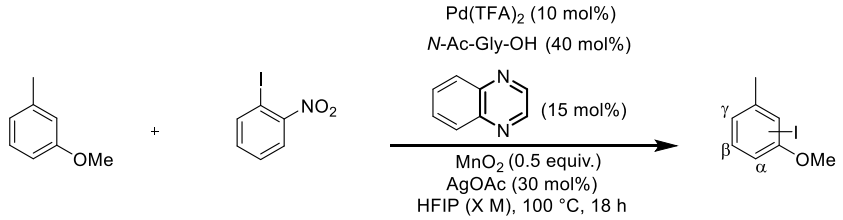


(0.1 mmol) (2.0 equiv.)

Entry	Solvent Mixture (1:1)	Conv.*/%	Yield*/%	α:β:γ
1	HFIP:DCE	30	23	10:87:3
2	HFIP:MeCN	18	2	-
3	HFIP:$CHCl_3$	33	26	11:86:3
4	HFIP:DMSO	15	0	-
5	HFIP:CF_3CH_2OH	50	34	16:80:4
6	HFIP:DMA	12	1	0:67:33
7	HFIP:DME	19	9	11:85:4
8	HFIP:EtOAc	21	10	10:86:4
9	HFIP:^{t}Amyl-OH	10	1	-
10	HFIP:Acetone	6	0	-
11	HFIP:DMF	9	0	-
12	HFIP (ref)	64	45	10:87:3

* GC-FID determination using mesitylene as internal standard

Scheme S25: Screening of reaction concentration.

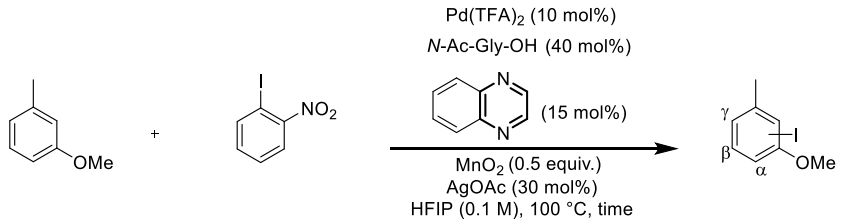


(0.1 mmol) (2.0 equiv.)

Entry	Concentration (M)	Conv.*/%	Yield*/%	α:β:γ
1	0.2 (0.5 mL)	73	49	13:82:4
2	0.14 (0.7 mL)	64	45	11:86:3
3	0.11 (0.9 mL)	65	46	12:84:3
4	0.1 (1.0 mL) (ref)	64	45	11:86:3
5	0.09 (1.1 mL)	65	47	11:84:5
6	0.083 (1.2 mL)	62	44	11:86:3
7	0.077 (1.3 mL)	65	47	12:85:3
8	0.071 (1.4 mL)	65	46	12:85:3
9	0.067 (1.5 mL)	61	45	11:86:3
10	0.05 (2.0 mL)	51	36	10:87:3

* GC-FID determination using mesitylene as internal standard

Scheme S26: Screening of reaction time.

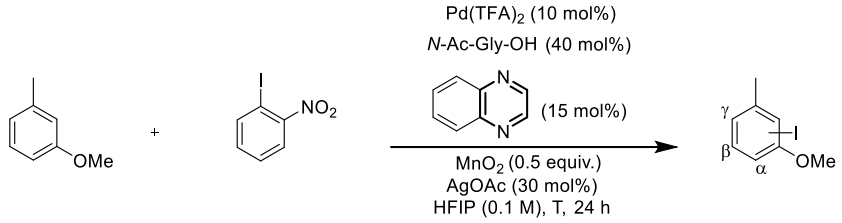


(0.1 mmol) (2.0 equiv.)

Entry	Time/h	Conv.*/%	Yield*/%	α:β:γ
1	6	39	26	11:85:3
2	10	44	31	11:86:3
3	18	66	47	11:86:3
4	24	72	48	13:84:3
5	30	72	51	12:84:3
6	48	77	51	13:84:4
7	72	79	52	12:84:4

* GC-FID determination using mesitylene as internal standard

Scheme S27: Screening of reaction temperature.

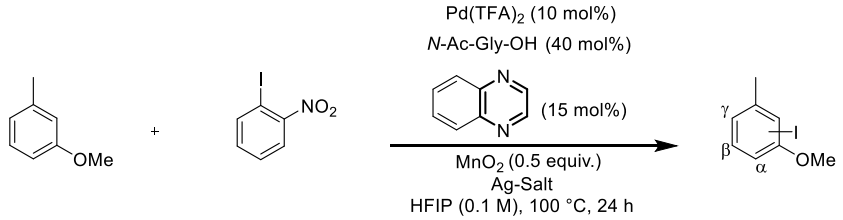


(0.1 mmol) (2.0 equiv.)

Entry	T/ °C	Conv.*/%	Yield*/%	α:β:γ
1	60	19	13	12:84:3
2	70	35	23	11:86:3
3	80	48	35	11:87:3
4	80**	73	50	9:88:3
5	90	60	41	10:87:3
6	100 (ref)	68	48	10:87:3
7	110	71	49	13:83:4
8	120	75	51	17:78:5
9	100***	71	48	13:83:3

* GC-FID determination using mesitylene as internal standard
** Reaction performed with 72 h reaction time.
*** 0.067 M, 48 h

Scheme S28: Re-screening of silver salts.

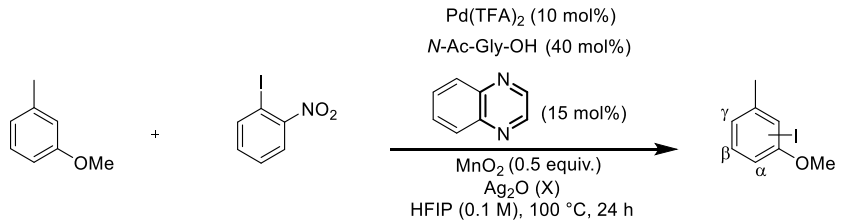


(0.1 mmol) (2.0 equiv.)

Entry	Ag-Salt	Conv.*/%	Yield*/%	α:β:γ
1	AgOAc (0.3 equiv.) (ref)	72	50	13:83:4
2	Ag_2CO_3 (0.15 equiv.)	73	50	12:84:3
3	Ag_2CO_3 (0.3 equiv.)	74	44	11:86:3
4	AgF (0.3 equiv.)	69	47	11:86:3
5	$AgNO_3$ (0.3 equiv.)	81	20	17:78:5
6	Ag_2O (0.15 equiv.)	71	50	12:85:3
7	Ag_2O (0.3 equiv.)	67	42	11:87:3
8	Ag_3PO_4 (0.1 equiv.)	32	25	32:59:9
9	Ag_3PO_4 (0.3 equiv.)	34	26	38:51:11

* GC-FID determination using mesitylene as internal standard

Scheme S29: Screening of Ag_2O amount.

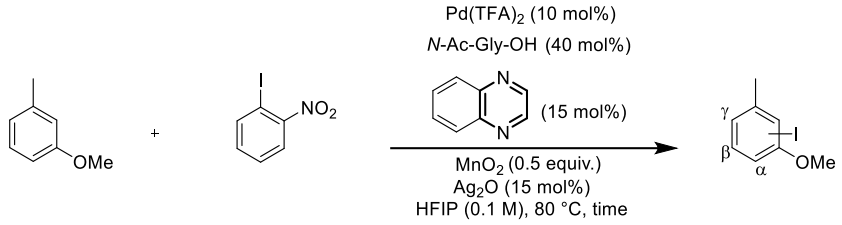


(0.1 mmol) (2.0 equiv.)

Entry	Amount Ag_2O (equiv.)	Conv.*/%	Yield*/%	α:β:γ
1	0.05	50	40	18:77:5
2	0.1	63	47	11:87:3
3	0.15	68	50	11:87:3
4	0.2	68	45	10:87:3
5	0.25	70	45	11:86:3

* GC-FID determination using mesitylene as internal standard

Scheme S30: Screening of reaction time at lower temperature.

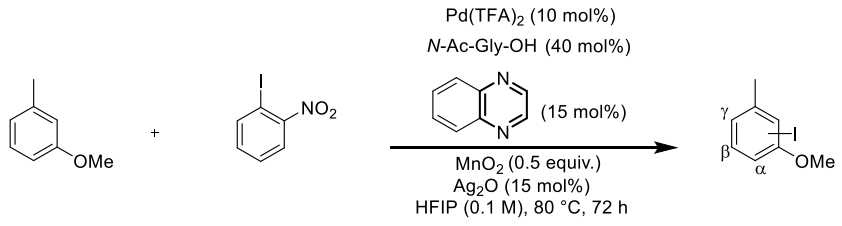


(0.1 mmol) (2.0 equiv.)

Entry	Time/h	Conv.*/%	Yield*/%	α:β:γ
1	24	49	36	10:87:3
2	48	68	47	10:88:2
3	72	74	50	9:88:2

* GC-FID determination using mesitylene as internal standard

Scheme S31: Screening of iodine reagent amount.

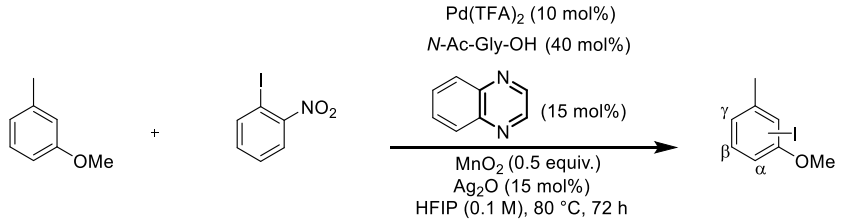


(0.1 mmol) (X equiv.)

Entry	I-Reagent/ Equiv.	Conv.*/%	Yield*/%	α:β:γ
1	2.0	74	50	11:86:3
2	2.5	73	51	11:86:3
3	3.0	78	54	11:86:3
4	3.5	79	54	10:87:3
5	4.0	80	55	11:85:3
6	2.0**	78	49	11:86:3

* GC-FID determination using mesitylene as internal standard
** Concentration: 0.2 M

Scheme S32: Control experiments with MnO_2.

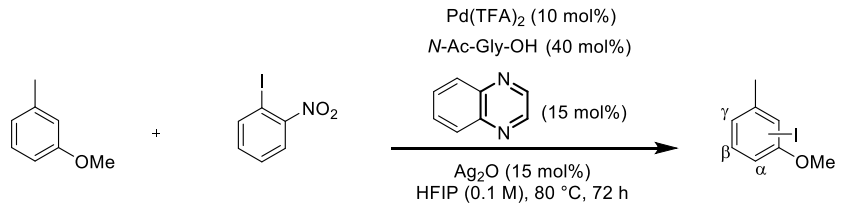


(0.1 mmol) (3.0 equiv.)

Entry	Changes	Conv.*/%	Yield*/%	α:β:γ
1	none (ref)	76	54	10:87:3
2	w/o $Pd(TFA)_2$	4	0	-
3	w/o N-Ac-Gly-OH	18	10	63:0:37
4	w/o Quinoxaline	53	37	49:7:44
5	w/o ligands	34	28	17:1:82
6	w/o MnO_2	76	53	11:86:3
7	w/o Ag_2O	27	21	58:29:13
8	15 mol% catalyst	83	56	10:87:3
9	x1.5 amount of reagents	81	56	9:89:2

* GC-FID determination using mesitylene as internal standard

Scheme S33: Control experiments without MnO_2.

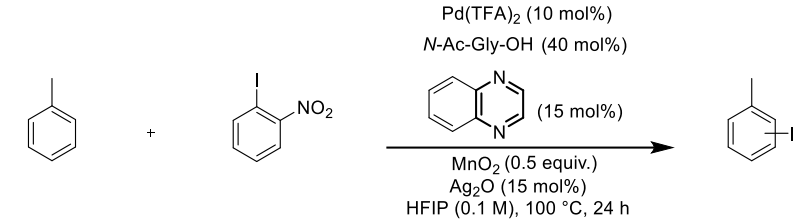


(0.1 mmol) (3.0 equiv.)

Entry	Changes	Conv.*/%	Yield*/%	α:β:γ
1	none (ref)	80	54	11:86:3
2	w/o $Pd(TFA)_2$	0	0	-
3	w/o N-Ac-Gly-OH	19	12	59:0:41
4	w/o Chinoxaline	54	39	46:6:48
5	w/o Ag_2O	21	18	62:25:13

* GC-FID determination using mesitylene as internal standard

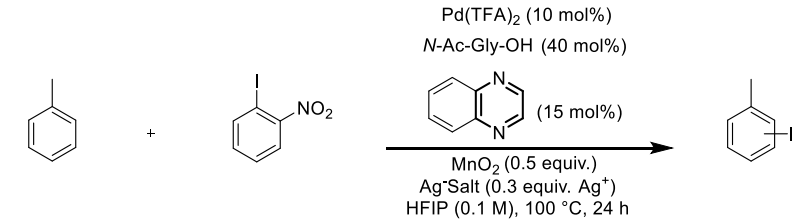
Scheme S34: Reaction using toluene (**1c**).



(0.1 mmol) (2.0 equiv.)

Entry	Changes	Conv.*/%	Yield*/%	o:m:p
1	none	90	52	0:67:33
2	no MnO_2	88	52	0:67:33
3	$AgNO_3$ (0.5 equiv.) instead of Ag_2O	92	42	0:67:33

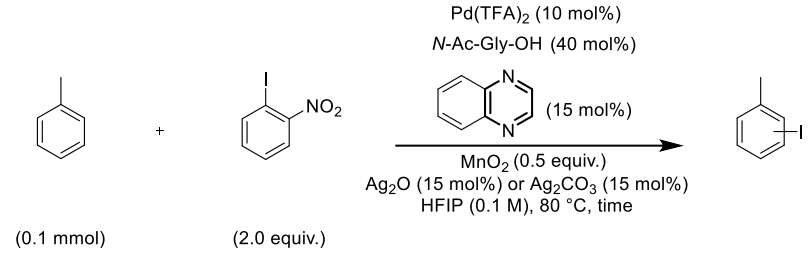
Scheme S35: Screening of silver salts.



(0.1 mmol) (2.0 equiv.)

Entry	Ag-Salt	Conv.*/%	Yield*/%	o:m:p
1	Ag_2O	92	47	0:67:33
2	AgOAc	91	49	0:66:34
3	Ag_2CO_3	91	51	0:67:33
4	$AgNO_3$	87	45	0:67:33

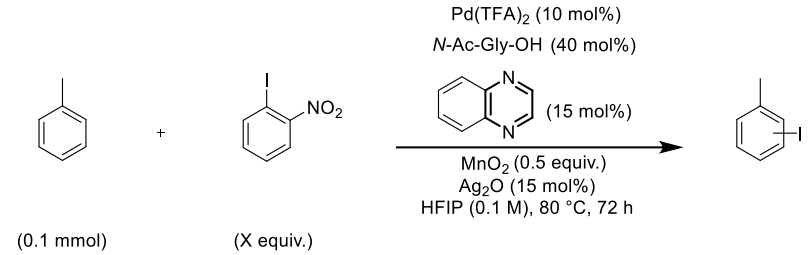
Scheme S36: Screening of reaction time using Ag_2O and Ag_2CO_3.



(0.1 mmol) (2.0 equiv.)

Entry	Conditions	Conv.*/%	Yield*/%	o:m:p
1	Ag_2O; 24 h	73	51	0:69:31
2	Ag_2O; 48 h	83	55	0:69:31
3	Ag_2O; 72 h	91	50	0:68:32
4	Ag_2CO_3; 24 h	75	52	0:69:31
5	Ag_2CO_3; 48 h	83	52	0:68:32
6	Ag_2CO_3; 72 h	93	46	0:67:33

Scheme S37: Screening of iodine reagent amount.

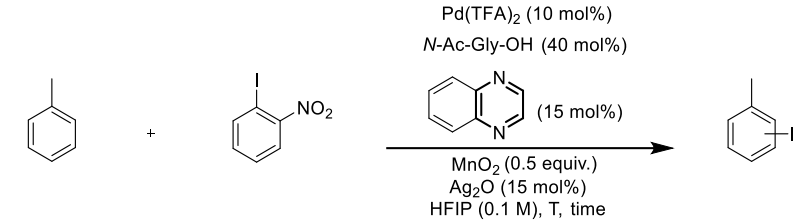


(0.1 mmol) (X equiv.)

Entry	Changes	Conv.*/%	Yield*/%	o:m:p
1	1.2	83	48	0:69:31
2	1.5	87	50	0:69:31
3	2.0**	87	54	0:68:32

* GC-FID determination using mesitylene as internal standard
** 70 °C

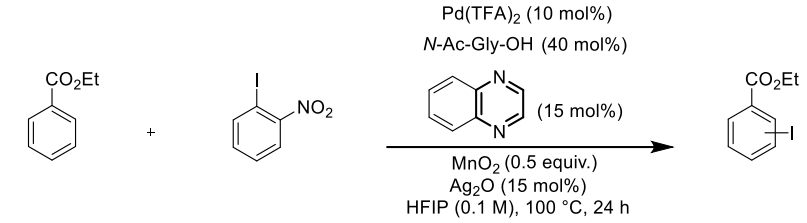
Scheme S38: Screening of temperature, reaction time and iodine reagent amount.



Entry	Conditions	Conv.*/%	Yield*/%	o:m:p
1	80 °C, 72 h, 3.0 equiv.	95	40	0:66:34
2	80 °C, 48 h, 3.0 equiv.	93	52	0:66:34
3	80 °C, 48 h, 2.0 equiv.	90	52	0:68:32
4	70 °C, 48 h, 2.0 equiv.	83	56	0:68:32
5	70 °C, 48 h, 3.0 equiv.	83	55	0:68:32
6	70 °C, 72 h, 3.0 equiv.	90	53	0:67:33
7	70 °C, 72 h, 2.0 equiv.	86	55	0:69:31

* GC-FID determination using mesitylene as internal standard.

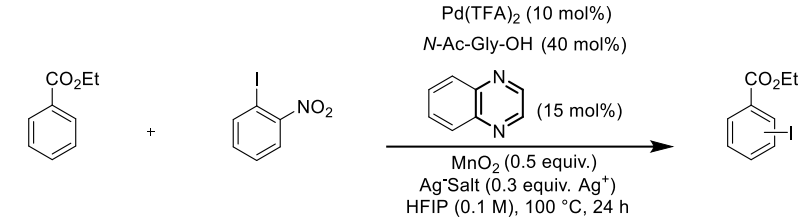
Scheme S39: Reaction using ethyl benzoate (**1h**).



(0.1 mmol) (2.0 equiv.)

Entry	Changes	Conv.*/%	Yield*/%	m:p
1	none	59	27	73:27
2	no MnO_2	59	27	73:27
3	$AgNO_3$ (0.5 equiv.) instead of Ag_2O	39	23	73:27

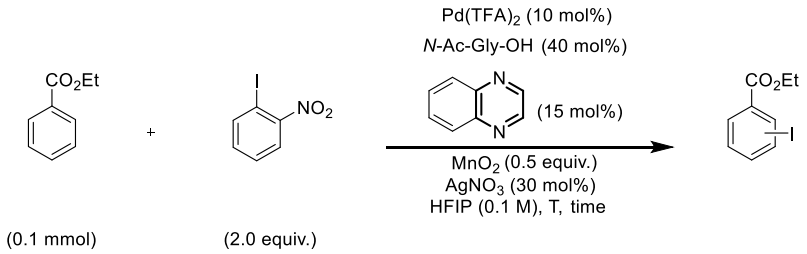
Scheme S40: Screening of silver salts.



(0.1 mmol) (2.0 equiv.)

Entry	Ag-Salt	Conv.*/%	Yield*/%	m:p
1	Ag_2O	59	29	72:28
2	AgOAc	56	28	73:27
3	Ag_2CO_3	60	28	72:28
4	$AgNO_3$	50	27	75:25

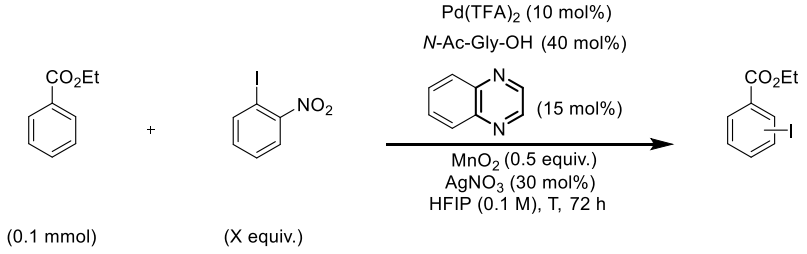
Scheme S41: Screening of temperature and reaction time.



Entry	Conditions	Conv.*/%	Yield*/%	m:p
1	90 °C; 48 h	47	27	74:26
2	90 °C; 72 h	57	31	76:24
3	100 °C; 48 h	58	31	74:26
4	100 °C; 72 h	63	31	73:27

* GC-FID determination using mesitylene as internal standard

Scheme S42: Screening of temperature and iodine reagent amount.

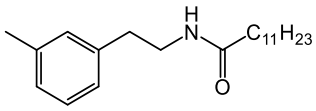


Entry	Conditions	Conv.*/%	Yield*/%	m:p
1	100 °C; 4.0 equiv.	66	37	73:27
2	100 °C; 5.0 equiv.	70	36	73:27
3	110 °C; 4.0 equiv.	67	34	71:29
4	110 °C; 5.0 equiv.	69	35	71:29
5	120 °C; 4.0 equiv.	66	34	72:28
6	120 °C; 5.0 equiv.	62	33	70:30

* GC-FID determination using mesitylene as internal standard

3 Preparation of Starting Materials.

a) *N*-(3-methylphenethyl)dodecanamide (1u):



At 0 °C dodecanoyl chloride (481 mg, 2.20 mmol, 1.1 equiv.) was added dropwise to a mixture of 2-(m-tolyl)ethan-1-amine (270 mg, 2.00 mmol, 1.0 equiv.) and NEt_3 (334 µL, 2.40 mmol, 1.2 equiv.) in CH_2Cl_2 (0.5 M). The reaction mixture was then stirred at 50 °C overnight. After allowing to cool to room temperature, water (20 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification via silica gel column chromatography using EtOAc : pentane = 3:7 as the eluent delivered the target compound **1u** as colorless solid (600 mg, 1.89 mmol, 94%).

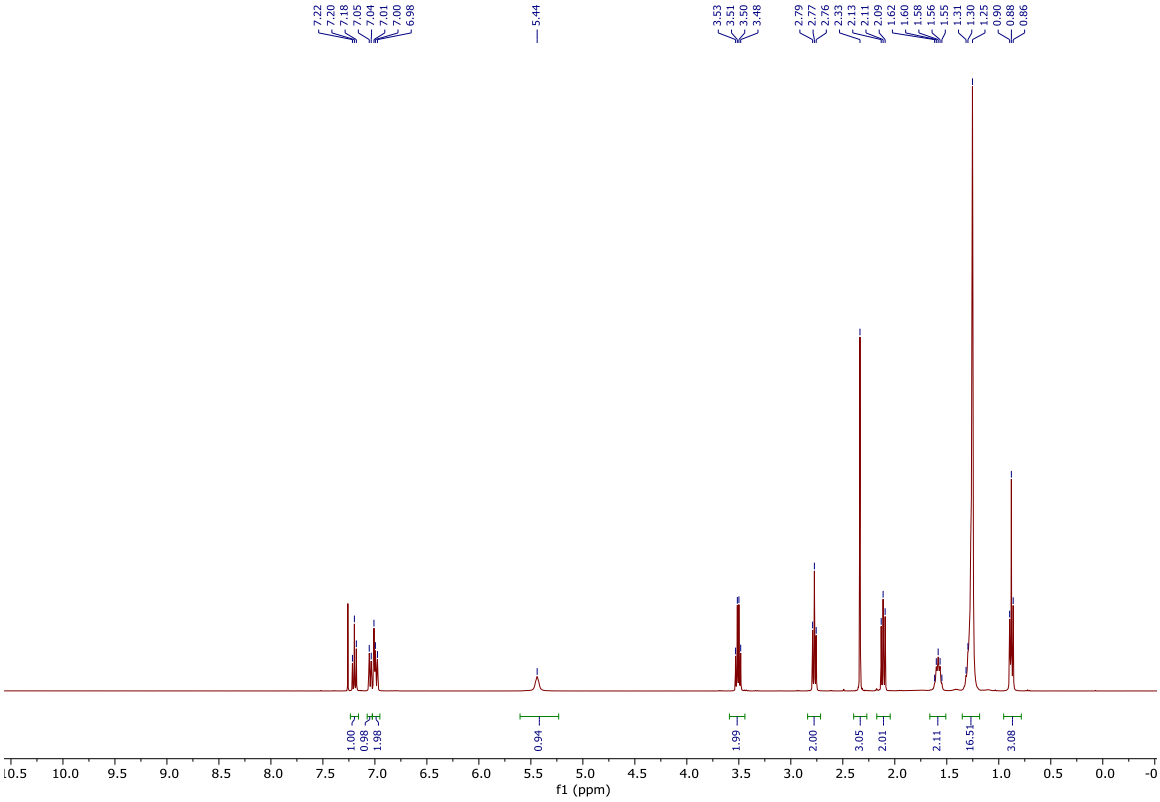
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.20 (t, J = 7.5 Hz, 1H), 7.04 (d, J = 7.6 Hz, 1H), 7.02-6.96 (m, 2H), 5.44 (s, NH), 3.57-3.43 (m, 2H), 2.77 (t, J = 6.9 Hz, 2H), 2.33 (s, 3H), 2.13-2.08 (m, 2H), 1.66-1.50 (m, 2H), 1.34-1.18 (m, 16H), 0.91-0.84 (m, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.3, 139.0, 138.4, 129.7, 128.6, 127.4, 125.9, 40.6, 37.0, 35.8, 32.1, 29.8, 29.7, 29.6, 29.5(1), 29.4(7), 29.4, 25.9, 22,8, 21.5, 14.3 ppm.

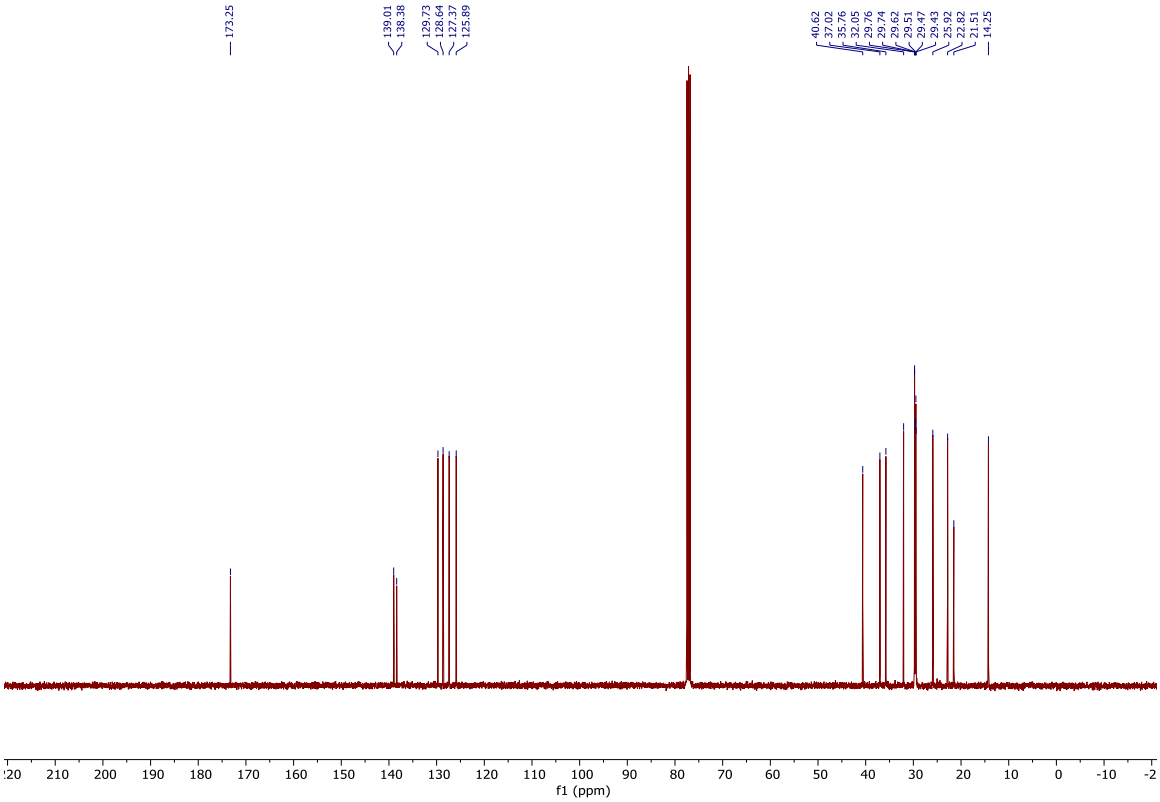
HRMS (ESI pos) m/z: Calcd for $C_{21}H_{35}NONa^+$ 340.2611, Found 340.2604.

IR (cm^{-1}): 3308, 2919, 2851, 1637, 1545, 1507, 699.

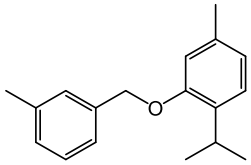
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



b) 1-isopropyl-4-methyl-2-((3-methylbenzyl)oxy)benzene (1am):



An oven dried 50 mL Schlenk tube was charged with NaH (60% in mineral oil, 104 mg, 2.60 mmol, 1.3 equiv.) and a THF:CH_2Cl_2 mixture (5:1, 10 mL). Thymol (300 mg, 2.00 mmol, 1.0 equiv.) was added slowly and the reaction mixture was stirred for 15 minutes. After cooling to 0 °C 1-(iodomethyl)-3-methylbenzene (557 mg, 2.40 mmol, 1.2 equiv.) was added dropwise. The reaction mixture was then stirred at 50 °C and 16 h. After allowing to cool to room temperature, water (20 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification via silica gel column chromatography using EtOAc : pentane = 3:7 as the eluent delivered the target compound **1u** as colorless oil (470 mg, 1.85 mmol, 93%).

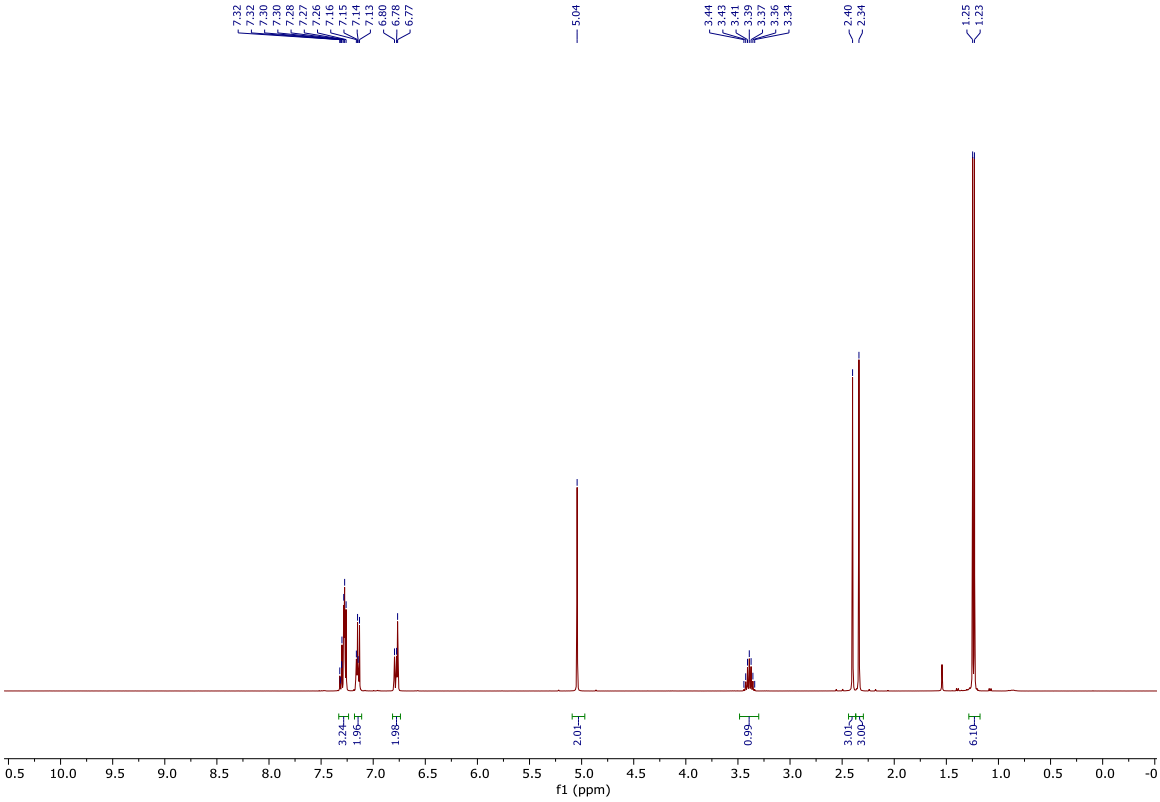
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33-7.25 (m, 3H), 7.17-7.12 (m, 2H), 6.81-6.75 (m, 2H), 5.04 (s, 2H), 3.39 (hept, J = 6.9 Hz, 1H), 2.40 (s, 3H), 2.34 (s, 3H), 1.24 (d, J = 6.9 Hz, 6H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.1, 138.3, 137.7, 136.5, 134.5, 128.5(7), 128,5(5), 128.0, 126.1, 124.4, 121.6, 112.9, 70.2, 26.7, 23.0, 21.6, 21.5 ppm.

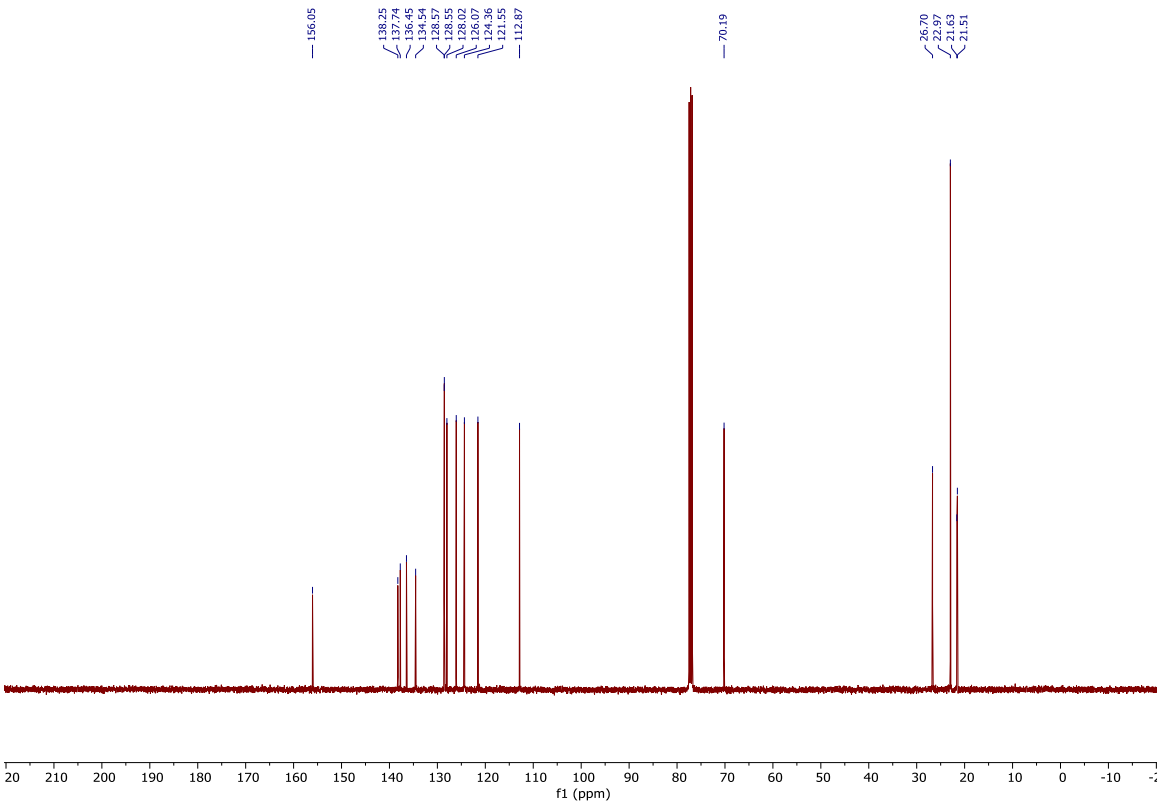
HRMS (EI pos) m/z: Calcd for $C_{18}H_{22}O^+$ 254.1665, Found 254.1665.

IR (cm^{-1}): 2959, 1610, 1490, 1506, 1457, 1288, 1255, 1166, 1026, 809, 763, 692.

^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:

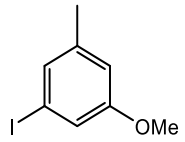


4 Scope of the Iodination

<u>General procedure B</u>: Iodination of arenes

An oven dried 10 mL Schlenk tube was charged with $Pd(TFA)_2$ (6.64 mg, 0.020 mmol, 10 mol%), quinoxaline (3.90 mg, 0.030 mmol, 15 mol%), *N*-acetyl-glycine (9.36 mg, 0.080 mmol, 40 mol%), Ag_2O (6.96 mg, 0.030 mmol, 15 mol%), the arene substrate (0.200 mmol, 1 equiv.), and 1-iodo-2-nitrobenzene (150 mg, 0.600 mmol, 3.0 equiv.), followed by HFIP (2.0 mL). The reaction vessel was tightly sealed and placed into the inside circle of an aluminum block (preheated to 80 °C) with a tightly fitting recess on a magnetic stirrer. The reaction mixture was stirred with 1000 rpm speed at this temperature for 72 h. After completion of the reaction, the mixture was allowed to cool to room temperature, transferred into a 100 mL round-bottom flask, and concentrated under reduced pressure. The product was then purified according to the procedure described for the respective substrate.

1-iodo-3-methoxy-5-methylbenzene (3a)



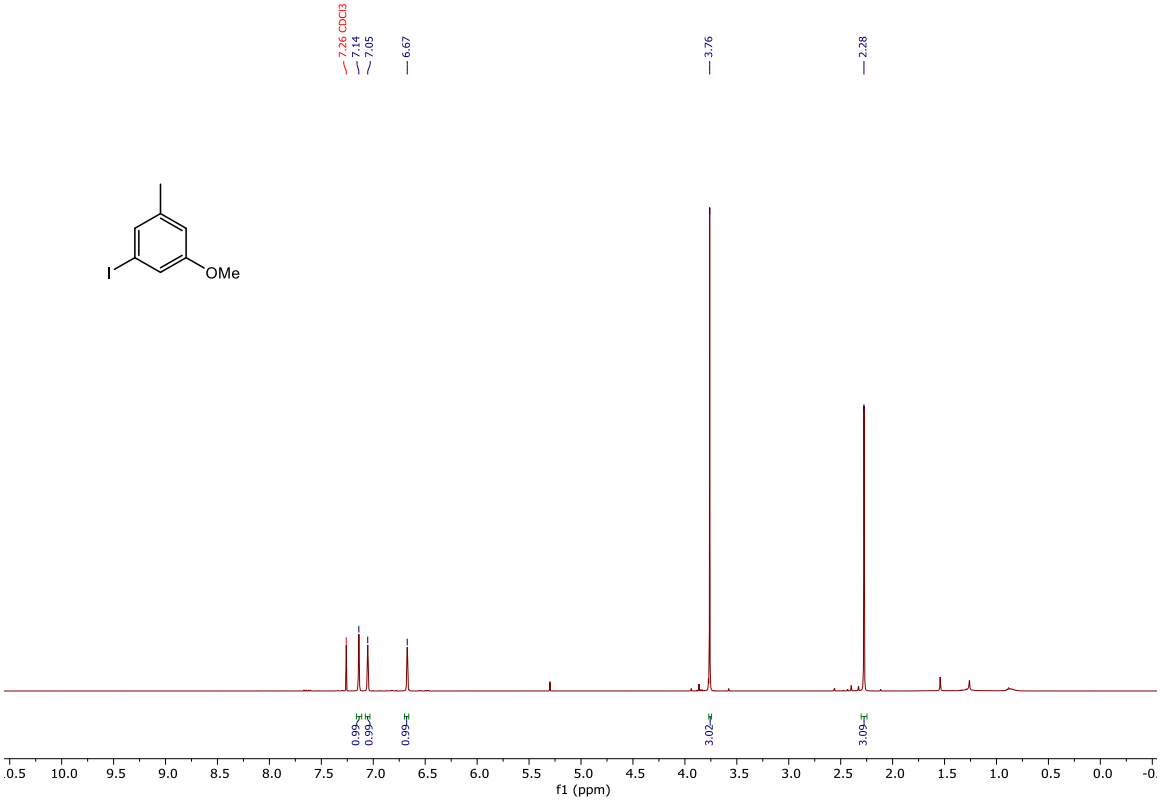
Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), 1-methoxy-3-methylbenzene (**1a**) (24.4 mg, 0.200 mmol), and purification via silica column chromatography using pentane:CH_2Cl_2 = 20:1 as the eluent, the target compound **3a** was obtained as a colorless liquid (24.7 mg, 50%). The assignment of the compound was achieved by comparison with the literature.[3]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.14 (s, 1H), 7.05 (s, 2H), 6.67 (s, 1H), 3.76 (s, 3H), 2.28 (s, 3H) ppm.

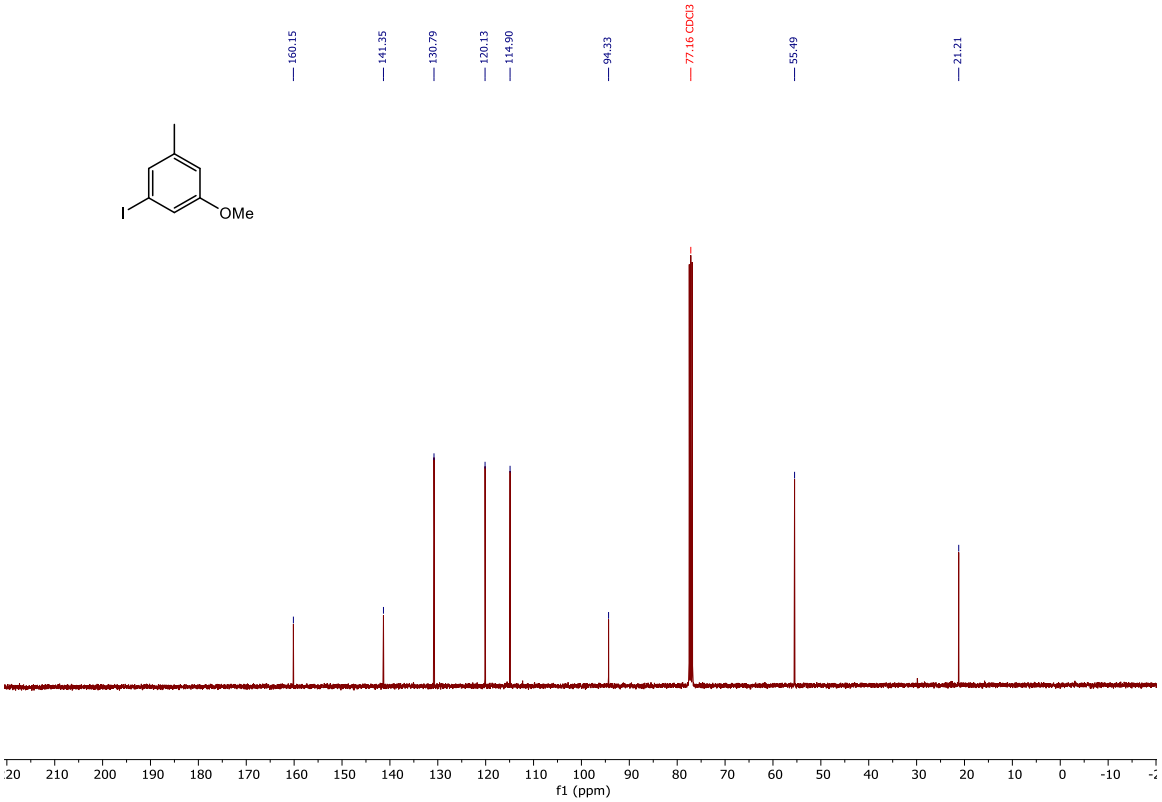
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.2, 141.4, 130.8, 120.1, 114.9, 94.3, 55.5, 21.2 ppm.

Due to coelution of α- and γ-isomers with remaining substrate **1a** and diiodinated arene **1a** only β-iodinated product was been isolated.

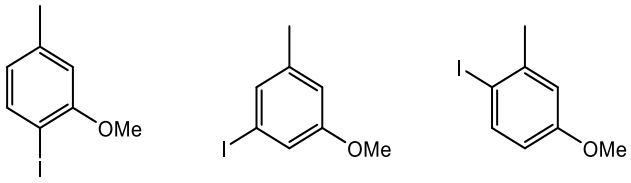
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



1-iodo-2-methoxy-4-methylbenzene (3a´-α), 1-iodo-3-methoxy-5-methylbenzene (3a´-β) and 1-iodo-4-methoxy-2-methylbenzene (3a´-γ)



3a-α **3a-β** **3a-γ**

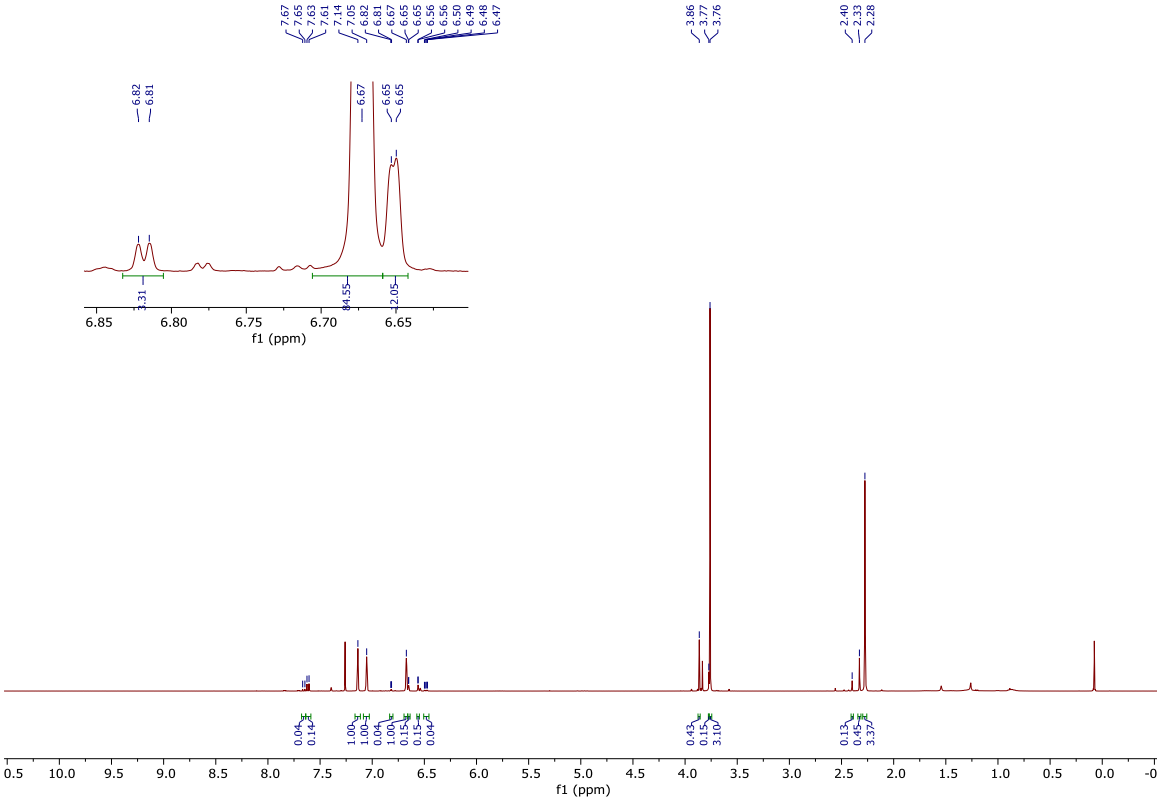
Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), 1-methoxy-3-methylbenzene (**1a**) (24.4 mg, 0.200 mmol), and purification via silica column chromatography using pentane:CH_2Cl_2 = 20:1 as the eluent, the target compound **3a** was obtained as a colorless liquid (27.4 mg, 55%, α:β:γ = 12:85:3). The assignment of the compound was achieved by comparison with the literature.[3]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.66 (d, J = 8.7 Hz, 1H$^{\gamma}$), 7.62 (d, J = 7.9 Hz, 1H$^{\alpha}$), 7.14 (s, 1H$^{\beta}$), 7.05 (s, 1H$^{\beta}$), 6.82 (d, J = 2.9 Hz, 1H$^{\gamma}$), 6.67 (s, 1H$^{\beta}$), 6.66-6.65 (m, 1H$^{\alpha}$), 6.57- 6.56 (m, 1H$^{\alpha}$), 6.48 (dd, J = 8.7, 2.9, 1H$^{\gamma}$), 3.86 (s, 3H$^{\alpha}$), 3.77 (s, 3H$^{\gamma}$), 3.76 (s, 3H$^{\beta}$), 2.40 (s, 3H$^{\gamma}$), 2.33 (s, 3H$^{\alpha}$), 2.28 (s, 3H$^{\beta}$) ppm.

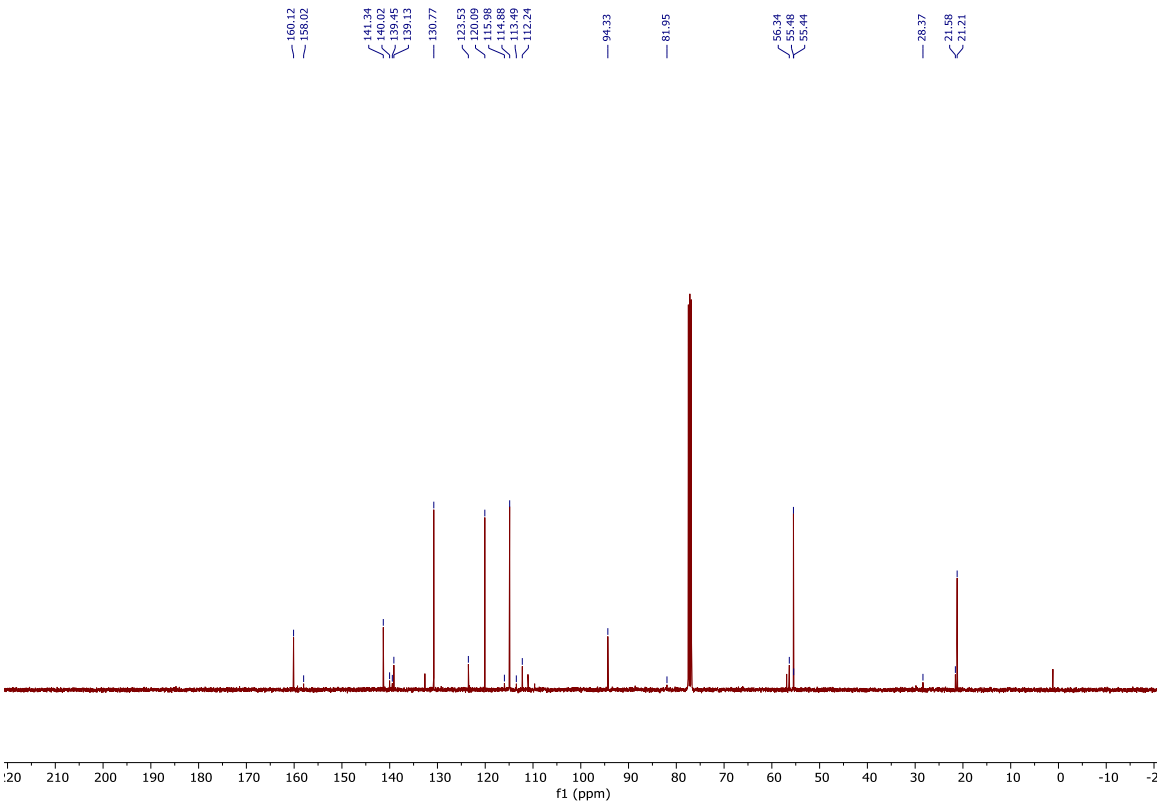
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.1, 158.0, 141.3, 140.0, 139.5, 139.1, 130.8, 123.5, 120.1, 116.0, 114.9, 113.5, 112.2, 111.1, 94.3, 82.0, 56.3, 55.5, 55.4, 28.4, 21.6, 21.2 ppm.

Product contains 6% diiodinated arene **1a**.

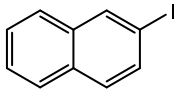
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



2-iodonaphthalene (3b)

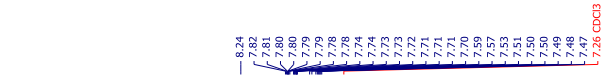


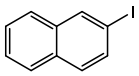
Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), naphthalene (**1b**) (25.6 mg, 0.200 mmol), and purification via silica column chromatography using pentane as the eluent, the target compound **3b** was obtained as a yellow liquid (18.3 mg, 36%). The assignment of the compound was achieved by comparison with the literature.[4]

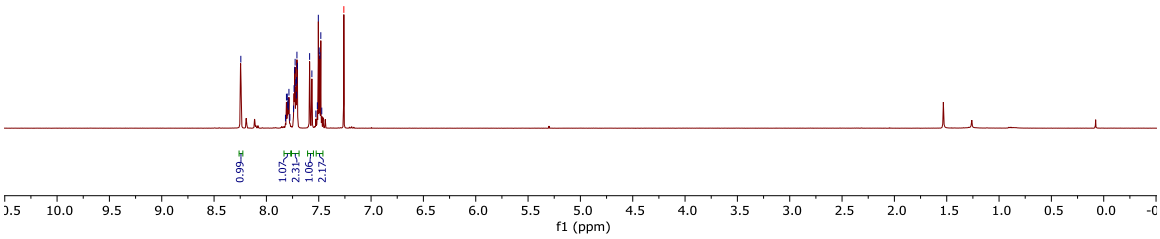
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.24 (s, 1H), 7.82-7.77 (m, 1H), 7.75-7.69 (m, 2H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.54-7.46 (m, 2H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 136.8, 135.2, 134.5, 132.3, 129.6, 128.0, 127.0, 126.8, 126.6, 91.6 ppm.

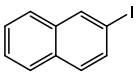
^{1}H NMR spectrum in $CDCl_3$:

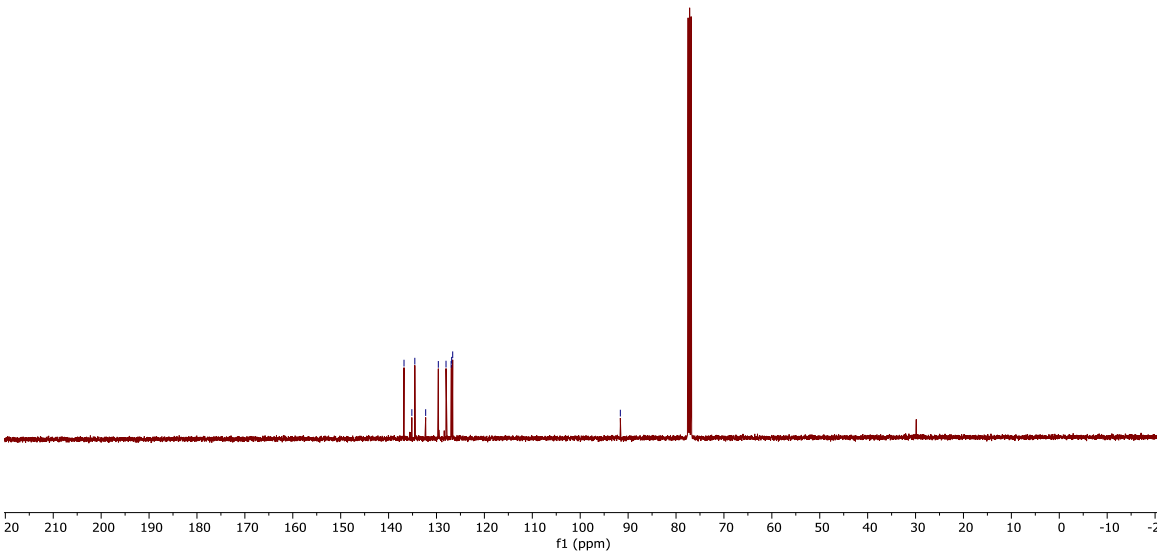




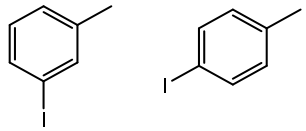


^{13}C NMR spectrum in $CDCl_3$:





1-iodo-3-methylbenzene (3c-meta) and 1-iodo-4-methylbenzene (3c-para)



3c-meta **3c-para**

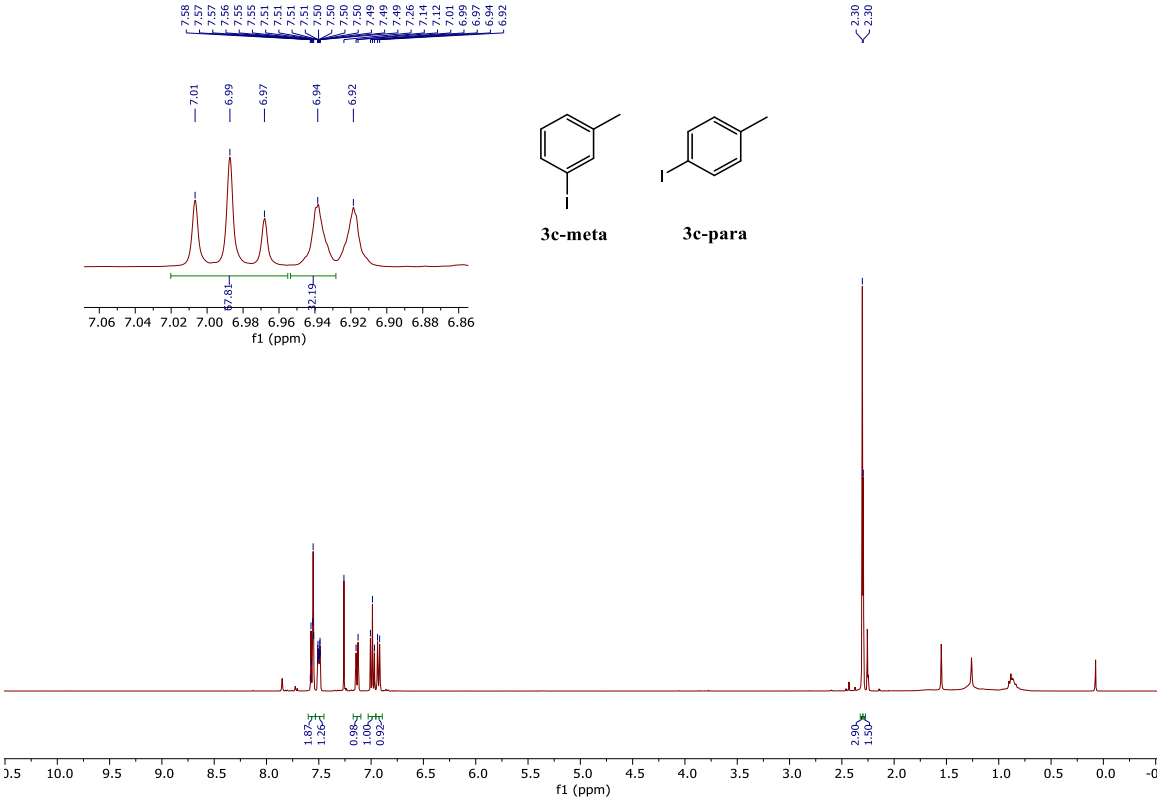
Following the general procedure B[a], using 1-iodo-2-nitrobenzene (**2**) (100 mg, 0.400 mmol, 2.0 equiv.), toluene (**1c**) (25.6 mg, 0.200 mmol), and purification via silica column chromatography using pentane as the eluent, the target compound **3c** was obtained as a colorless liquid (23.6 mg, 54%, m:p = 68:32). The assignment of **3c-meta** and **3c-para** was achieved by comparison with the literature.[4,5]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.59-7.53 (m, $1H^m$ + $2H^p$), 7.52-7.47 (m, $1H^m$), 7.13 (d, *J* = 7.7 Hz, $1H^m$), 6.99 (t, *J* = 7.7 Hz, $1H^m$), 6.93 (d, J = 7.6, $2H^p$), 2.30 (s, $3H^m$), 2.30 (s, $3H^p$) ppm.

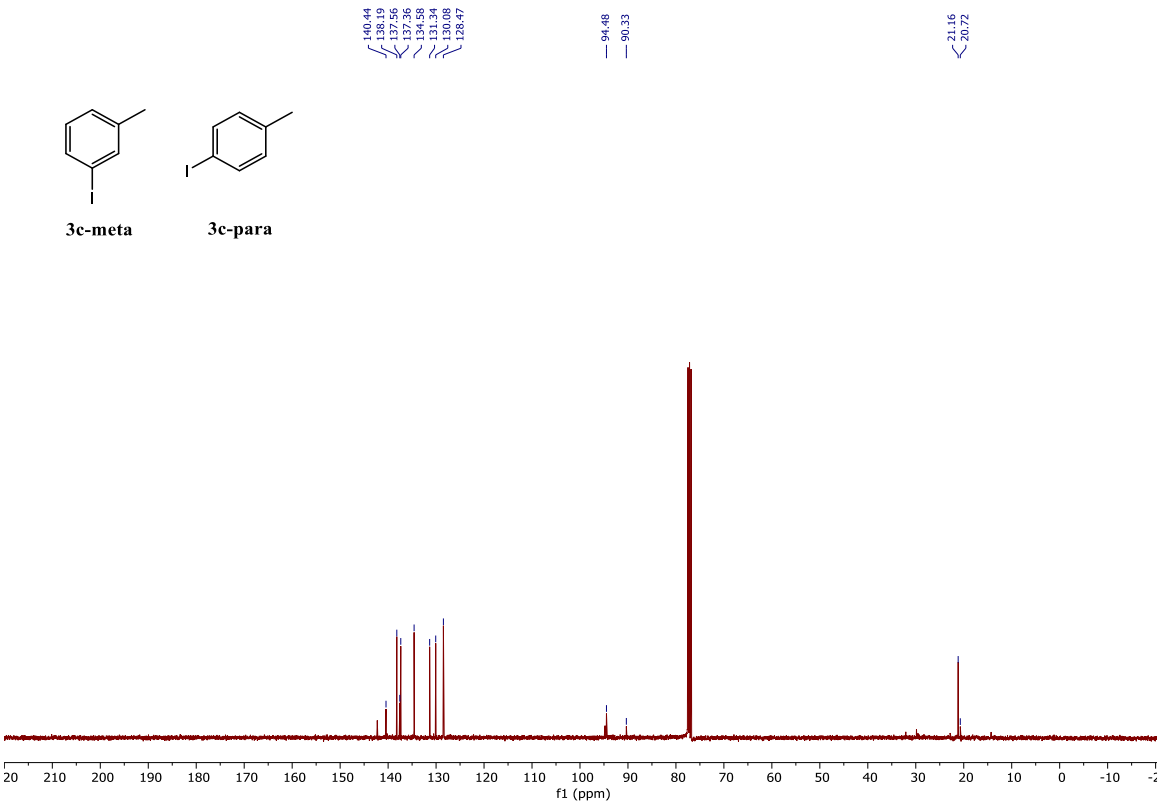
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 140.4, 138.2, 137.6, 137.4, 134.6, 131.3, 130.1, 128.5, 94.5, 90.3, 21.2, 20.7 ppm.

[a] Reaction was performed at 70 °C and 48 h reaction time.

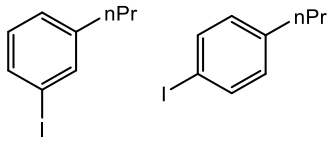
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



1-iodo-3-propylbenzene (3d-meta) and 1-iodo-4-propylbenzene (3d-para)



3d-meta **3d-para**

Following the general procedure B[a], using 1-iodo-2-nitrobenzene (**2**) (100 mg, 0.400 mmol, 2.0 equiv.), propylbenzene (**1d**) (24.0 mg, 0.200 mmol), and purification via silica column chromatography using pentane as the eluent, the target compound **3d** was obtained as a colorless liquid (31.5 mg, 64%, m:p = 72:28).

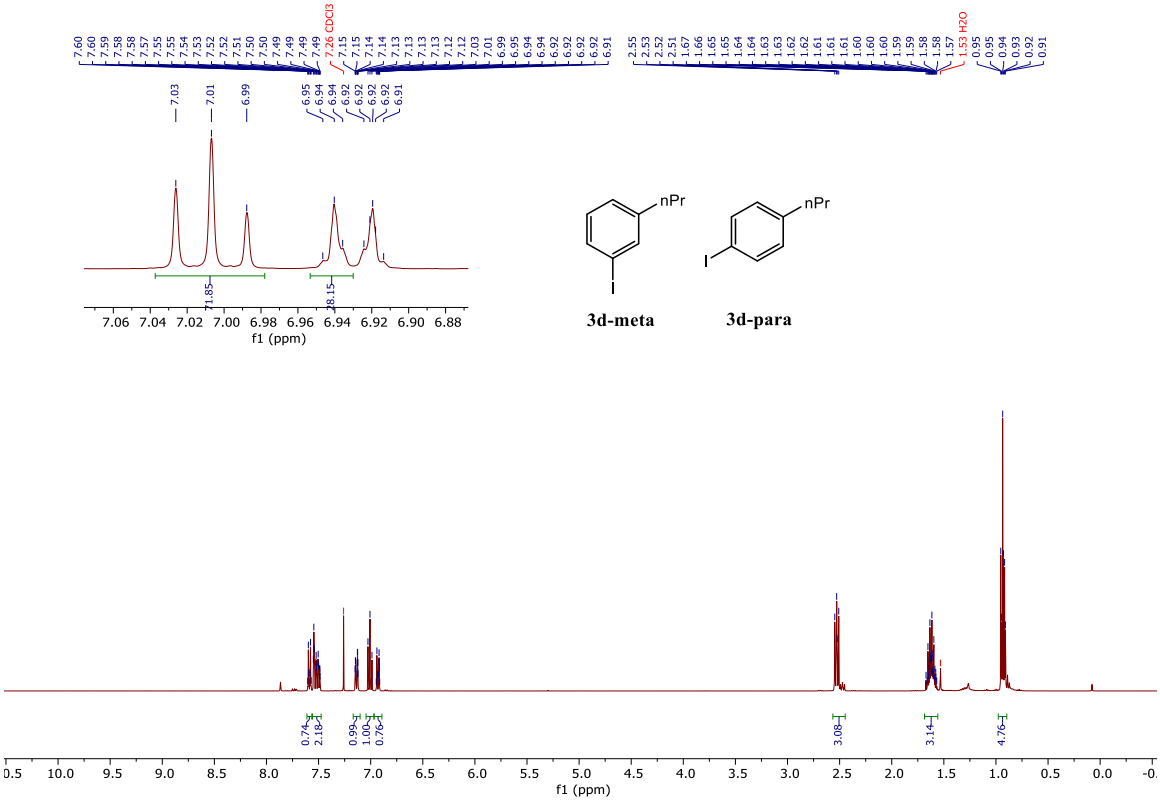
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.61-7.56 (m, $2H^p$), 7.56-7.47 (m, $2H^m$), 7.16-7.11 (m, $1H^m$), 7.01 (t, *J* = 7.7 Hz, $1H^m$), 6.96-6.90 (m, $2H^p$), 2.56-2.43 (m, $2H^m$+$2H^p$), 1.68-1.56 (m, $2H^m$+$2H^p$), 0.98-0.87 (m, $3H^m$ + $3H^p$) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 145.3, 137.6, 137.4, 137.0, 134.9, 130.8, 130.1, 127.9, 94.5, 90.7, 37.7(1), 37.6(5), 24.5, 24.3, 13.9, 13.8 ppm.

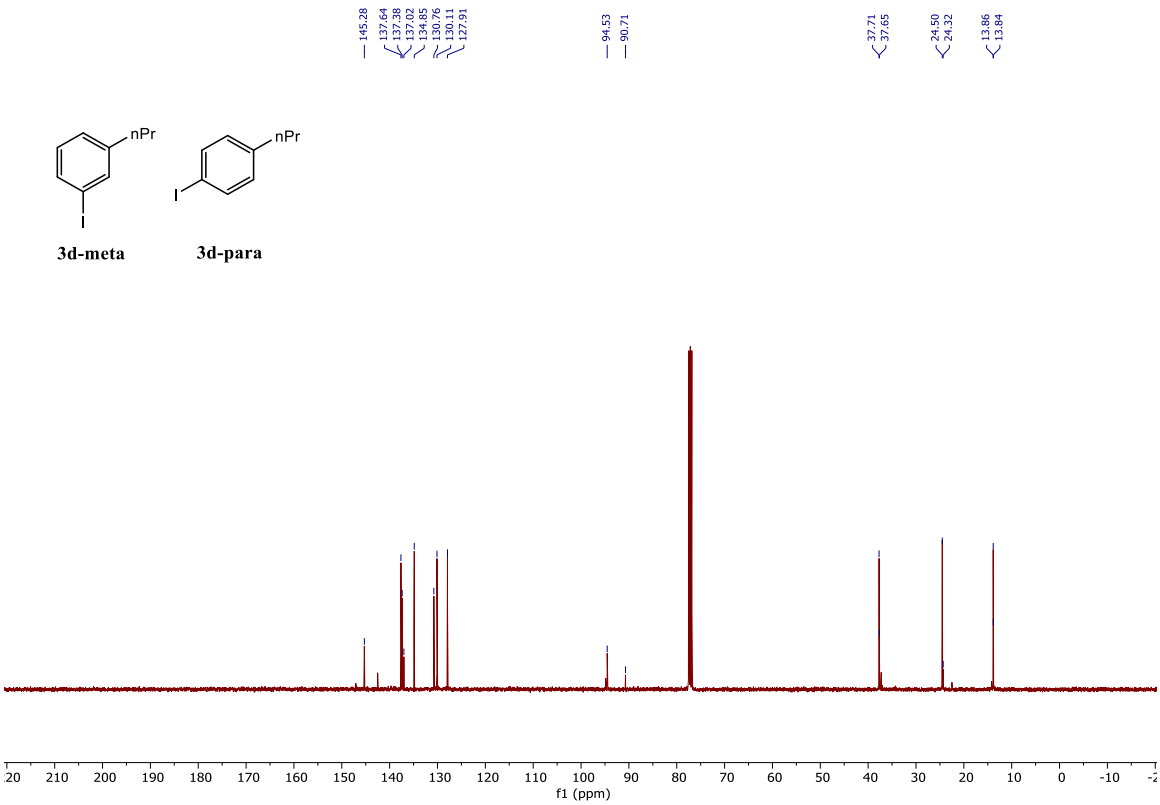
HRMS (EI pos) m/z: Calcd for $C_9H_{11}I^+$ 245,9905, Found 245,9907.

[a] Reaction was performed at 70 °C and 48 h reaction time.

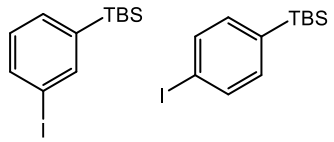
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



tert-butyl(3-iodophenyl)dimethylsilane (3e-meta) and _tert_-butyl(4-iodophenyl)dimethylsilane (3e-para)



3e-meta **3e-para**

Following the general procedure B[a], using 1-iodo-2-nitrobenzene (**2**) (100 mg, 0.400 mmol, 2.0 equiv.), *tert*-butyldimethyl(phenyl)silane (**1e**) (38.5 mg, 0.200 mmol), and purification via silica column chromatography using pentane as the eluent, the target compound **3e** was obtained as a colorless oil (30.6 mg, 48%, m:p = 82:18).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.81-7.79 (m, $1H^m$), 7.71-7.67 (m, $1H^m$+$2H^p$), 7.45 (dt, *J* = 7.3, 1.1 Hz, $1H^m$), 7.25-7.20 (m, $2H^p$), 7.09 (t, *J* = 7.6 Hz, $1H^m$), 0.89-0.86 (m, $9H^m$+ $9H^p$), 0.27-0.24 (m, $6H^m$+$6H^p$) ppm.

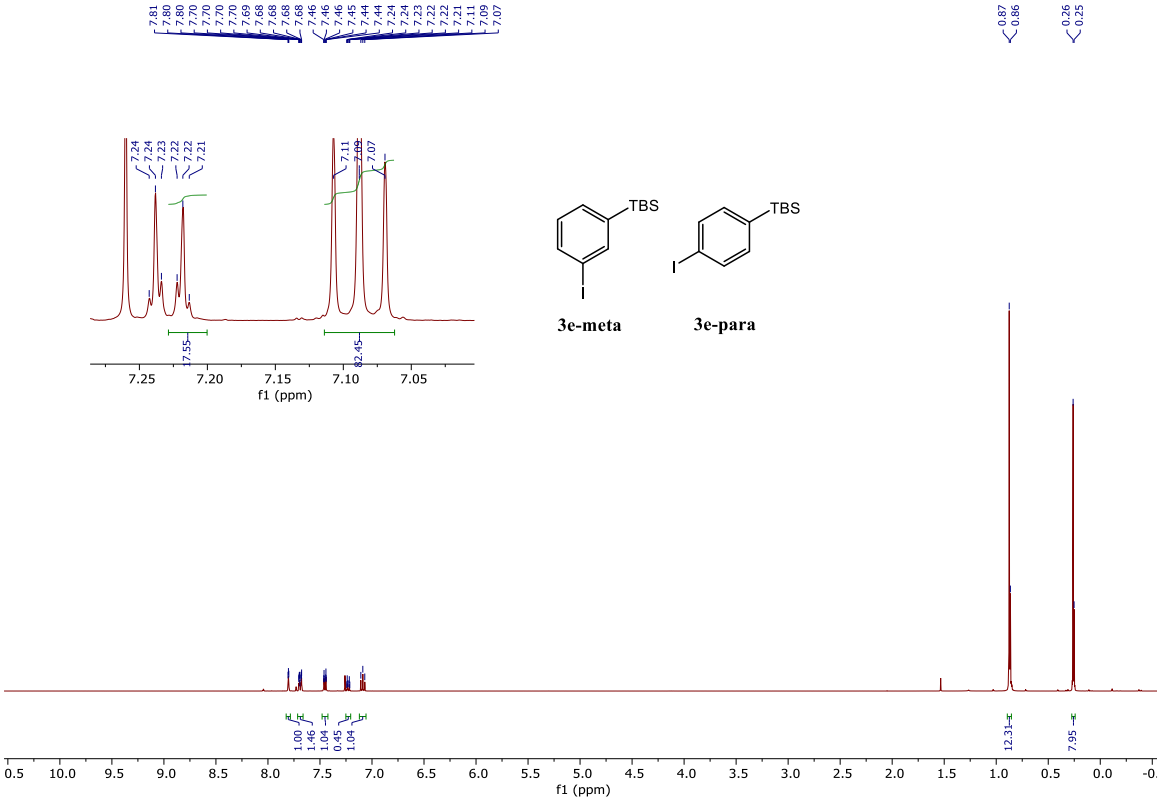
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 143.1, 142.0, 141.7, 137.8, 136.7, 136.3, 133.5, 129.6, 96.0 95.4, 26.6, 26.5, 17.0, 16.9, –6.1, –6.2 ppm.

HRMS (EI pos) m/z: Calcd for $C_{12}H_{19}ISi^+$ 318.0295, Found 318.0295.

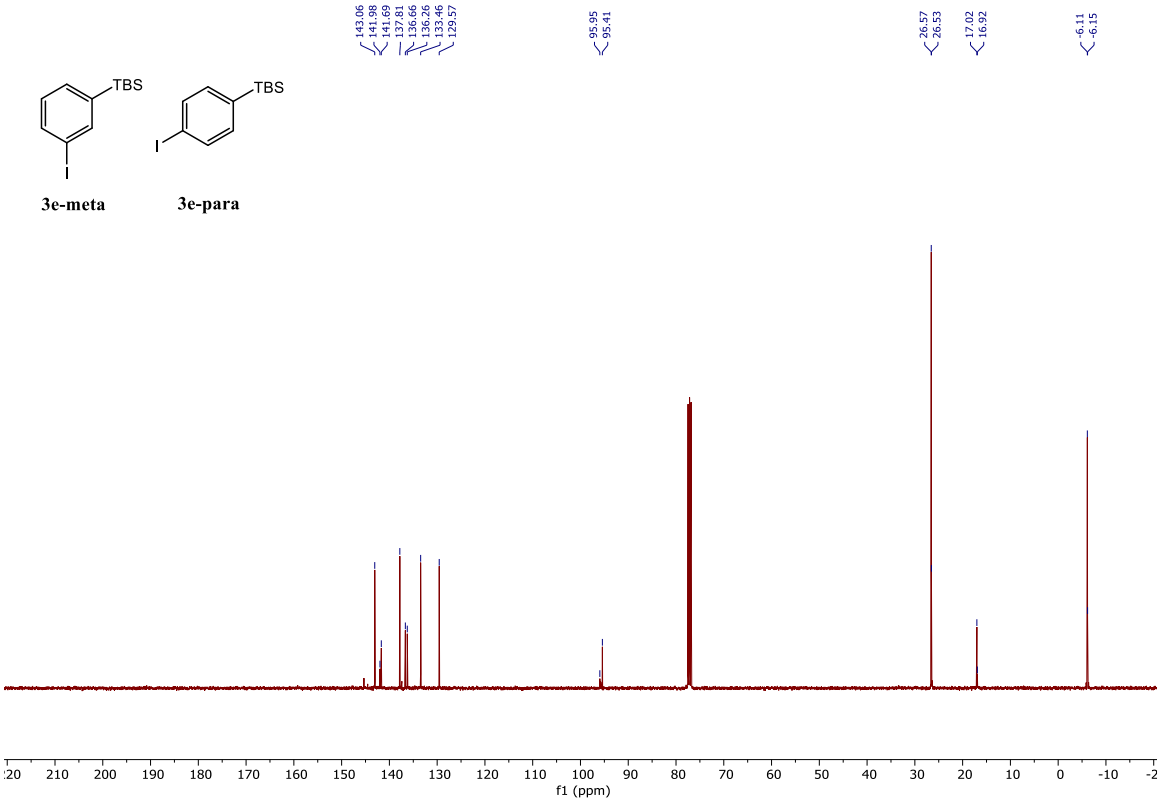
Due to coelution of the para-isomer with substrate **1e** as well as with di-iodinated substrate a meta to para ratio significantly different from the expected statistical meta to para ratio of 2:1 resulted.

[a] Reaction was performed at 70 °C and 48 h reaction time.

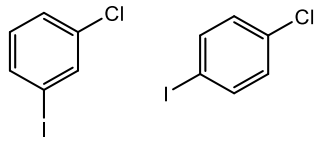
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



1-chloro-3-iodobenzene (3f-meta) and 1-chloro-4-iodobenzene (3f-para)



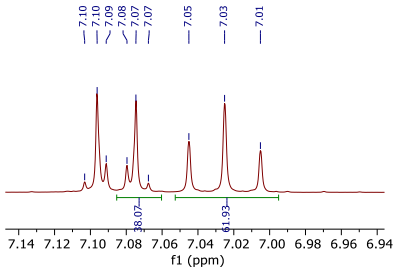
3f-meta **3f-para**

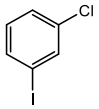
Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), chlorobenzene (**1f**) (22.5 mg, 0.200 mmol), and purification via silica column chromatography using pentane as the eluent, the target compound **3f** was obtained as a colorless liquid (23.3 mg, 49%, m:p = 62:38).). The assignment of **3f-meta** and **3f-para** was achieved by comparison with the literature.[4,6]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.72 (t, *J* = 1.8 Hz, $1H^{m}$), 7.63-7.57 (m. $1H^{m}$+$2H^{p}$), 7.34-7.30 (m, $1H^{m}$), 7.11-7.06 (m, $2H^{p}$), 7.03 (t, *J* = 8.0 Hz, $1H^{m}$) ppm.

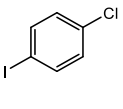
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 138.9, 137.3, 135.8, 135.2, 134.4, 131.1, 130.7, 128.1, 94.2, 91.3 ppm.

^{1}H NMR spectrum in $CDCl_3$:

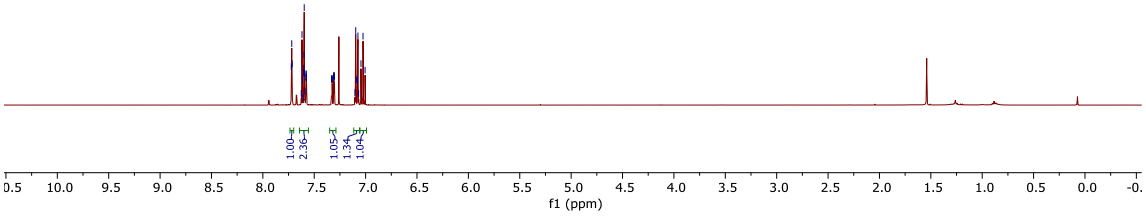




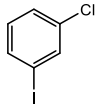
3f-meta



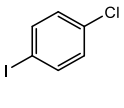
3f-para



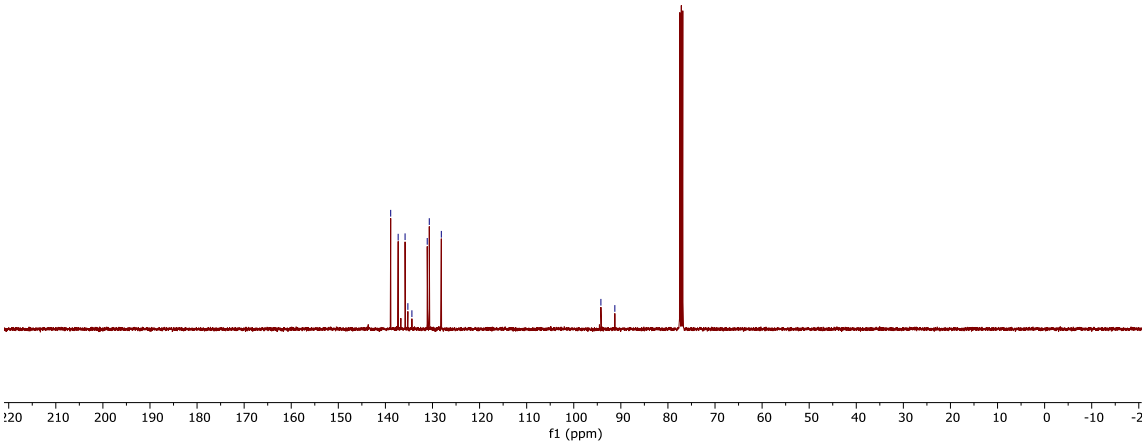
^{13}C NMR spectrum in $CDCl_3$:



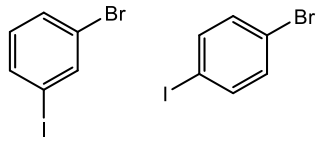
3f-meta



3f-para



1-bromo-3-iodobenzene (3g-meta) and 1-bromo-4-iodobenzene (3g-para)



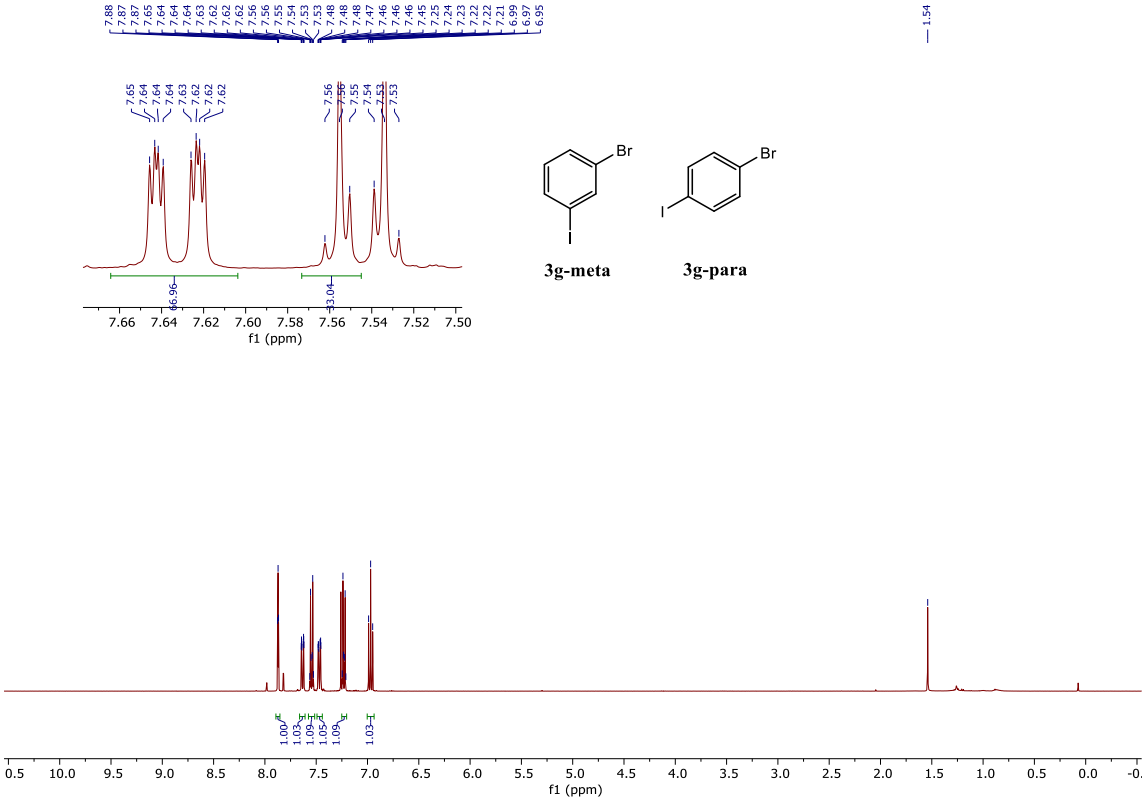
3g-meta **3g-para**

Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), bromobenzene (**1g**) (31.4 mg, 0.200 mmol), and purification via silica column chromatography using pentane as the eluent, the target compound **3g** was obtained as a colorless liquid (30.8 mg, 55%, m:p = 67:33). The assignment of **3g-meta** and **3g-para** was achieved by comparison with the literature.[6,7]

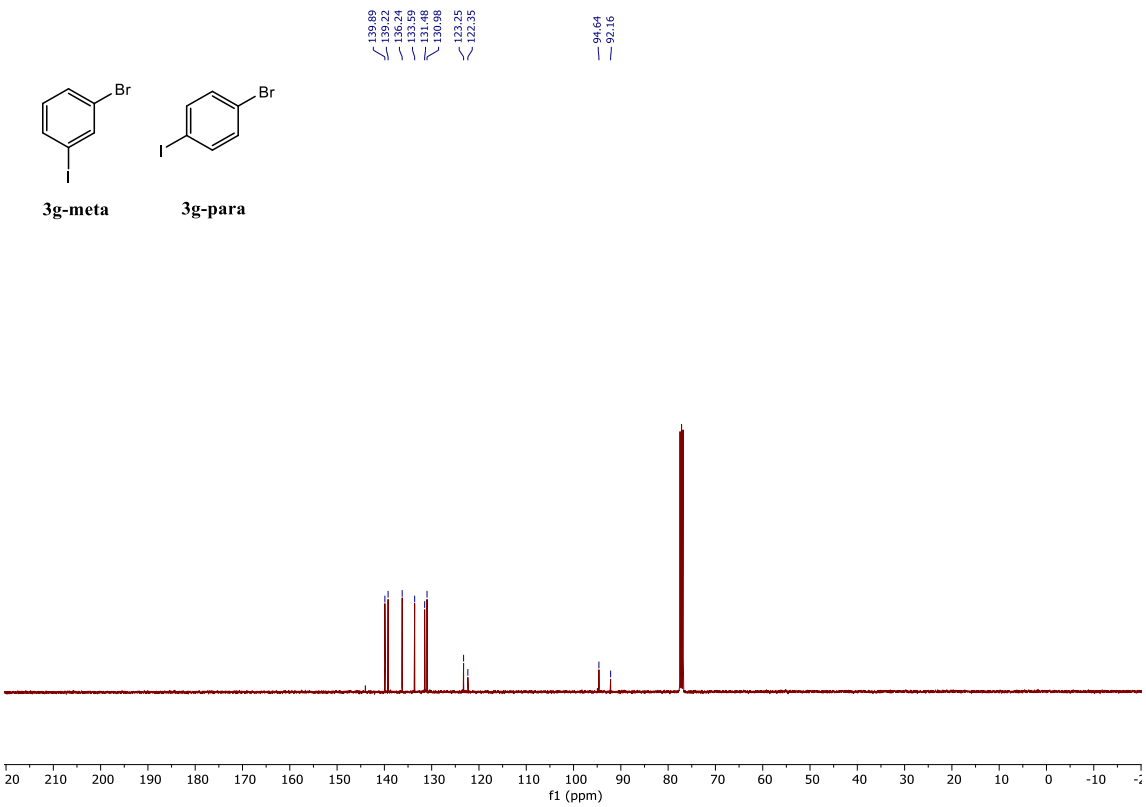
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.87 (t, *J* = 1.8 Hz, $1H^{m}$), 7.65-7.62 (m, $1H^{m}$), 7.57-7.52 (m, $2H^{p}$), 7.49-7.45 (m, $1H^{m}$), 7.25-7.21 (m, $2H^{p}$), 6.97 (t, *J* = 8.0 Hz, $1H^{m}$) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 139.9, 139.2, 136.2, 133.6, 131.5, 131.0, 123.3, 122.4, 94.6, 92.2 ppm.

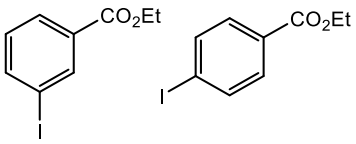
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



ethyl 3-iodobenzoate (3h-meta) and ethyl 4-iodobenzoate (3h-para)



3h-meta **3h-para**

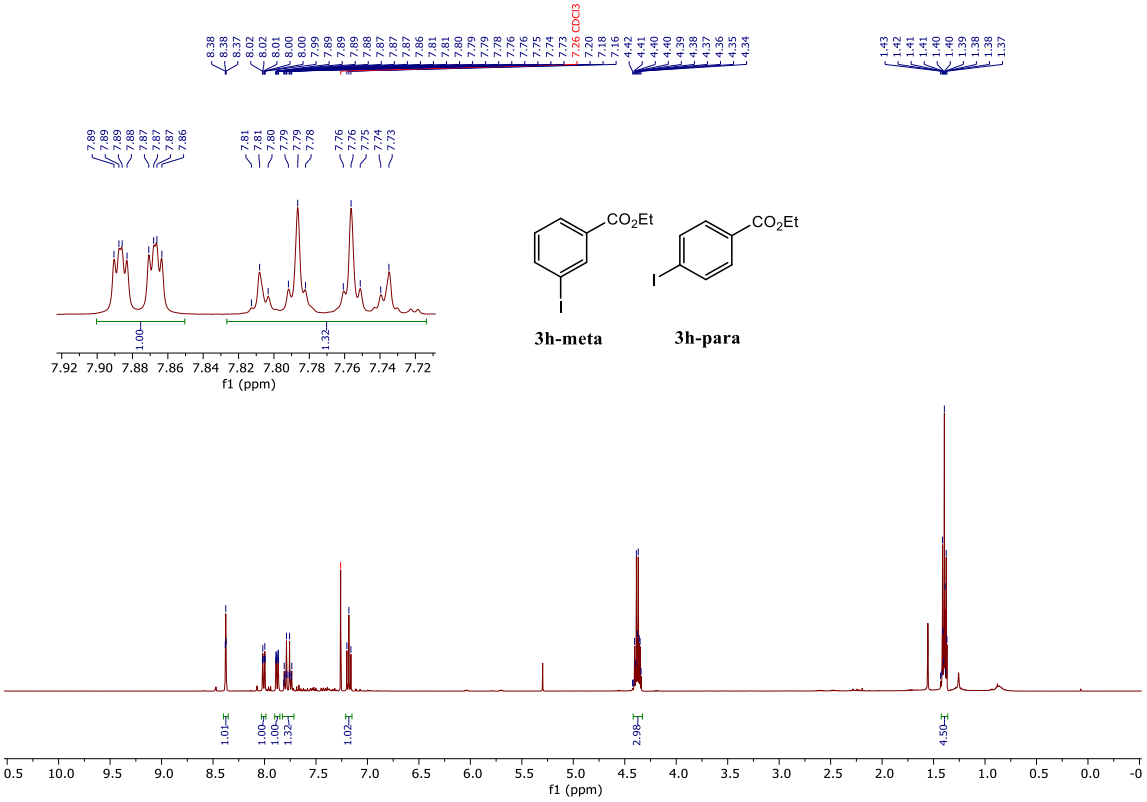
Following the general procedure B[a], using 1-iodo-2-nitrobenzene (**2**) (200 mg, 0.800 mmol, 4.0 equiv.), ethyl benzoate (**1h**) (30.0 mg, 0.200 mmol), and purification via silica column chromatography using pentane:CH_2Cl_2 = 4:1 as the eluent, the target compound **3h** was obtained as a yellow oil (19.3 mg, 35%, m:p = 75:25). The assignment of **3h-meta** and **3h-para** was achieved by comparison with the literature.[6,8]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.38 (t, *J* = 1.7 Hz, 1H^m), 8.03-7.99 (m, 1H^m), 7.90-7.86 (m, 1H^m), 7.82-7.73 (m, 4H^p), 7.18 (t, J = 7.8 Hz, 1H^m), 4.43-4.33 (m, 2H^m+2H^p), 1.44-1.36 (m, 3H^m+3H^p) ppm.

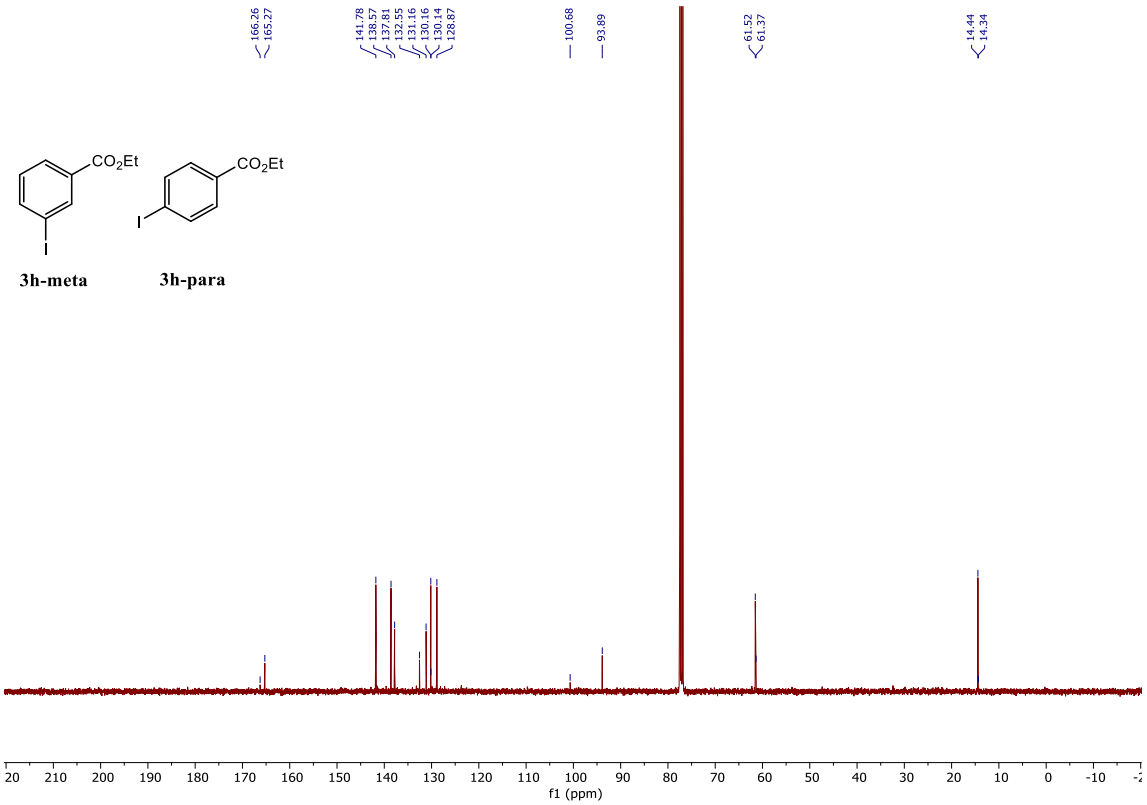
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.3, 165.3, 141.8, 138.6, 137.8, 132.6, 131.2, 130.2, 130.1, 128.9, 100.7, 93.9, 61.5, 61.4, 14.4, 14.3 ppm.

[a] Reaction was performed at 100 °C and with 30 mol% $AgNO_3$ instead of 15 mol% Ag_2O.

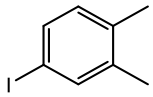
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



4-iodo-1,2-dimethylbenzene (3i)



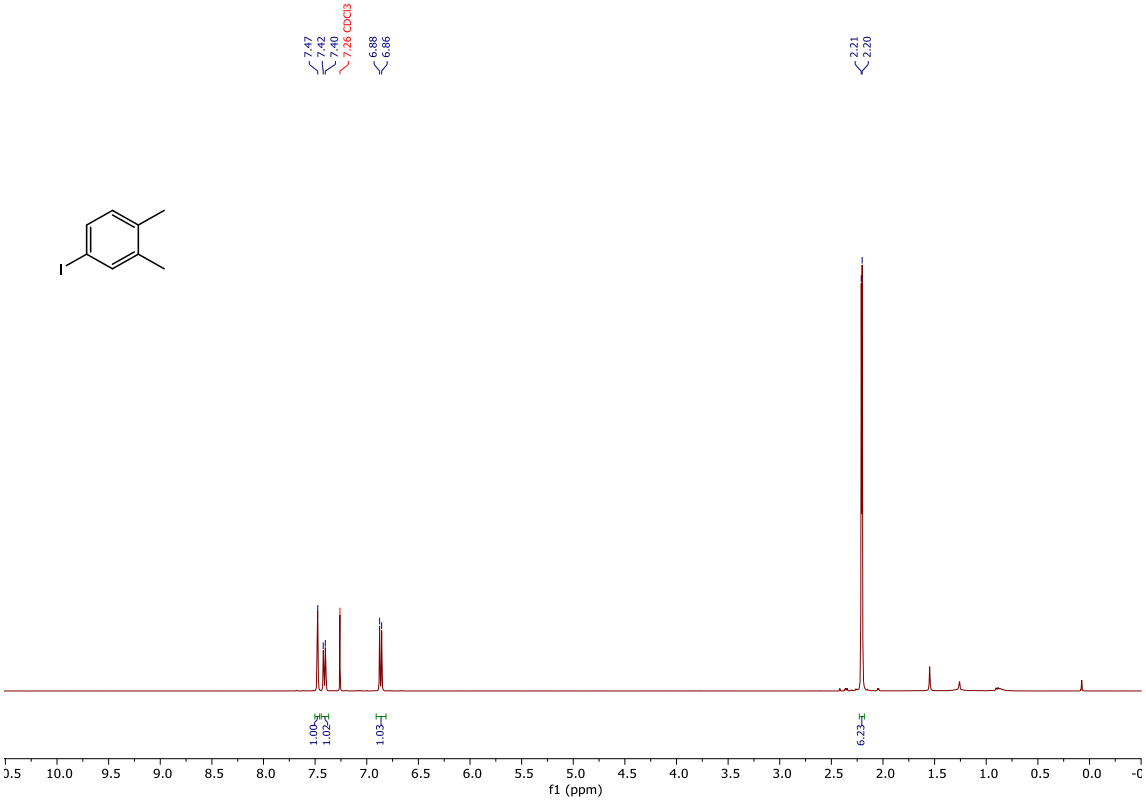
Following the general procedure B[a], using 1-iodo-2-nitrobenzene (**2**) (100 mg, 0.400 mmol, 2.0 equiv.), *ortho*-xylene (**1i**) (21.2 mg, 0.200 mmol), and purification via silica column chromatography using pentane as the eluent, the target compound **3i** was obtained as a colorless liquid (24.2 mg, 52%). The assignment of the compound was achieved by comparison with the literature.[9]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.47 (s, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 6.87 (d, *J* = 7.9 Hz, 1H), 2.21 (s, 3H), 2.20 (s, 3H) ppm.

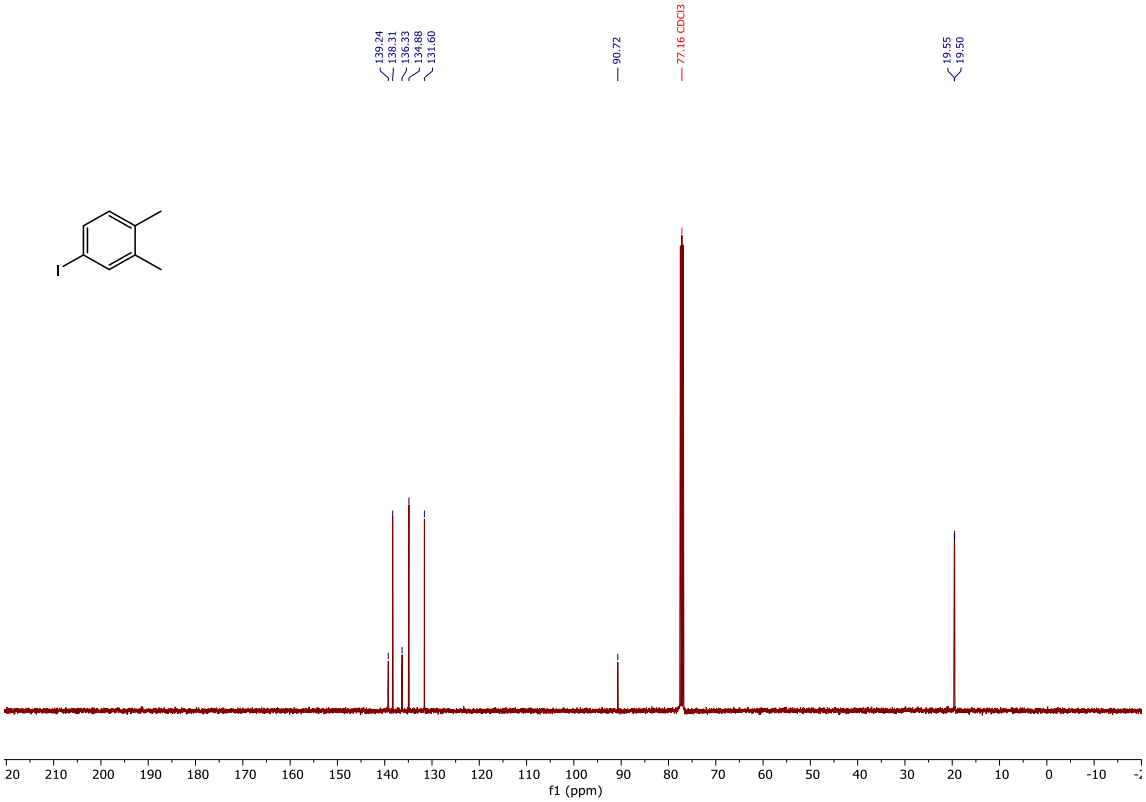
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 139.2, 138.3, 136.3, 134.9, 131.6, 90.7, 19.6, 19.5 ppm.

[a] Reaction was performed at 70 °C and 48 h reaction time.

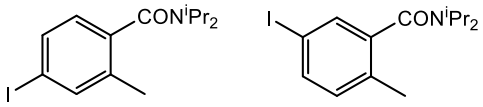
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



4-iodo-*N*,*N*-diisopropyl-2-methylbenzamide (3j-β) and 5-iodo-*N*,*N*-diisopropyl-2-methylbenzamide (3j-β´)



3j-β **3j-β´**

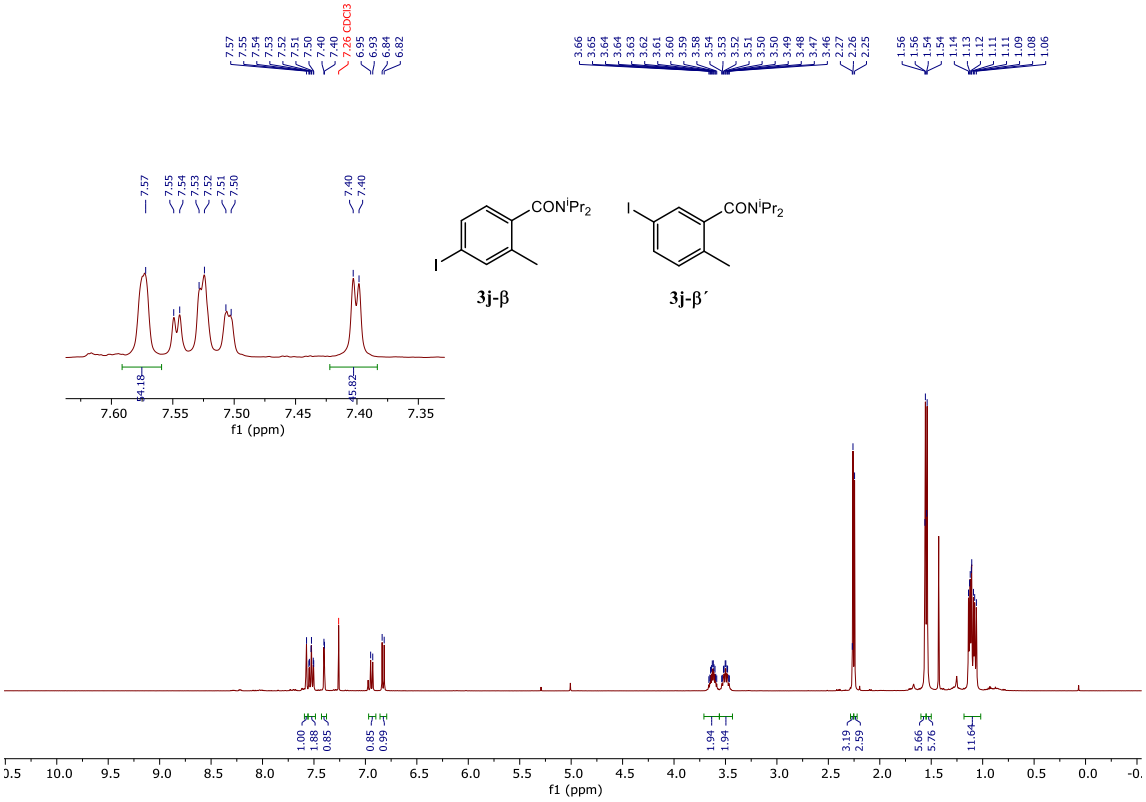
Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), *N*,*N*-diisopropyl-2-methylbenzamide (**1j**) (43.9 mg, 0.200 mmol), and purification via silica column chromatography using pentane:Et_2O = 4:1 as the eluent, the target compound **3j** was obtained as a colorless solid (38.0 mg, 55%, β:β´ = 46:54).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.57 (s, $1H^{\beta'}$), 7.56-7.48 (m, $1H^{\beta}$ +$1H^{\beta'}$), 7.40 (d, *J* = 1.9 Hz, $1H^{\beta}$), 6.94 (d, *J* = 8.1 Hz, $1H^{\beta}$), 6.83 (d, *J* = 8.0 Hz, $1H^{\beta'}$), 3.70-3.57 (m, $1H^{\beta}$+$1H^{\beta'}$), 3.55-3.43 (m, $1H^{\beta}$+$1H^{\beta'}$), 2.26 (s, $3H^{\beta'}$), 2.25 (s, $3H^{\beta}$), 1.60-1.51 (m, $6H^{\beta}$+$6H^{\beta'}$), 1.17-1.03 (m, $6H^{\beta}$+$6H^{\beta'}$) ppm.

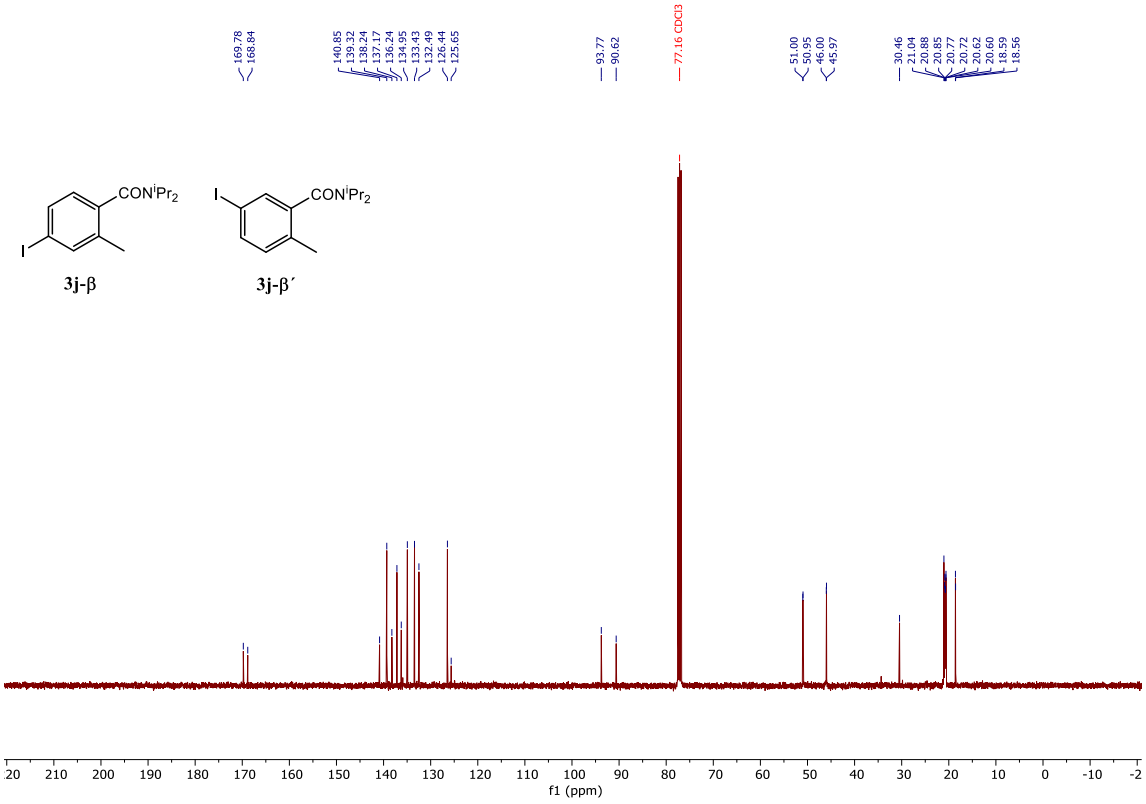
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.8, 168.8, 140.9, 139.3, 138.2, 137.2, 136.2, 135.0, 133.4, 132.5, 126.4, 125.7, 93.8, 90.6, 51.0(0), 50.9(5), 46.0(0), 45.9(7), 30.5, 21.0, 20.8(8), 20.8(5), 20.8, 20.7, 20.6(2), 20.6(0), 18.5(9), 18.5(6) ppm.

HRMS (ESI pos) m/z: Calcd for $C_{14}H_{20}NOINa^+$ 368.0482, Found 368.0480.

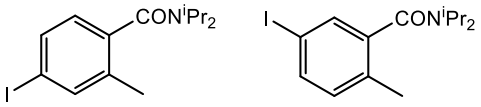
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



4-iodo-*N*,*N*-diisopropyl-2-methylbenzamide (3j´-β) and 5-iodo-*N*,*N*-diisopropyl-2-methylbenzamide (3j´-β´)



3j´-β **3j´-β´**

Following the general procedure B[a], using 1-iodo-2-nitrobenzene (**2**) (200 mg, 0.800 mmol, 4.0 equiv.), *N*,*N*-diisopropyl-2-methylbenzamide (**1j**) (43.9 mg, 0.200 mmol), and purification via silica column chromatography using pentane:Et_2O = 4:1 as the eluent, the target compound **3j´** was obtained as a colorless solid (39.4 mg, 57%, β:β´ = 53:47).

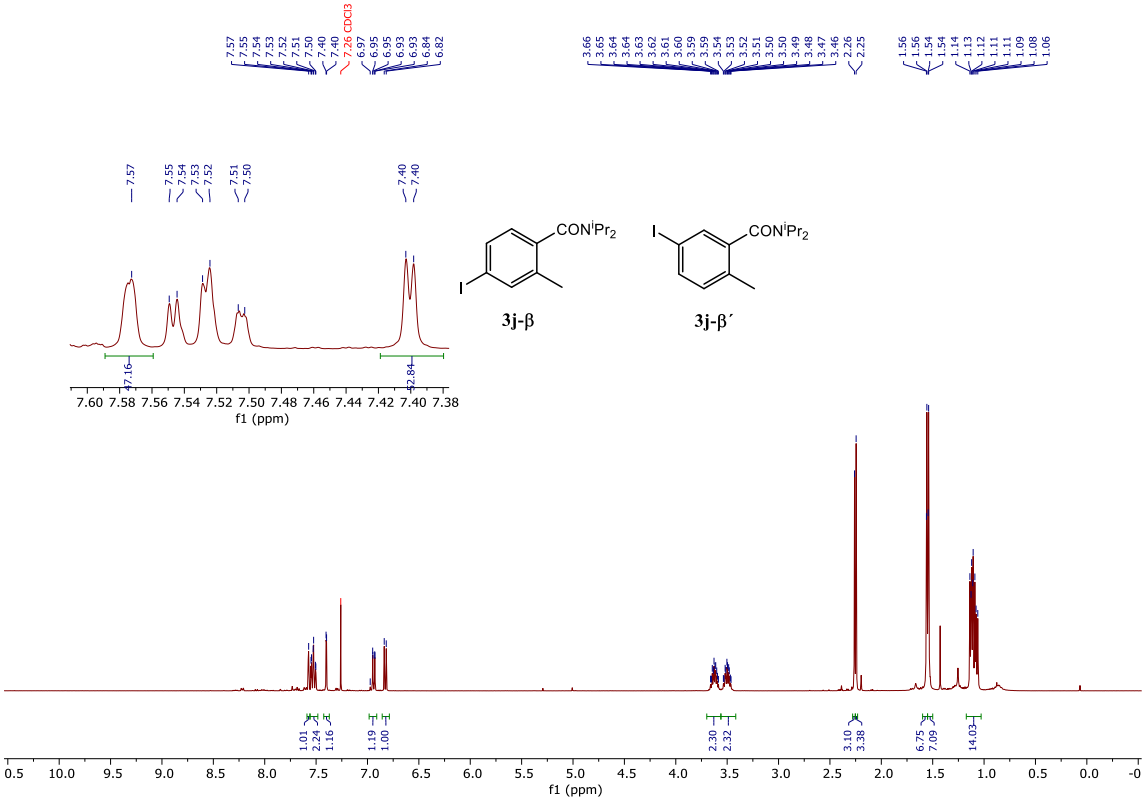
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.57 (s, $1H^{\beta'}$), 7.56-7.49 (m, $1H^{\beta}$ +$1H^{\beta'}$), 7.40 (d, *J* = 1.9 Hz, $1H^{\beta}$), 6.94 (d, *J* = 8.1 Hz, $1H^{\beta}$), 6.83 (d, *J* = 7.9 Hz, $1H^{\beta'}$), 3.68-3.56 (m, $1H^{\beta}$+$1H^{\beta'}$), 3.55-3.45 (m, $1H^{\beta}$+$1H^{\beta'}$), 2.26 (s, $3H^{\beta'}$), 2.25 (s, $3H^{\beta}$), 1.56-1.53 (m, $6H^{\beta}$+$6H^{\beta'}$), 1.15-1.04 (m, $6H^{\beta}$+$6H^{\beta'}$) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.8, 168.8, 140.9, 139.3, 138.2, 137.2, 136.2, 135.0, 133.4, 132.5, 126.4, 125.7, 93.8, 90.6, 51.0(0), 50.9(5), 46.0(1), 45.9(7), 30.5, 21.0, 20.8(8), 20.8(5), 20.8, 20.7, 20.6(2), 20.6(0), 18.5(9), 18.5(6) ppm.

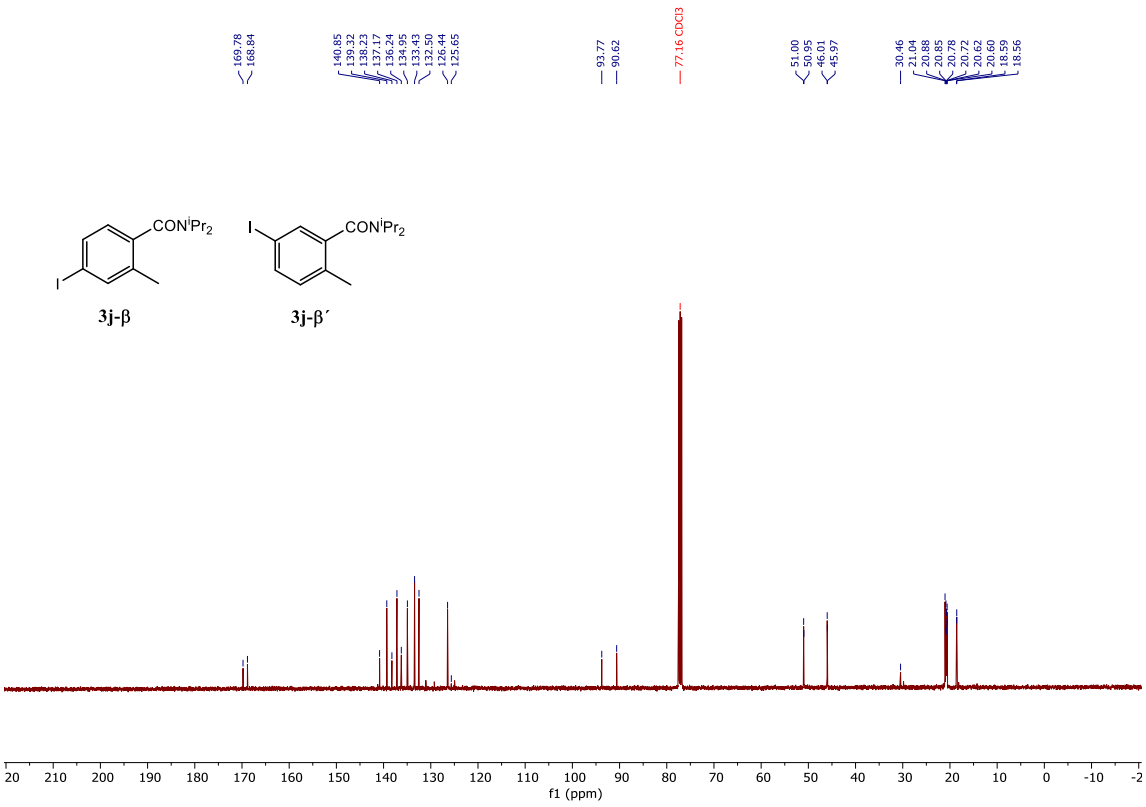
HRMS (ESI pos) m/z: Calcd for $C_{14}H_{20}NOINa^+$ 368.0482, Found 368.0480.

[a] Reaction was performed at 100 °C and with 30 mol% $AgNO_3$ instead of 15 mol% Ag_2O.

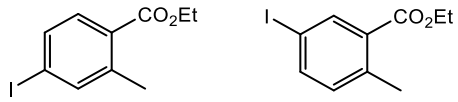
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



ethyl 4-iodo-2-methylbenzoate (3k-β) and ethyl 5-iodo-2-methylbenzoate (3k-β´)



3k-β **3k-β´**

Following the general procedure B[a], using 1-iodo-2-nitrobenzene (**2**) (200 mg, 0.800 mmol, 4.0 equiv.), ethyl 2-methylbenzoate (**1k**) (32.8 mg, 0.200 mmol), and purification via silica column chromatography using pentane:CH_2Cl_2 = 3:1 as the eluent, the target compound **3k** was obtained as a yellow oil (23.8 mg, 41%, β:β´ = 38:62).

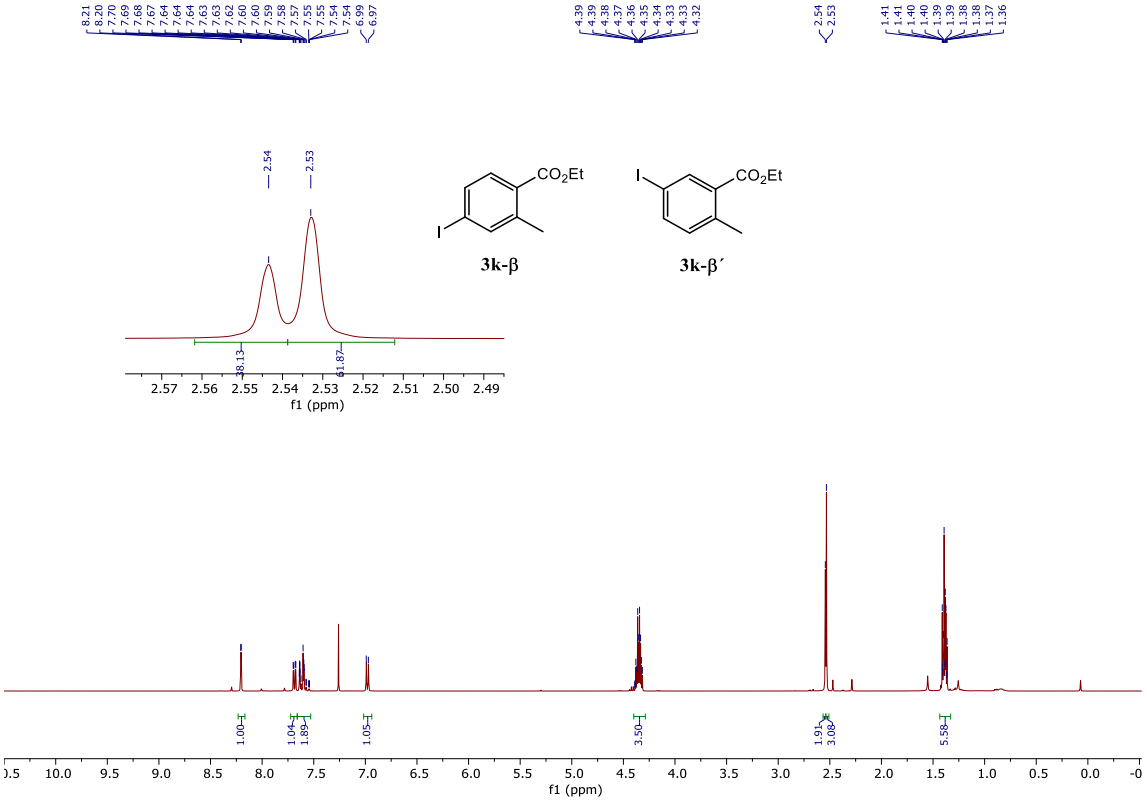
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.20 (d, J = 2.0 Hz, 1H$^{\beta´}$), 7.69 (dd, J = 8.1, 2.0 Hz, 1H$^{\beta´}$), 7.66-7.52 (m, 3H$^{\beta}$), 6.98 (d, J = 8.1 Hz, 1H$^{\beta´}$), 4.41-4.29 (m, 2H$^{\beta}$+2H$^{\beta´}$), 2.54 (s, 3H$^{\beta}$), 2.53 (s, 3H$^{\beta´}$), 1.42-1.36 (m, 3H$^{\beta}$+3H$^{\beta´}$) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.3, 166.3, 144.1, 142.2, 140.7(0), 140.6(5), 139.8, 139.2, 135.1, 133.6, 132.0, 129.6, 99.4, 90.0, 61.2, 61.1, 21.5, 21.4, 14.5, 14.4 ppm.

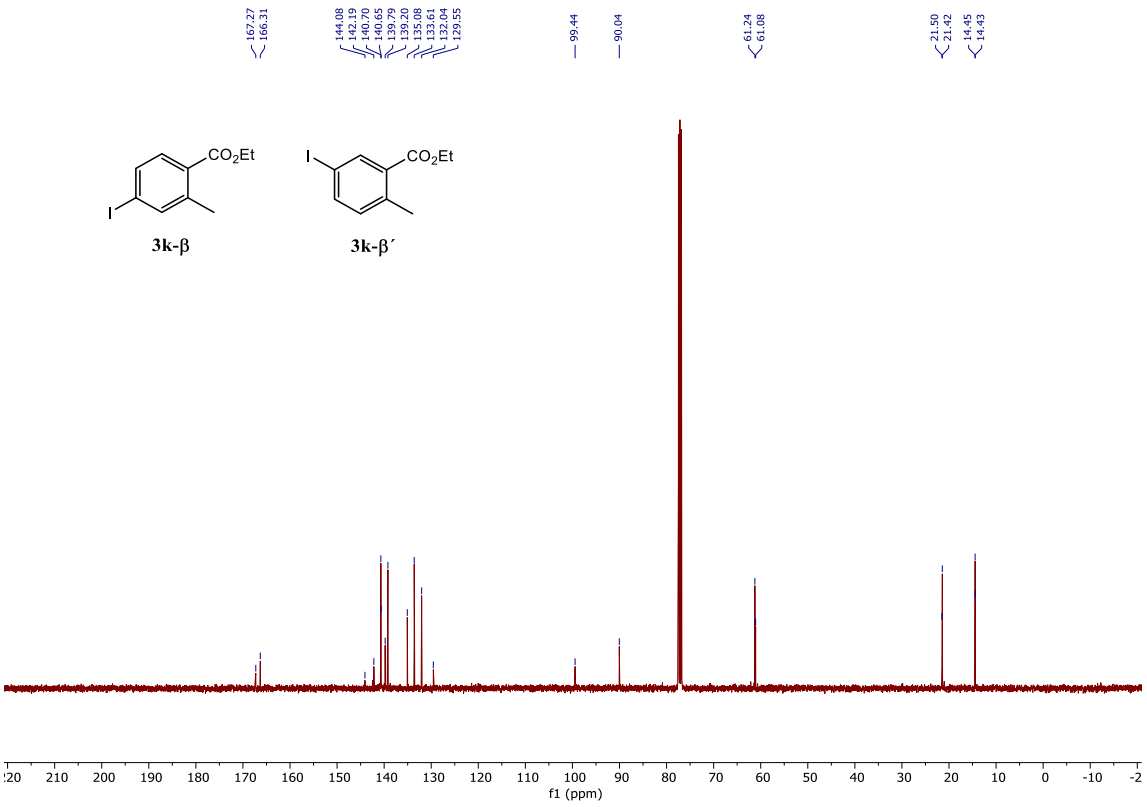
HRMS (ESI pos) m/z: Calcd for $C_{10}H_{11}O_2INa^+$ 312.9696, Found 312.9697.

[a] Reaction was performed at 100 °C and with 30 mol% $AgNO_3$ instead of 15 mol% Ag_2O.

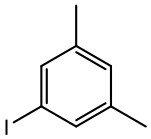
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



1-iodo-3,5-dimethylbenzene (3l)

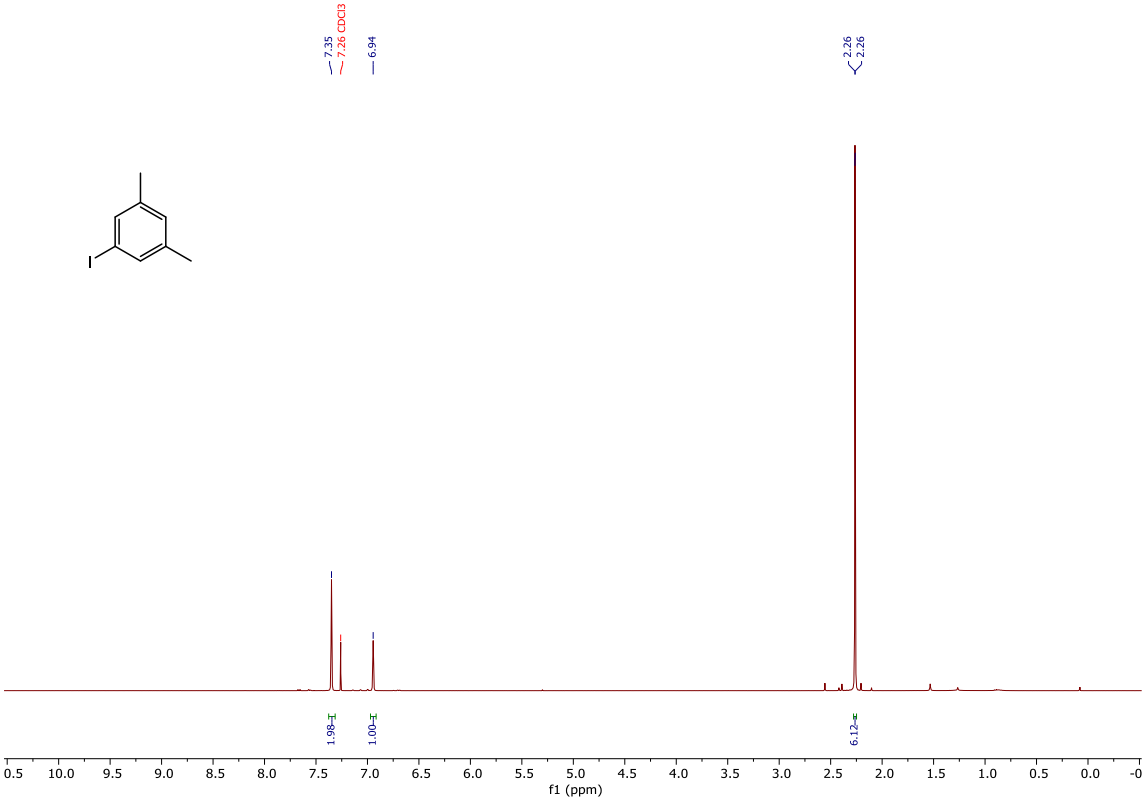


Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), *meta*-xylene (**1l**) (21.2 mg, 0.200 mmol), and purification via silica column chromatography using pentane as the eluent, the target compound **3l** was obtained as a colorless liquid (27.6 mg, 60%). The assignment of the compound was achieved by comparison with the literature.[3]

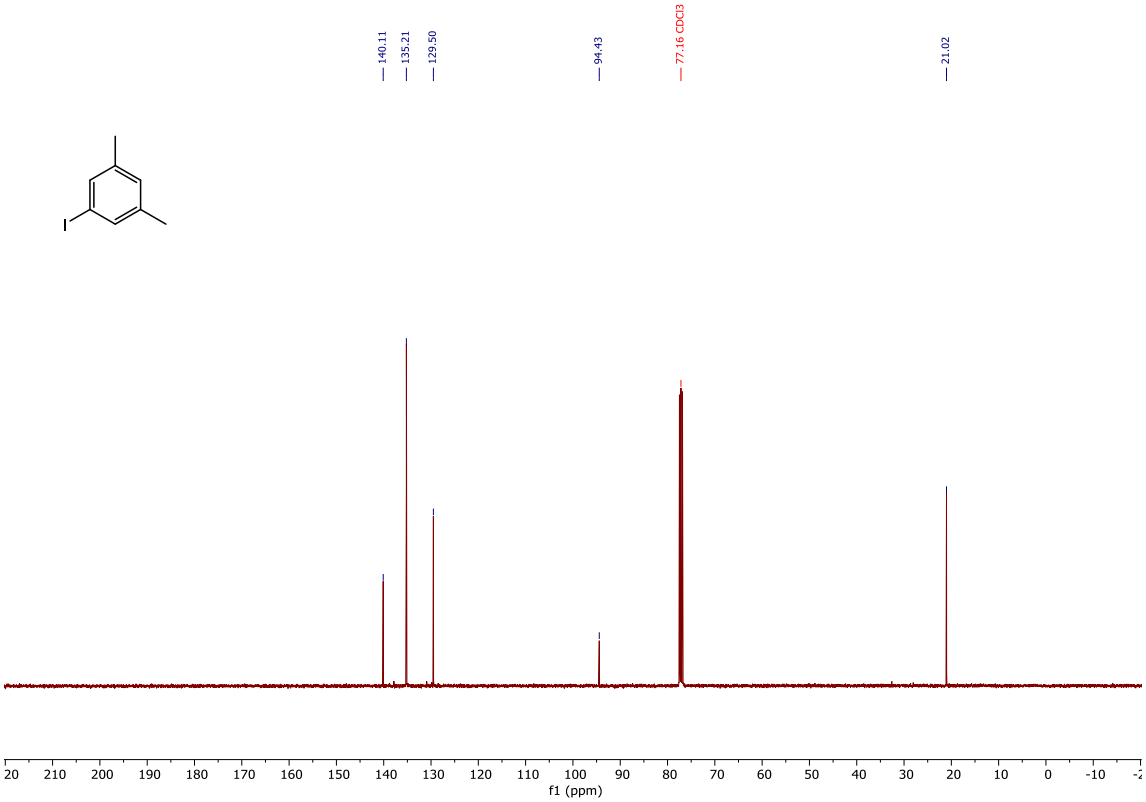
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.35 (s, 2H), 6.94 (s, 1H), 2.26 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 140.1, 135.2, 129.5, 94.4, 21.0 ppm.

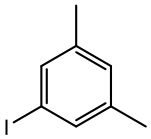
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



1-iodo-3,5-dimethylbenzene (3l´)

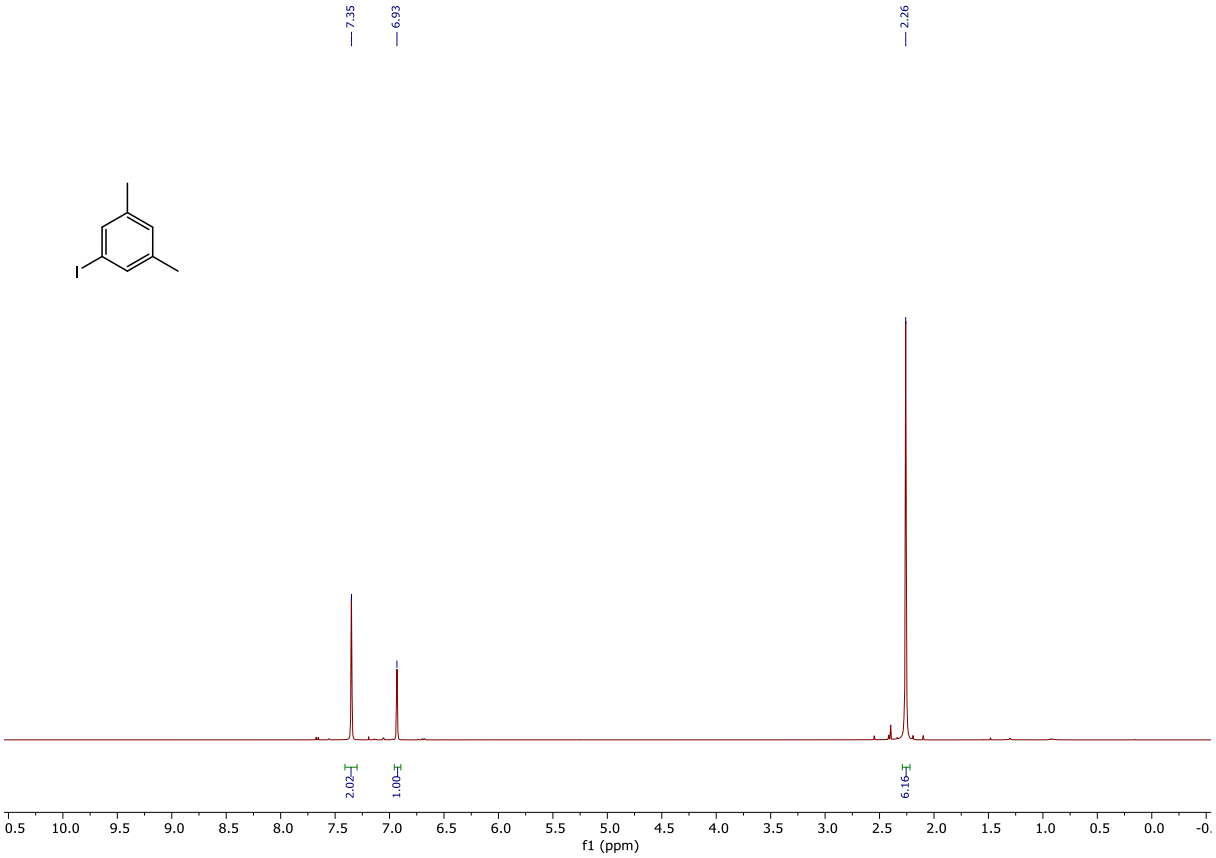


Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (2.250 g, 9.000 mmol, 3.0 equiv.), *meta*-xylene (**1l**) (318.6 mg, 3.000 mmol), and purification via silica column chromatography using pentane as the eluent, the target compound **3l´** was obtained as a colorless liquid (480 mg, 69%). The assignment of the compound was achieved by comparison with the literature.[3]

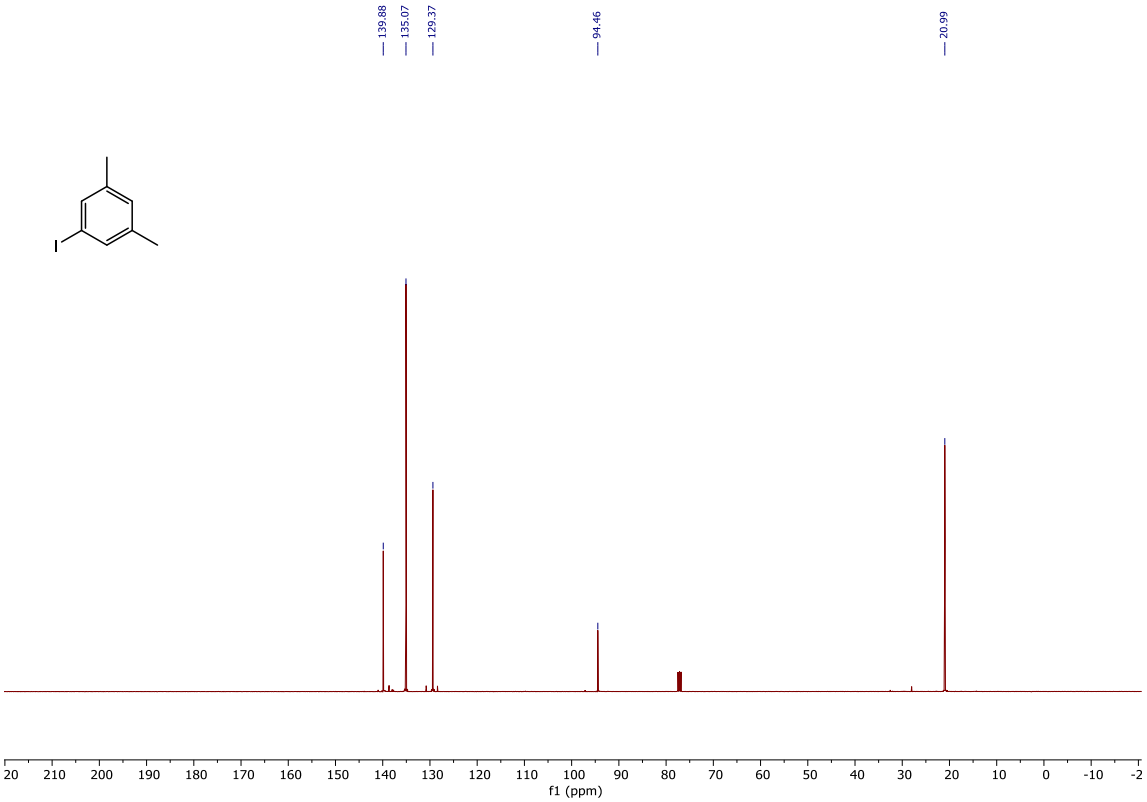
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.35 (s, 2H), 6.93 (s, 1H), 2.26 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 139.9, 135.1, 129.4, 94.5, 21.0 ppm.

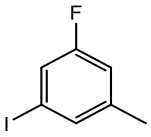
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



1-fluoro-3-iodo-5-methylbenzene (3m)



Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), 1-fluoro-3-methylbenzene (**1m**) (22.0 mg, 0.200 mmol), and purification via silica column chromatography using pentane as the eluent, the target compound **3m** was obtained as a colorless liquid (23.3 mg, 49%).

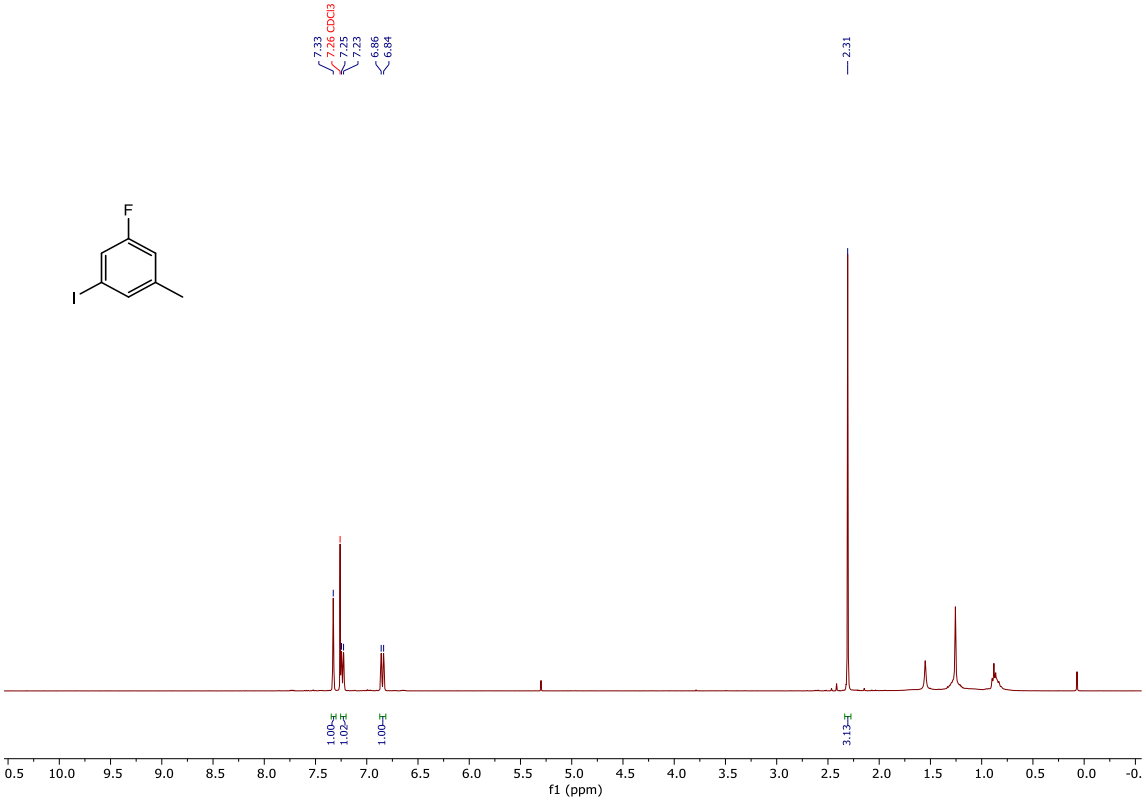
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33 (s, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 6.85 (d, *J* = 9.6 Hz, 1H), 2.31 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.4 (d, *J* = 250.8 Hz), 142.2 (d, *J* = 7.8 Hz), 134.2 (d, *J* = 2.9 Hz), 122.0 (d, *J* = 23.7 Hz), 115.9 (d, *J* = 20.8 Hz), 93.4 (d, *J* = 8.7 Hz), 21.0 (d, *J* = 1.8 Hz) ppm.

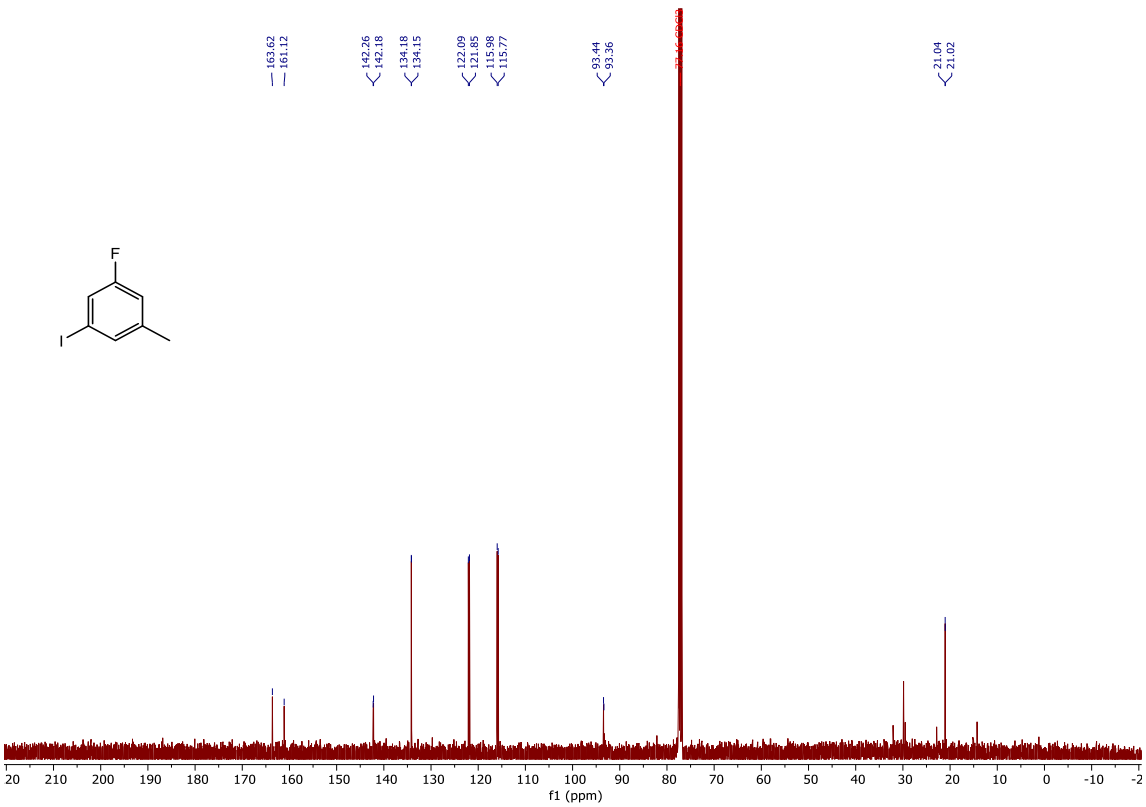
^{19}F NMR ($CDCl_3$, 375 MHz): δ = –112.0 ppm.

HRMS (EI pos) m/z: Calcd for $C_7H_6FI^+$ 235,9498, Found 235,9495.

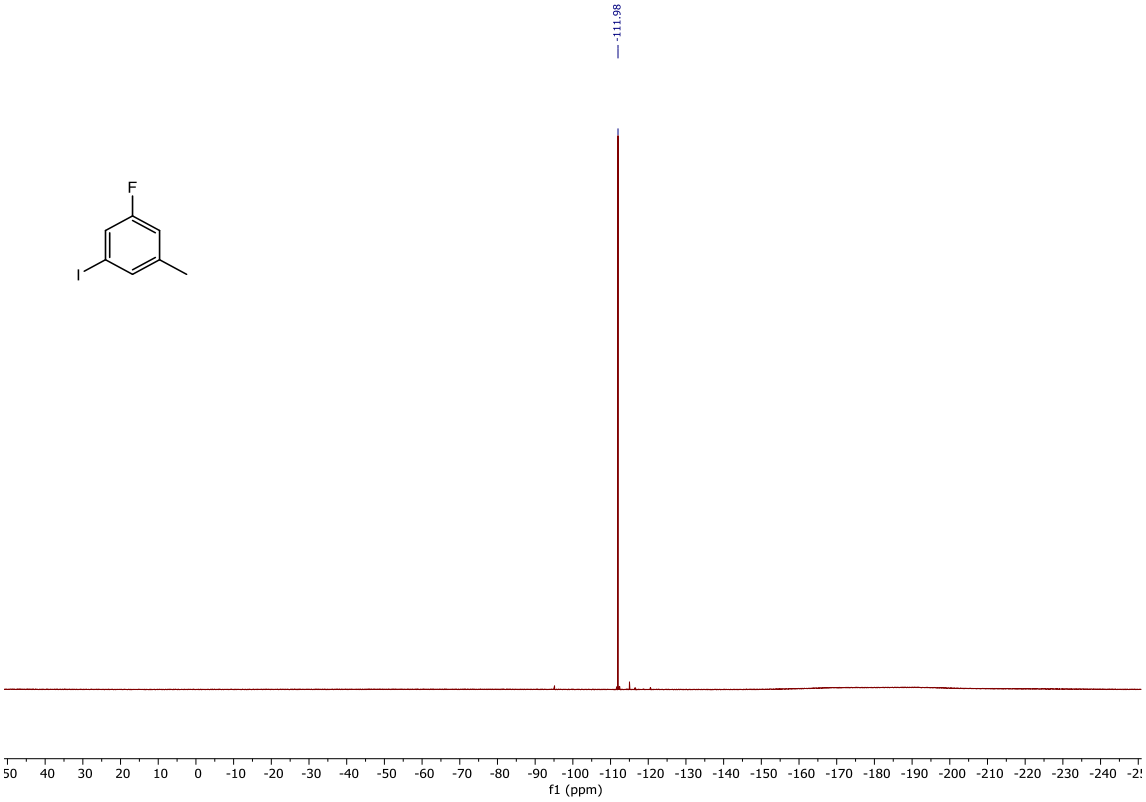
^{1}H NMR spectrum in $CDCl_3$:



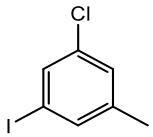
^{13}C NMR spectrum in $CDCl_3$:



^{19}F NMR spectrum in $CDCl_3$:



1-chloro-3-iodo-5-methylbenzene (3n)

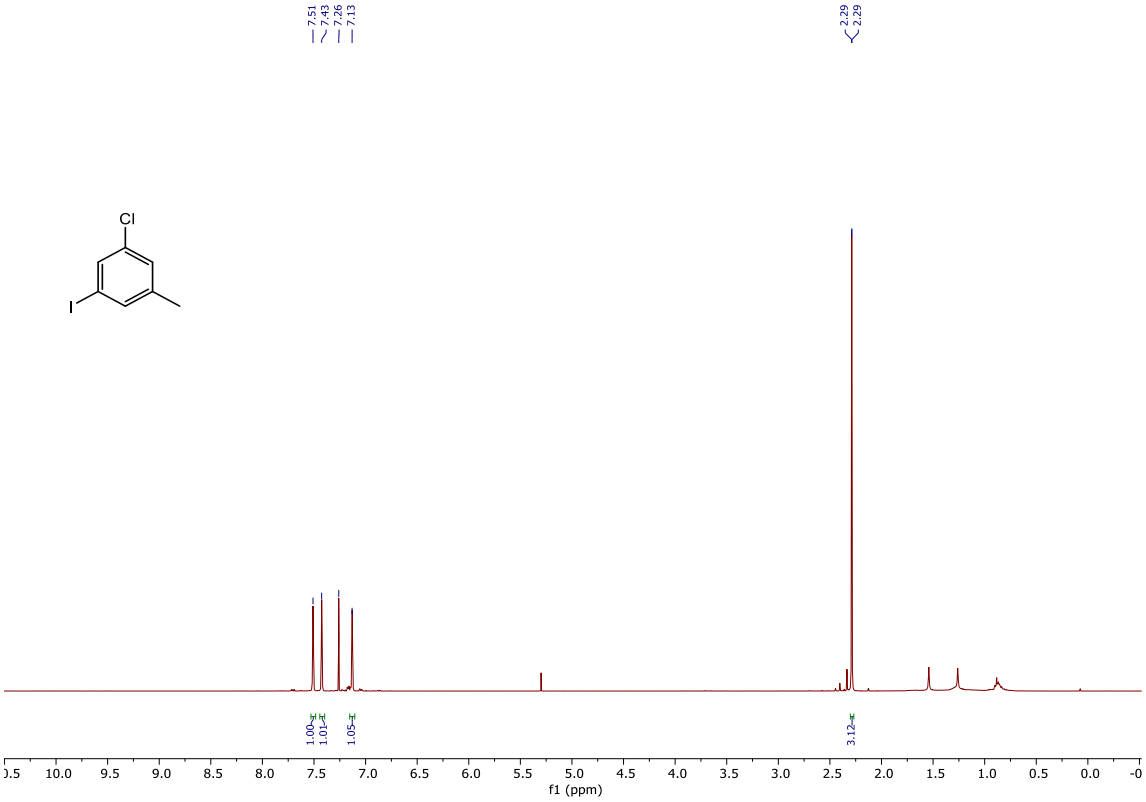


Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), 1-chloro-3-methylbenzene (**1n**) (25.3 mg, 0.200 mmol), and purification via silica column chromatography using pentane as the eluent, the target compound **3n** was obtained as a colorless liquid (27.8 mg, 55%). The assignment of the compound was achieved by comparison with the literature.[10]

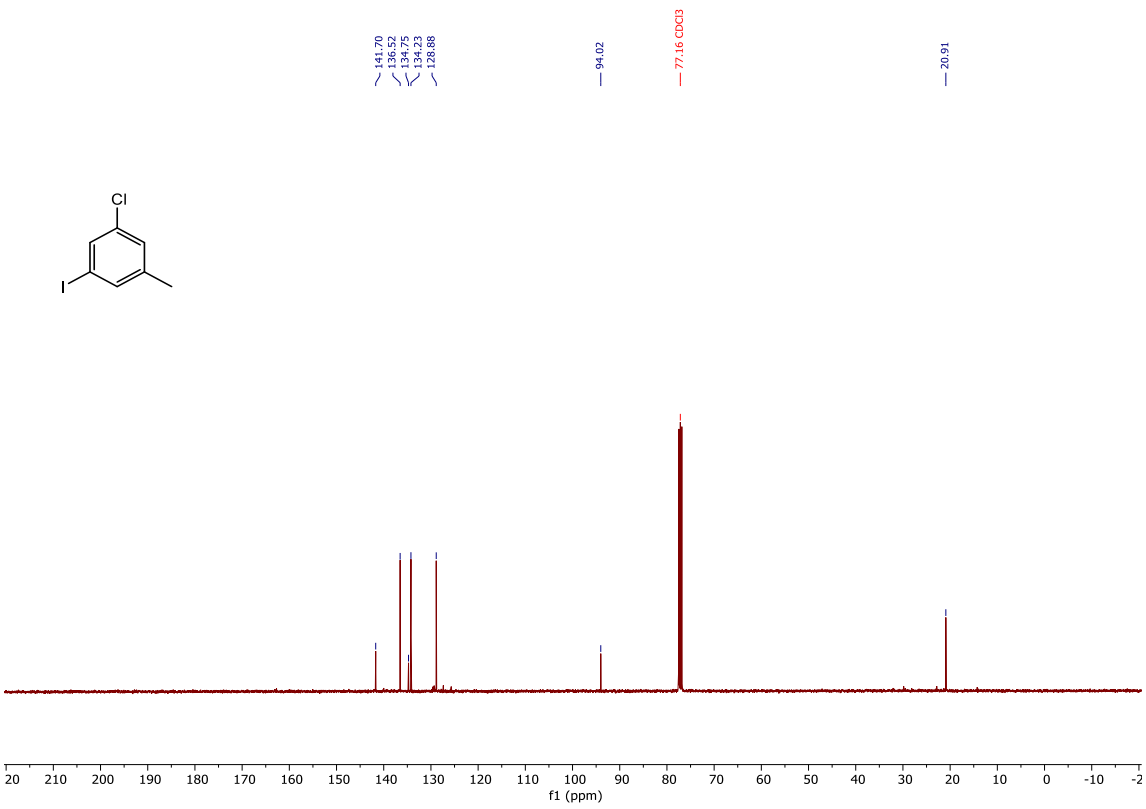
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.51 (s, 1H), 7.43 (s, 1H), 7.13 (s, 1H), 2.29 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 141.7, 136.5, 134.8, 134.2, 128.9, 94.0, 20.9 ppm.

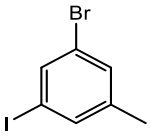
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



1-bromo-3-iodo-5-methylbenzene (3o)



Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), 1-bromo-3-methylbenzene (**1o**) (34.2 mg, 0.200 mmol), and purification via silica column chromatography using pentane as the eluent, the target compound **3o** was obtained as a colorless liquid (36.8 mg, 62%).

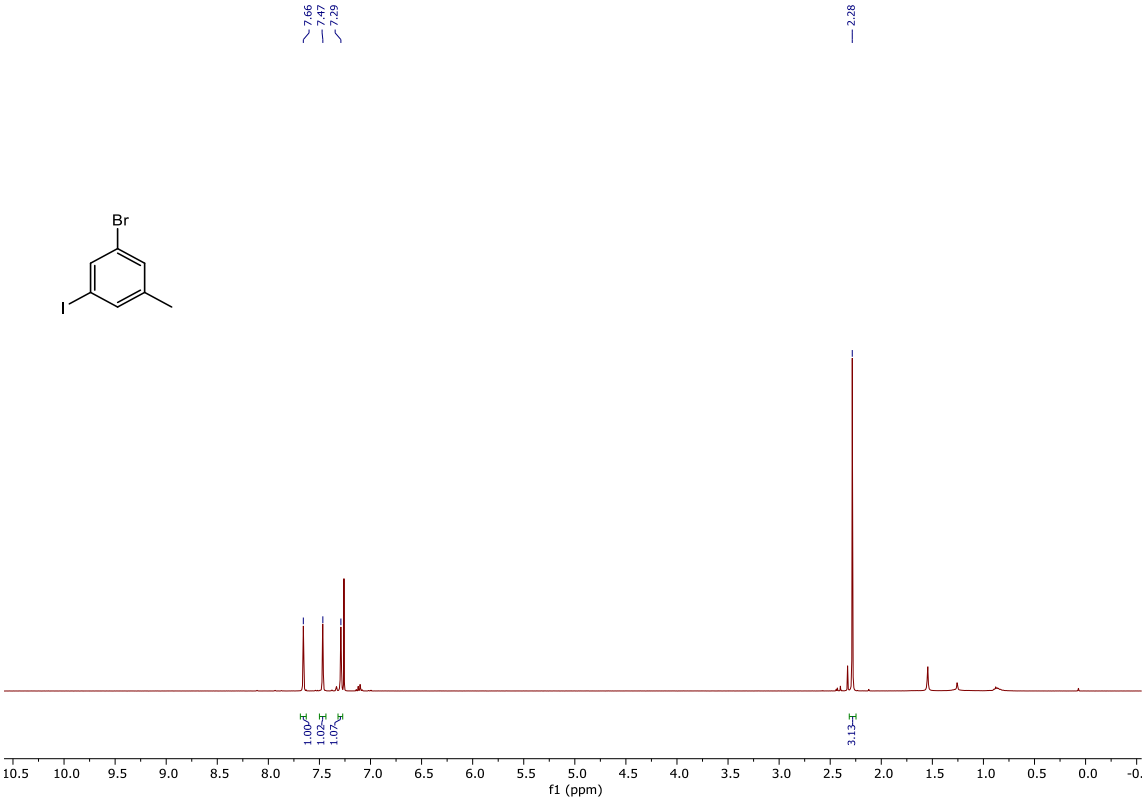
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.66 (s, 1H), 7.47 (s, 1H), 7.29 (s, 1H), 2.28 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 142.1, 137.0, 136.8, 131.7, 122.8, 94.4, 20.9 ppm.

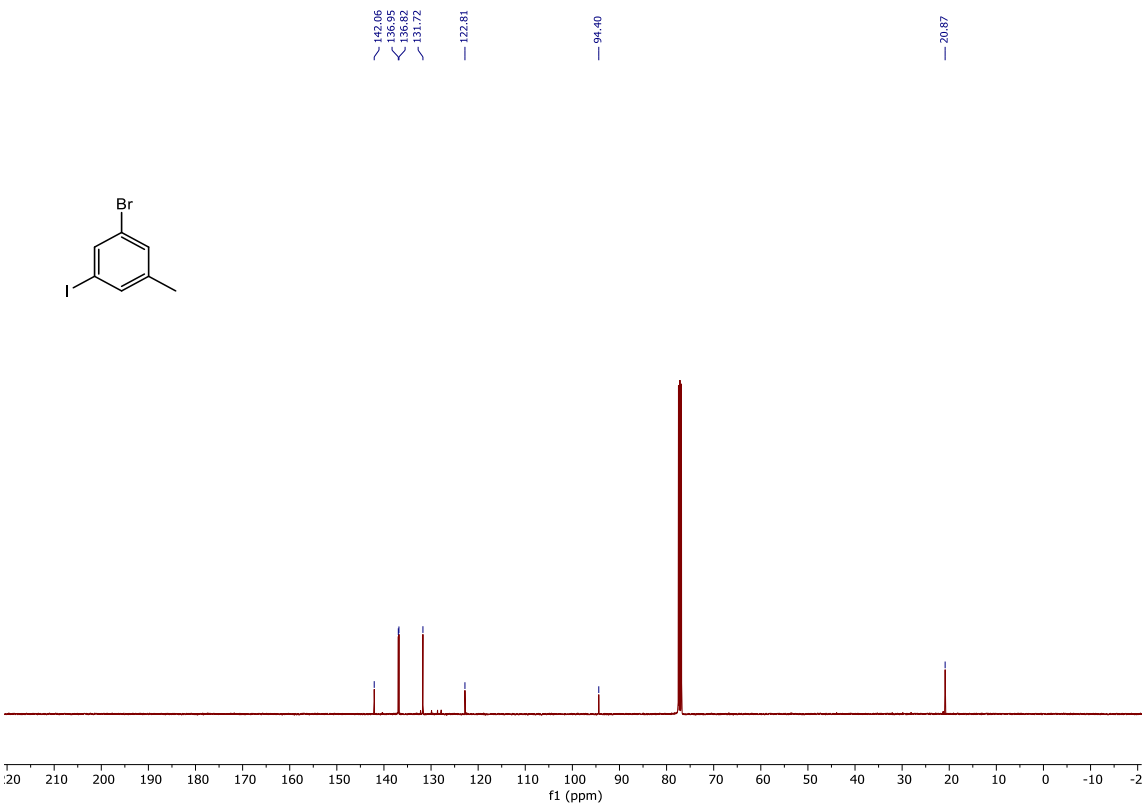
HRMS (EI pos) m/z: Calcd for $C_7H_6BrI^+$ 295.8692, Found 295.8691.

IR (cm^{-1}): 1579, 1546, 1424, 842, 724, 667, 559.

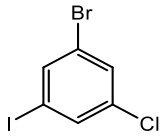
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



1-bromo-3-chloro-5-iodobenzene (3p)

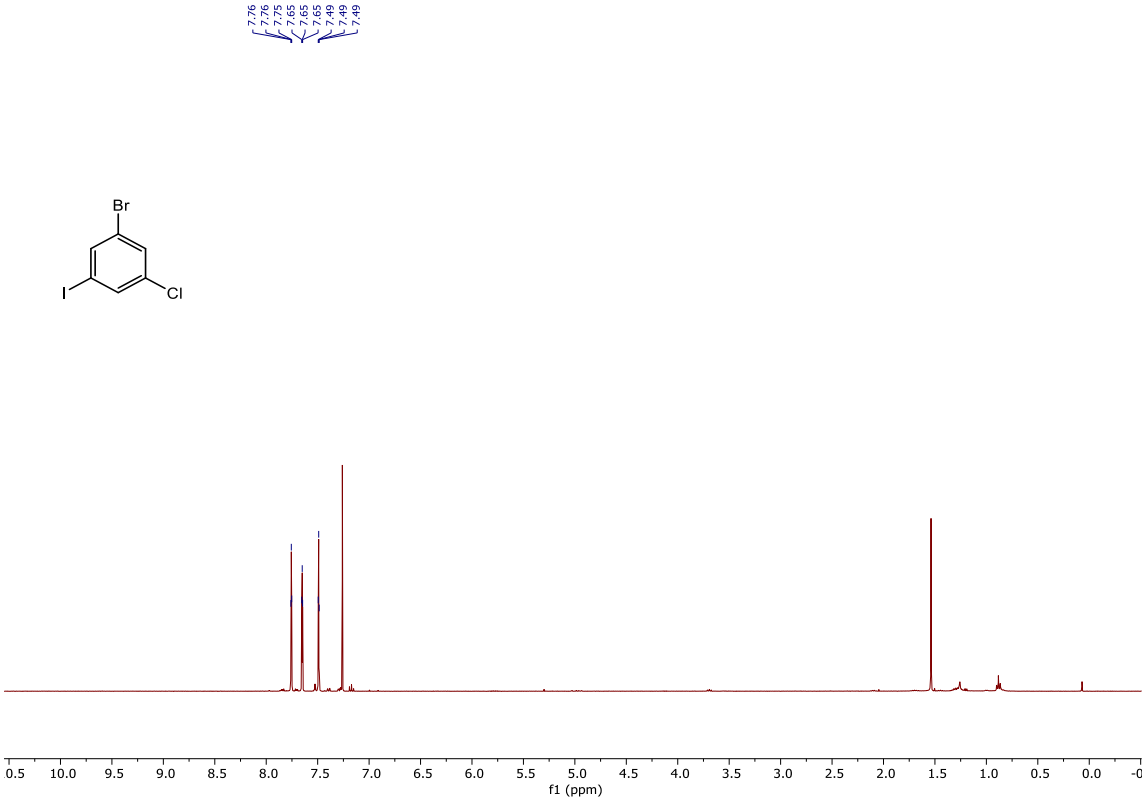


Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), 1-bromo-3-chlorobenzene (**1p**) (38.3 mg, 0.200 mmol), and purification via silica column chromatography using pentane as the eluent, the target compound **3p** was obtained as a colorless liquid (13.3 mg, 21%). The assignment of the compound was achieved by comparison with the literature.[3]

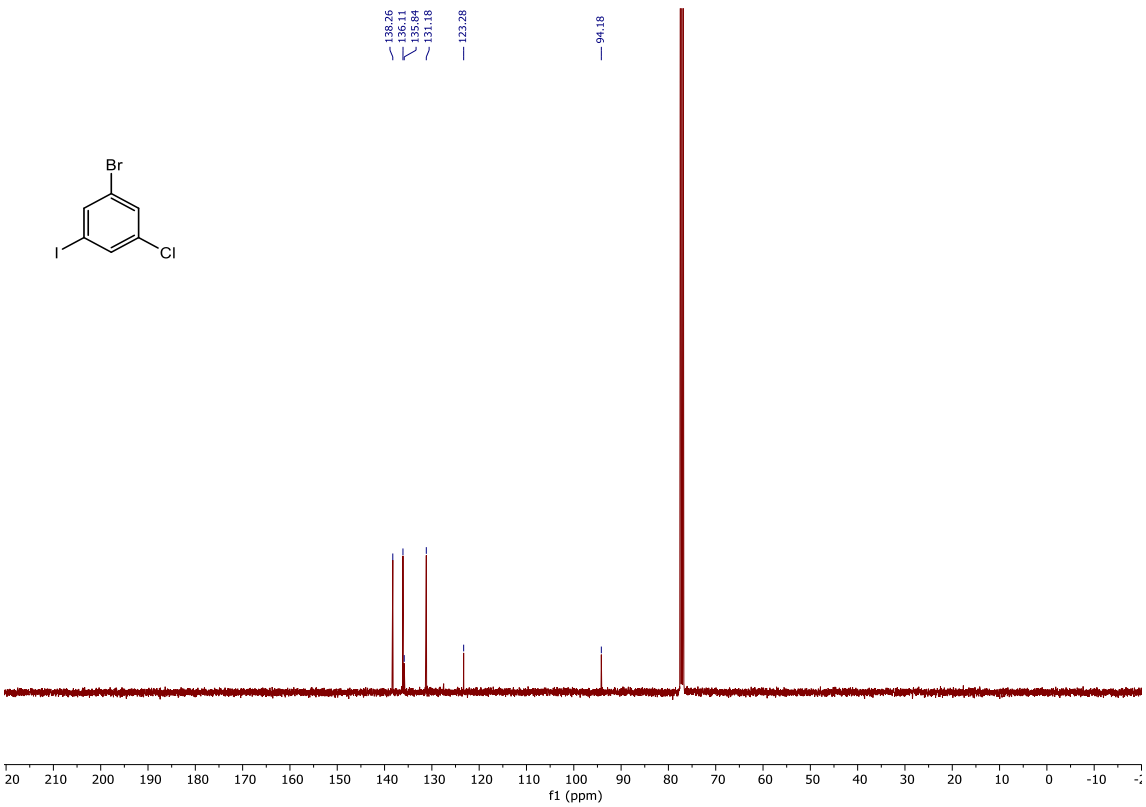
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.76 (t, *J* = 1.6 Hz, 1H), 7.66-7.64 (m, 1H), 7.49 (t, *J* = 1.8 Hz, 1H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 138.3, 136.1, 135.8, 131.2, 123.3, 94.2 ppm.

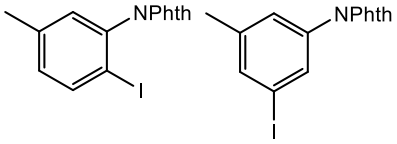
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



2-(2-iodo-5-methylphenyl)isoindoline-1,3-dione (3q-α) and 2-(3-iodo-5-methylphenyl)isoindoline-1,3-dione (3q-β)



3q-α **3q-β**

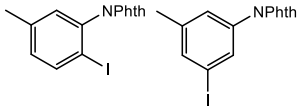
Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), 2-(*m*-tolyl)isoindoline-1,3-dione (**1q**) (47.5 mg, 0.200 mmol), and purification via silica column chromatography using pentane:CH_2Cl_2 = 1:1 as the eluent, the target compound **3q** was obtained as a colorless solid (26.1 mg, 36%, α:β = 22:78).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.00-7.92 (m, $2H^{\alpha}$+$2H^{\beta}$), 7.85-7.77 (m, $3H^{\alpha}$+$2H^{\beta}$), 7.61-7.58 (m, $2H^{\beta}$), 7.23 (s, $1H^{\beta}$), 7.13 (d, *J* = 2.1 Hz, $1H^{\alpha}$), 7.02 (dd, *J* = 8.2, 2.1 Hz, $1H^{\alpha}$), 2.38 (s, $3H^{\beta}$), 2.37 (s, $3H^{\alpha}$) ppm.

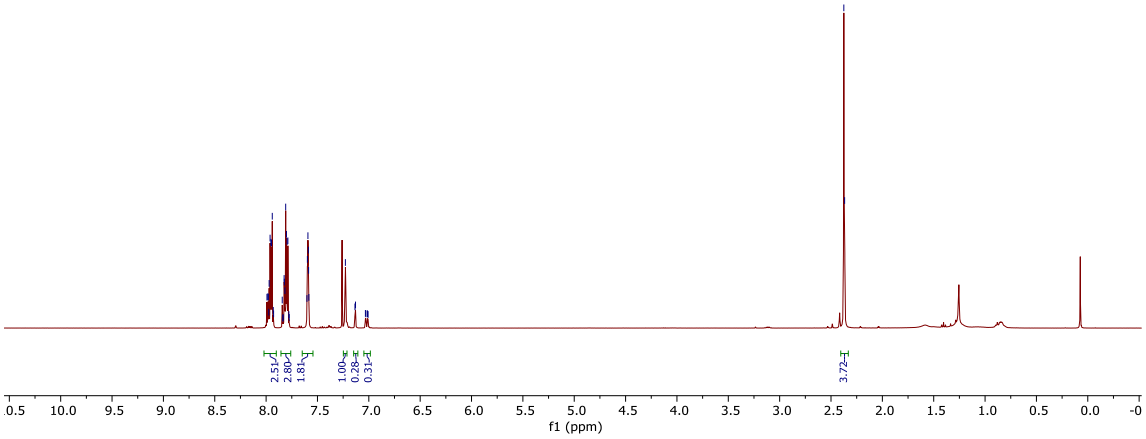
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.1, 166.8, 141.1, 140.0, 139.6, 138.1, 135.0, 134.7, 134.6, 132.6(2), 132.6, 132.2, 132.1, 131.8, 131.1, 126.9, 124.1, 124.0, 94.8, 93.7, 21.1, 21.0 ppm.

HRMS (ESI pos) m/z: Calcd for $C_{15}H_{10}NO_2INa^+$ 385.9648, Found 385.9646.

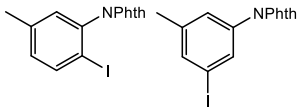
^{1}H NMR spectrum in $CDCl_3$:



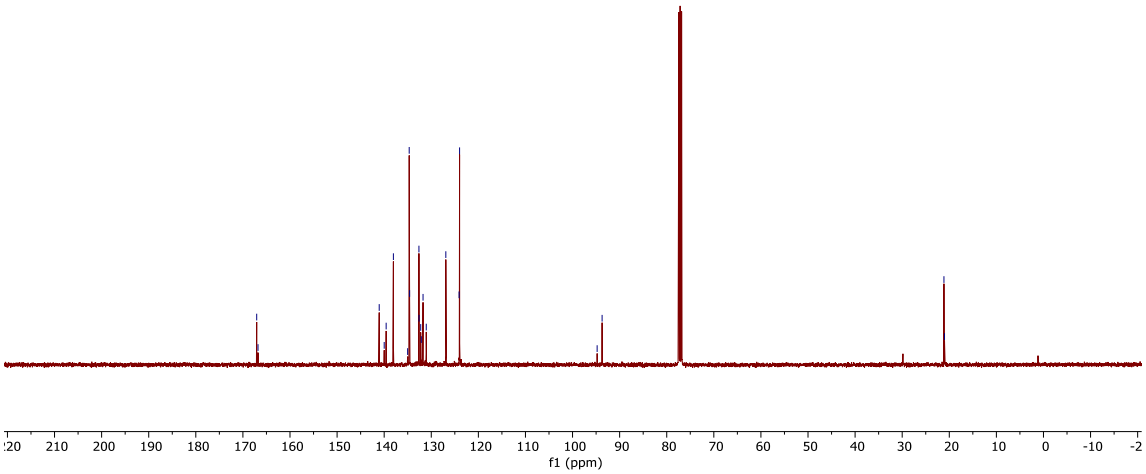
3q-α **3q-β**



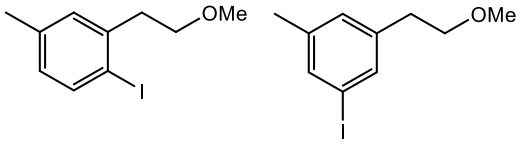
^{13}C NMR spectrum in $CDCl_3$:



3q-α **3q-β**



1-iodo-2-(2-methoxyethyl)-4-methylbenzene (3r-α) and 1-iodo-3-(2-methoxyethyl)-5-methylbenzene (3r-β)



3r-α **3r-β**

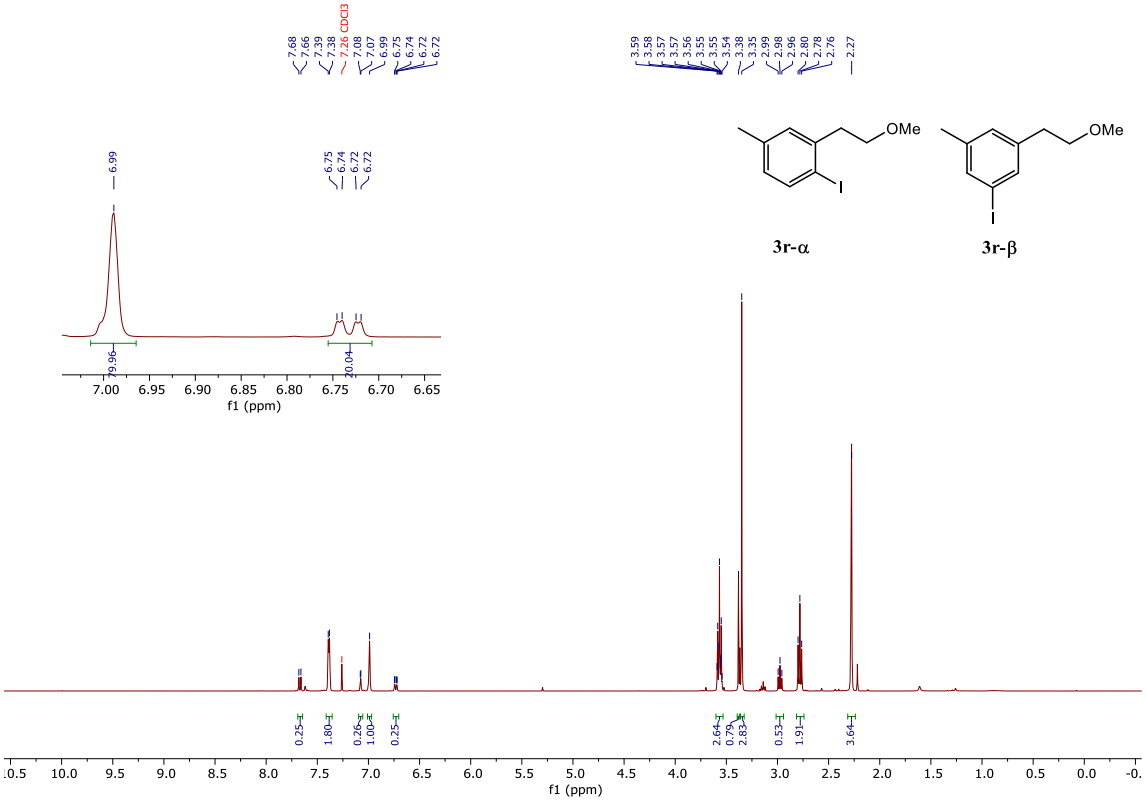
Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), 1-(2-methoxyethyl)-3-methylbenzene (**1r**) (30.0 mg, 0.200 mmol), and purification via silica column chromatography using pentane:CH_2Cl_2 = 1:1 as the eluent, the target compound **3r** was obtained as a colorless liquid (40.0 mg, 73%, α:β = 20:80).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.67 (d, *J* = 8.0 Hz, $1H^{\alpha}$), 7.39 (s, $1H^{\beta}$), 7.38 (s, $1H^{\beta}$), 7.08 (d, *J* = 1.8 Hz, $1H^{\alpha}$), 6.99 (s, $1H^{\beta}$), 6.73 (dd, *J* = 8.0, 1.8 Hz, $1H^{\alpha}$), 3.60-3.54 (m, $2H^{\alpha}$+$2H^{\beta}$), 3.38 (s, $3H^{\alpha}$), 3.35 (s, $3H^{\beta}$), 2.98 (t, *J* = 7.2 Hz, $2H^{\alpha}$), 2.78 (t, *J* = 6.9 Hz, $2H^{\beta}$), 2.28-2.27 (m, $3H^{\alpha}$+$3H^{\beta}$) ppm.

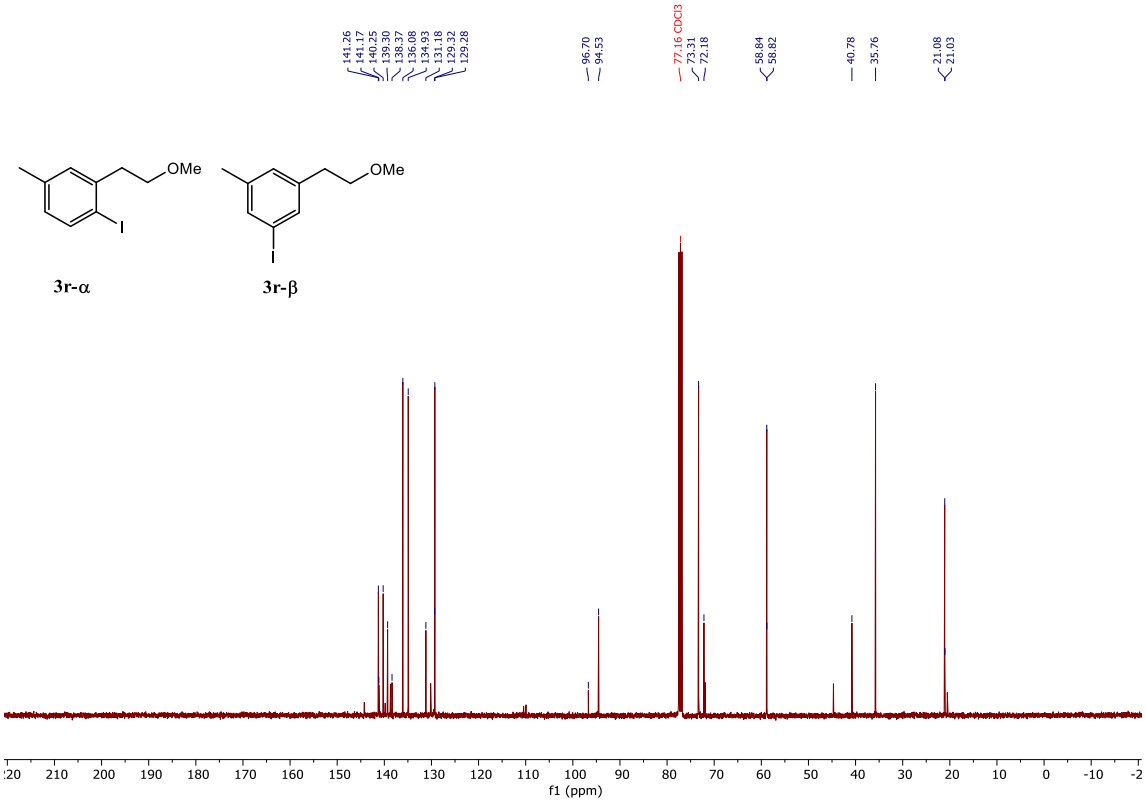
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 141.3, 141.2, 140.3, 139.3, 138.4, 136.1, 134.9, 131.2, 129.3(2), 129.2(8), 96.7, 94.5, 73.3, 72.2, 58.8(4), 58.8(2), 40.8, 35.8, 21.1, 21.0 ppm.

HRMS (ESI pos) m/z: Calcd for $C_{10}H_{13}OINa^+$ 298.9903, Found 298.9905.

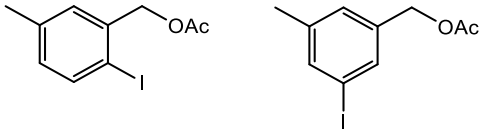
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



2-iodo-5-methylbenzyl acetate (3s-α) and 3-iodo-5-methylbenzyl acetate (3s-β)



3s-α **3s-β**

Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), 3-methylbenzyl acetate (**1s**) (32.8 mg, 0.200 mmol), and purification via silica column chromatography using pentane:CH_2Cl_2 = 1:1 as the eluent, the target compound **3s** was obtained as a colorless liquid (38.9 mg, 67%, α:β = 8:92).

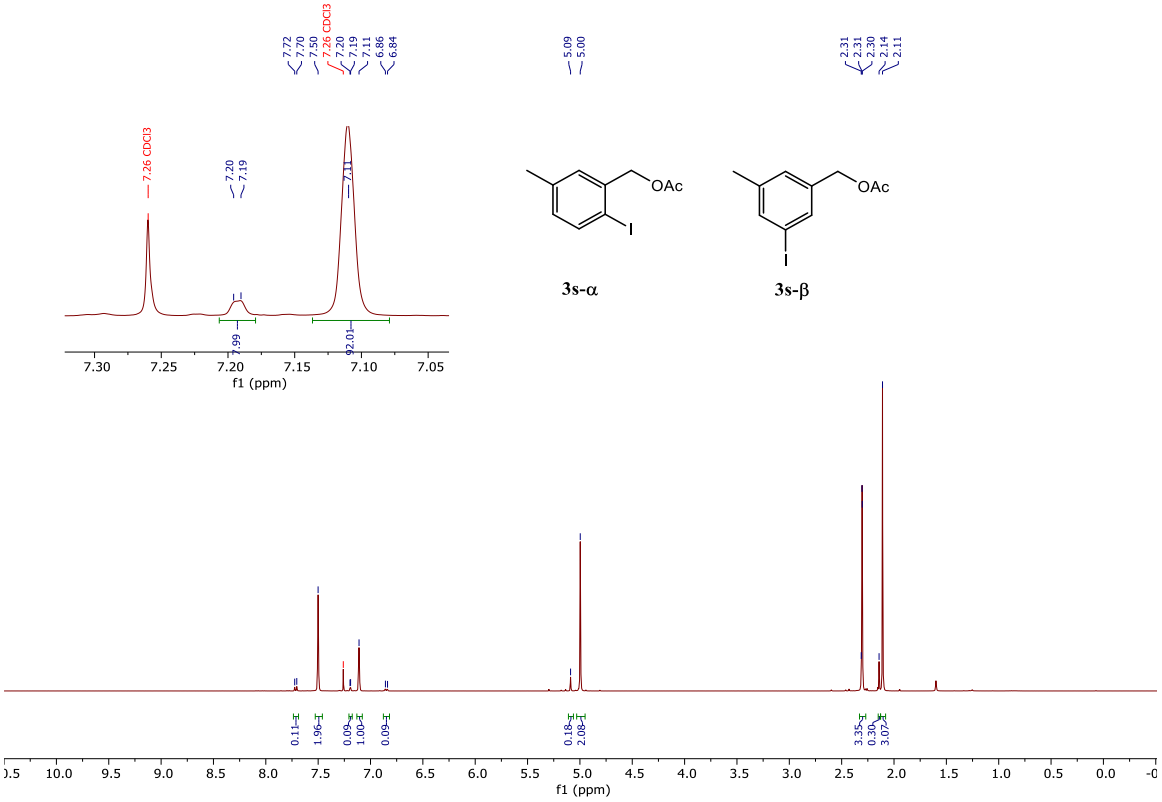
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.71 (d, *J* = 8.0 Hz, 1H$^\alpha$), 7.50 (s, 2H$^\beta$), 7.19 (s, 1H$^\alpha$), 7.11 (s, 1H$^\beta$), 6.85 (d, *J* = 8.0 Hz, 1H$^\alpha$), 5.09 (s, 2H$^\alpha$), 5.00 (s, 2H$^\beta$), 2.33-2.28 (m, 3H$^\alpha$+3H$^\beta$), 2.14 (s, 3H$^\alpha$), 2.11 (s, 3H$^\beta$) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.9, 170.8, 140.6, 139.4, 138.6, 138.0(3), 138.0(1), 134.2, 131.0, 130.7, 128.4, 94.5, 94.4, 70.2, 65.4, 21.1(2), 21.0(8), 21.0(6) ppm.

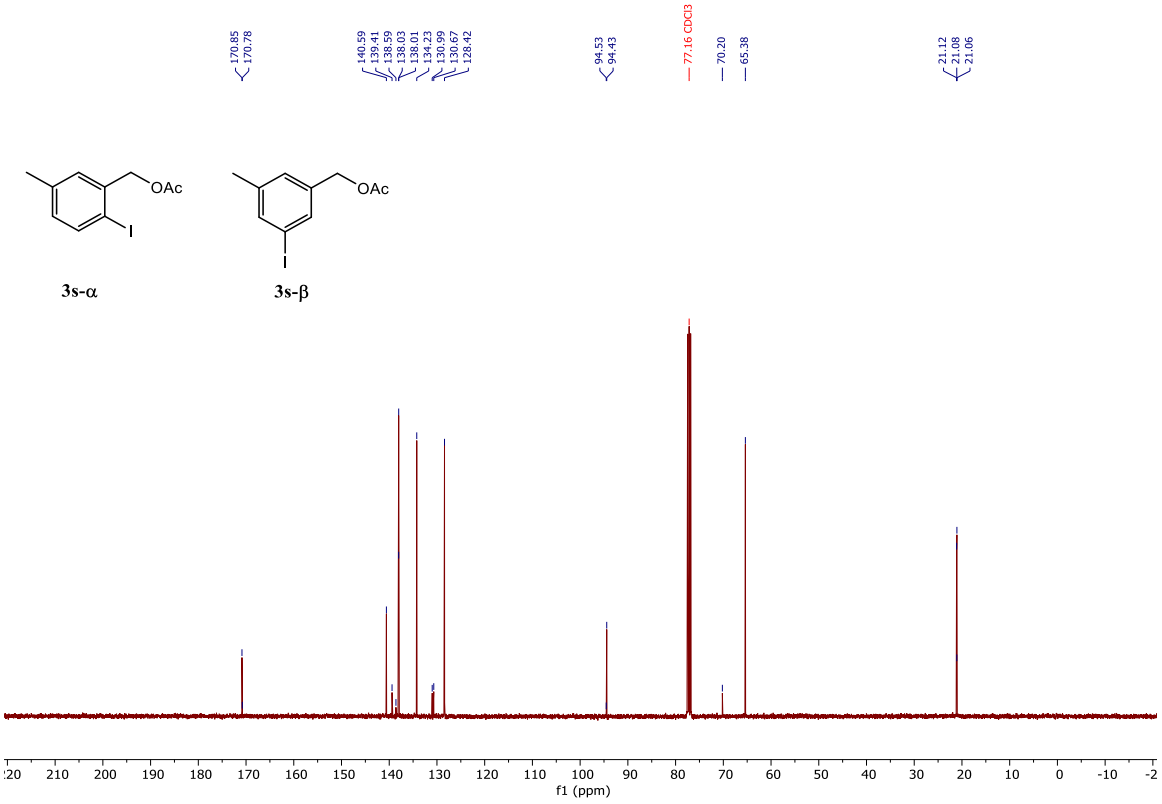
HRMS (ESI pos) m/z: Calcd for $C_{10}H_{11}O_2INa^+$ 312.9696, Found 312.9696.

IR (cm^{-1}): 1734, 1374, 1359, 1220, 1028, 848, 797, 561.

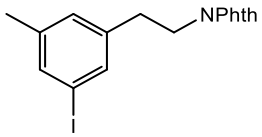
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



2-(3-iodo-5-methylphenethyl)isoindoline-1,3-dione (3t)



Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), 2-(3-methylphenethyl)isoindoline-1,3-dione (**1t**) (53.1 mg, 0.200 mmol), and purification via silica column chromatography using pentane:CH_2Cl_2 = 1:4 as the eluent, the target compound **3t** was obtained as a colorless liquid (54.0 mg, 69%).

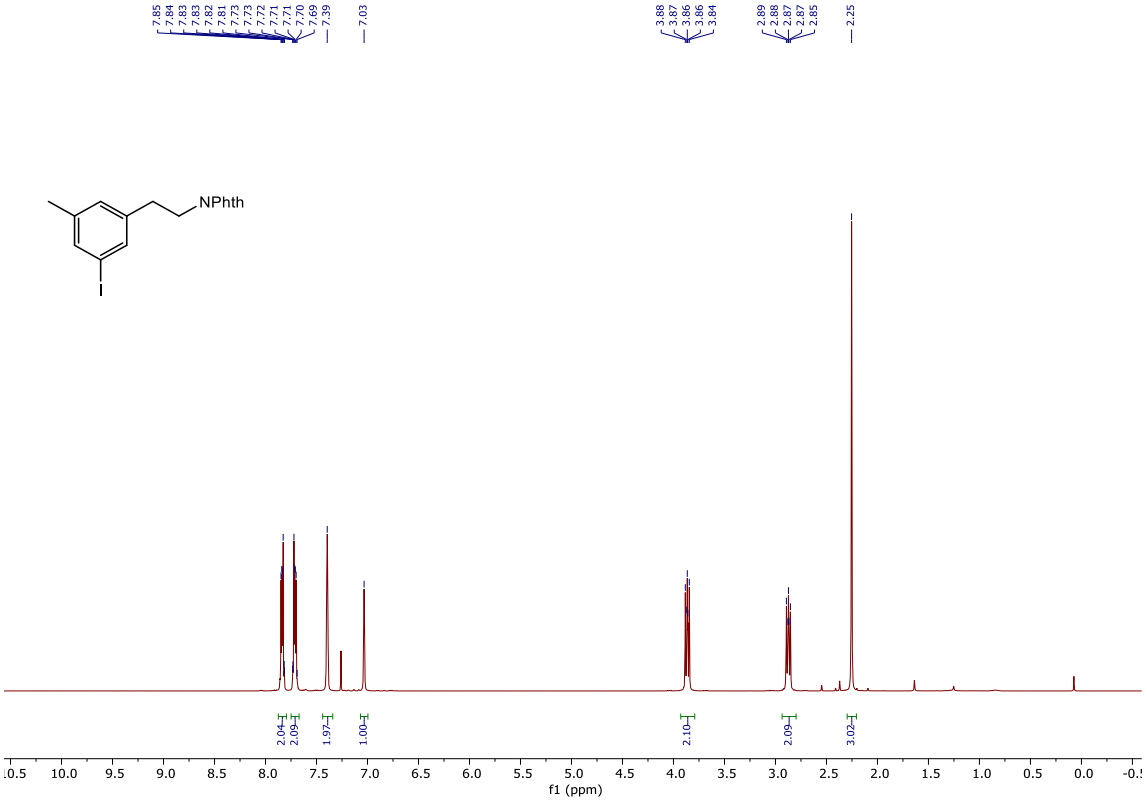
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.86-7.80 (m, 2H), 7.74-7.69 (m, 2H), 7.39 (s, 2H), 7.03 (s, 1H), 3.90-3.82 (m, 2H), 2.91-2.82 (m, 2H), 2.25 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.2, 140.5, 140.2, 136.5, 135.0, 134.1, 132.2, 129.2, 123.4, 94.6, 39.1, 34.2, 21.0 ppm.

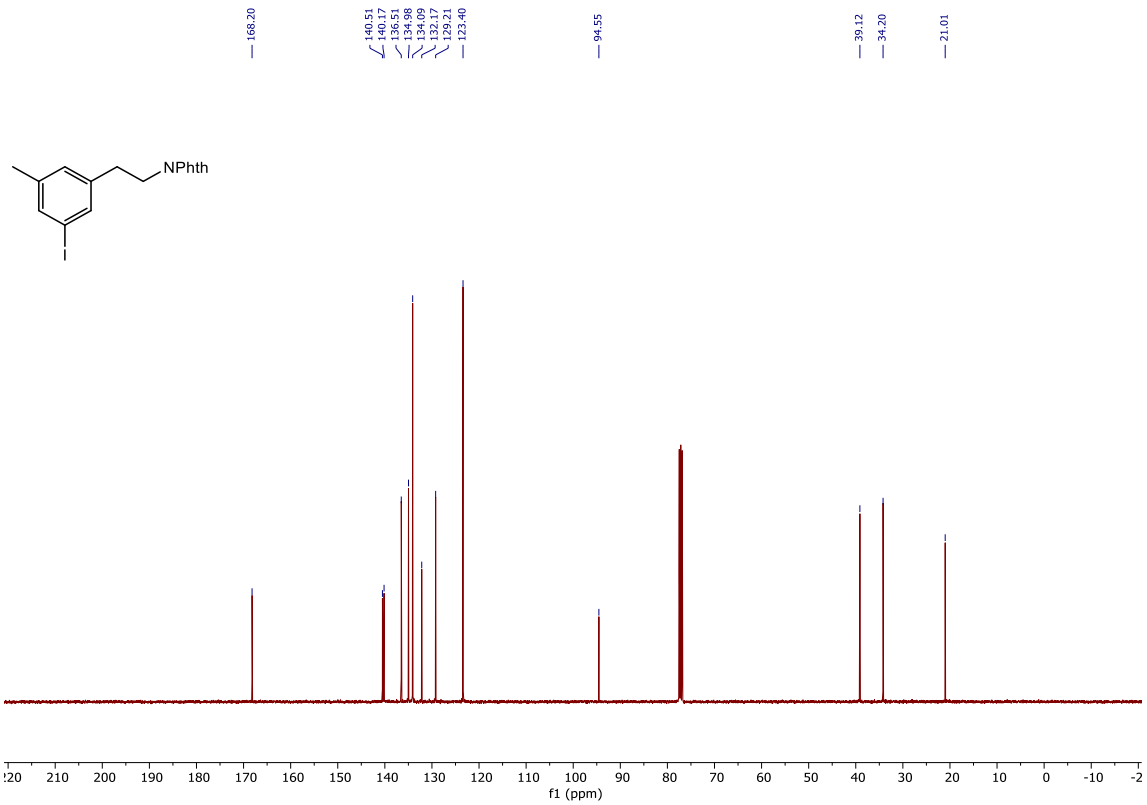
HRMS (ESI pos) m/z: Calcd for $C_{17}H_{14}NO_2INa^+$ 413.9961, Found 413.9956.

IR (cm^{-1}): 1771, 1704, 1433, 1395, 1359, 1087, 1009, 993, 869, 851, 714, 692.

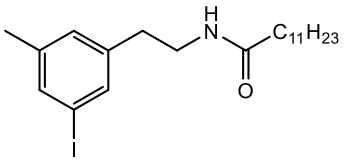
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



_N_-(3-iodo-5-methylphenethyl)dodecanamide (3u)



Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), *N*-(3-methylphenethyl)dodecanamide (**1u**) (63.5 mg, 0.200 mmol), and purification via silica column chromatography using pentane:EtOAc = 3:1 as the eluent, the target compound **3u** was obtained as a colorless solid (50.0 mg, 56%).

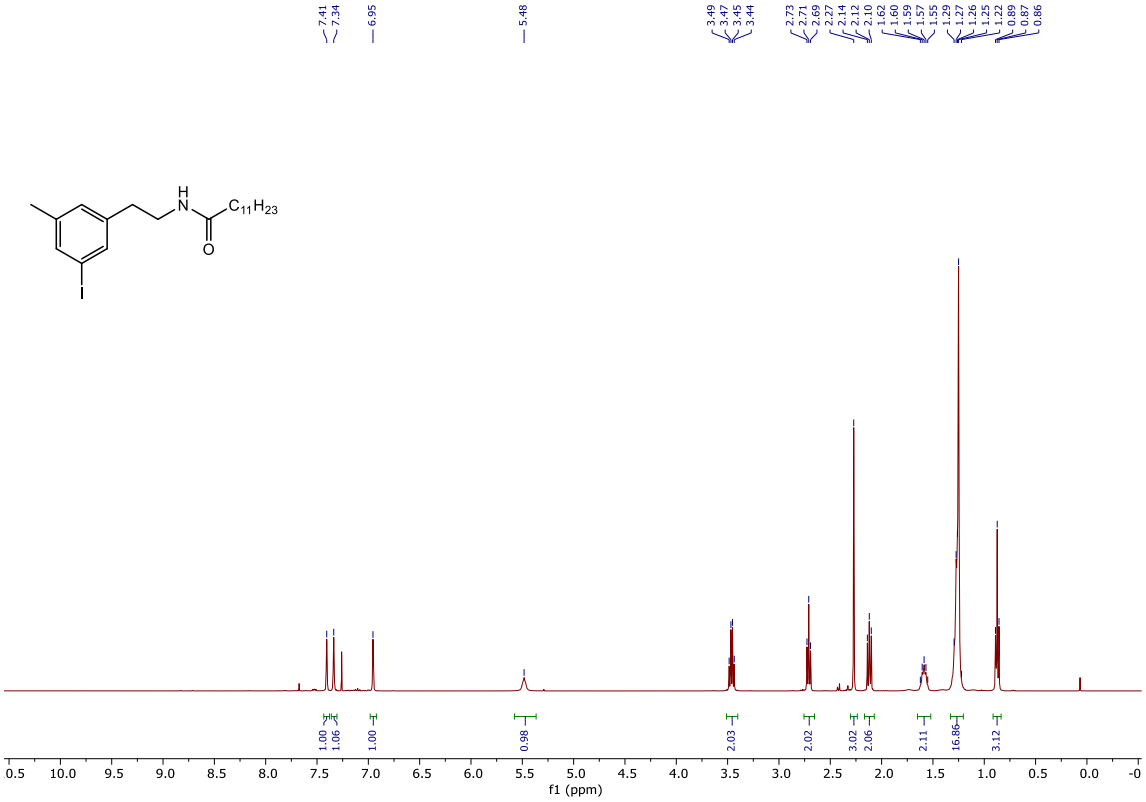
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.41 (s, 1H), 7.34 (s, 1H), 6.95 (s, 1H), 5.48 (s, NH), 3.46 (q, *J* = 6.9 Hz, 2H), 2.71 (t, *J* = 6.9 Hz, 2H), 2.27 (s, 3H), 2.15-2.09 (m, 2H), 1.64-1.52 (m, 2H), 1.31-1.19 (m, 16H), 0.90-0.84 (m, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 173.3, 141.3, 140.6, 136.3, 134.9, 129.2, 94.7, 40.5, 37.0, 35.3, 32.0, 29.8, 29.7, 29.6, 29.5(1), 29.4(6), 29.4, 25.9, 22.8, 21.1, 14.2 ppm.

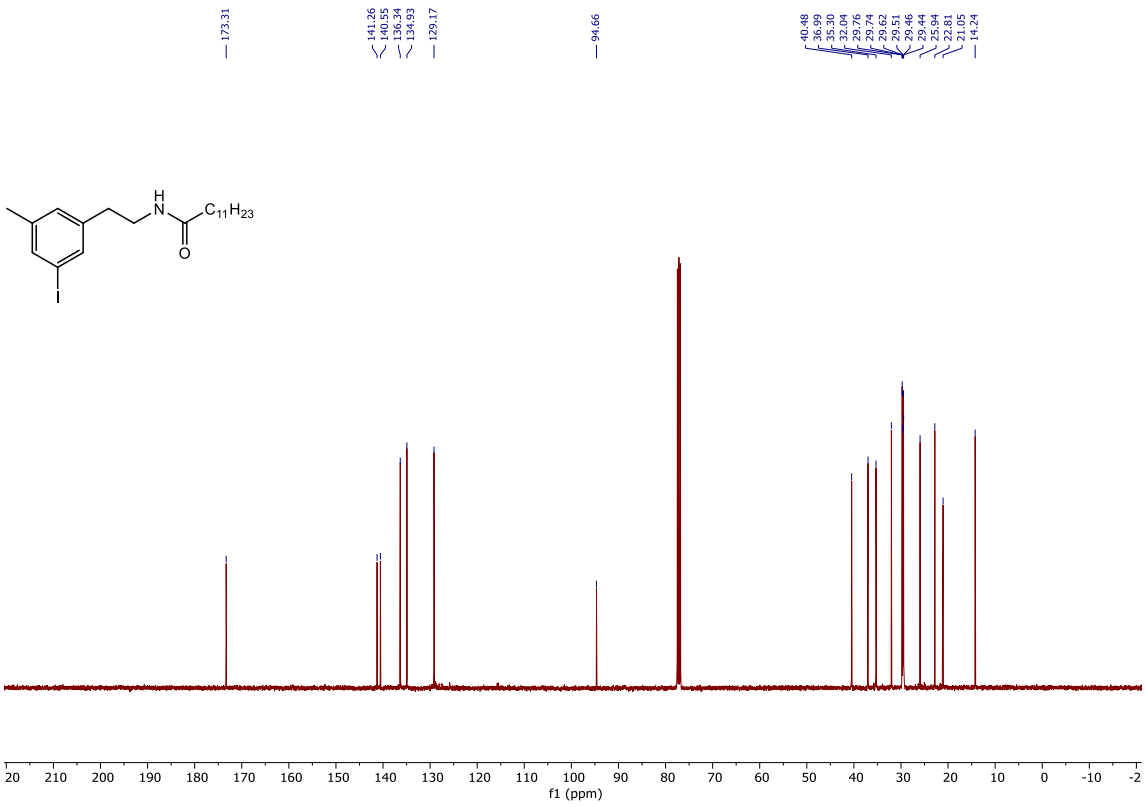
HRMS (ESI pos) m/z: Calcd for $C_{21}H_{34}NOINa^+$ 466.1577, Found 466.1569.

IR (cm^{-1}): 3291, 2917, 2850, 1635, 1559, 847, 799, 691, 566.

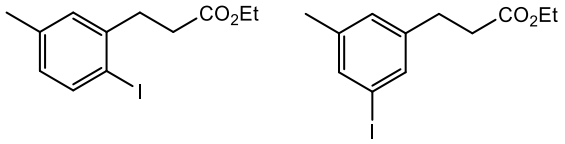
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



ethyl 3-(2-iodo-5-methylphenyl)propanoate (3v-α) and ethyl 3-(3-iodo-5-methylphenyl)propanoate (3v-β)



3v-α **3v-β**

Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), ethyl 3-(*m*-tolyl)propanoate (**1v**) (38.5 mg, 0.200 mmol), and purification via silica column chromatography using pentane:CH_2Cl_2 = 9:1 as the eluent, the target compound **3v** was obtained as a colorless liquid (49.6 mg, 78%, α:β = 6:94).

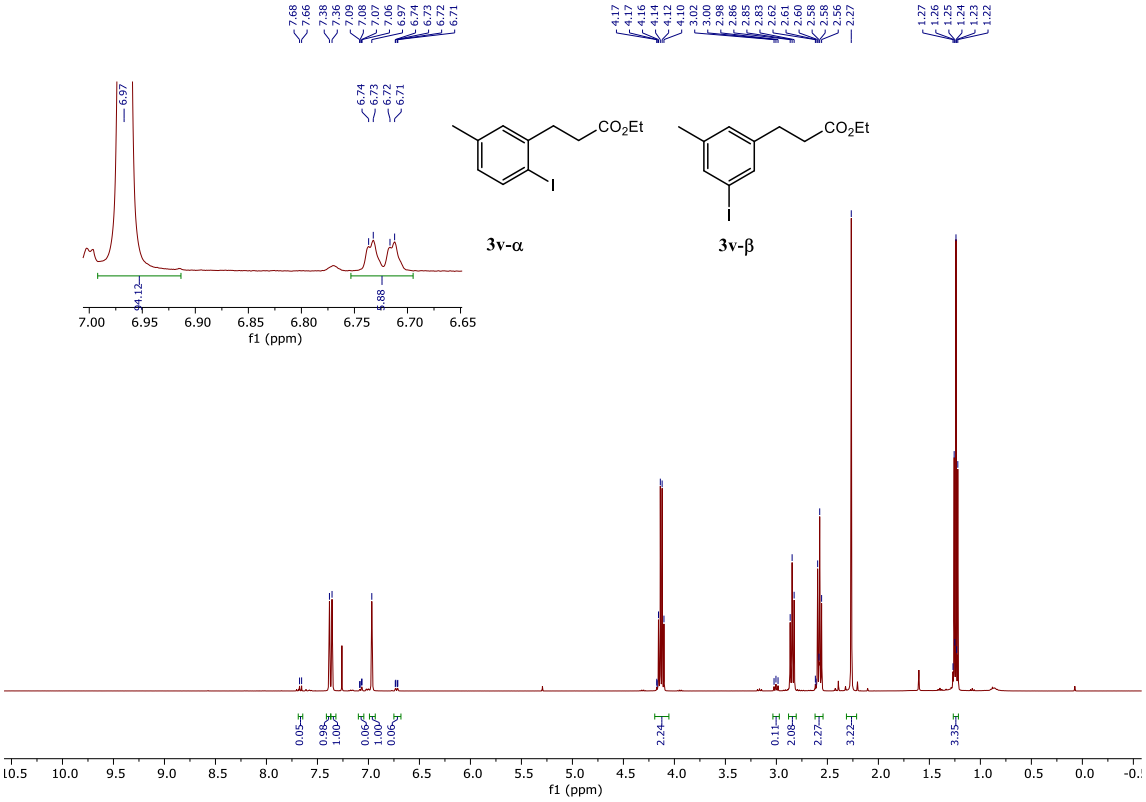
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.67 (d, J = 8.0 Hz, $1H^{\alpha}$), 7.38 (s, $1H^{\beta}$), 7.36 (s, $1H^{\beta}$), 7.07 (dd, J = 7.5, 1.8 Hz, $2H^{\alpha}$), 6.97 (s, $1H^{\beta}$), 6.72 (dd, J = 8.0, 1.8 Hz, $1H^{\alpha}$), 4.20-4.08 (m, $2H^{\alpha}$+$2H^{\beta}$), 3.04-2.97 (m, $2H^{\alpha}$), 2.85 (t, J = 7.7 Hz, $2H^{\beta}$), 2.63-2.54 (m, $2H^{\alpha}$+$2H^{\beta}$), 2.27-2.26 (m, $3H^{\alpha}$+$3H^{\beta}$), 1.27-1.21 (m, $3H^{\alpha}$+$3H^{\beta}$) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 172.7, 142.8, 140.4, 139.4, 136.1,134.5, 130.6, 129.3,128.8, 96.3, 94.5, 60.6, 35.9, 35.8, 34.7, 30.5, 21.1, 14.4 ppm.

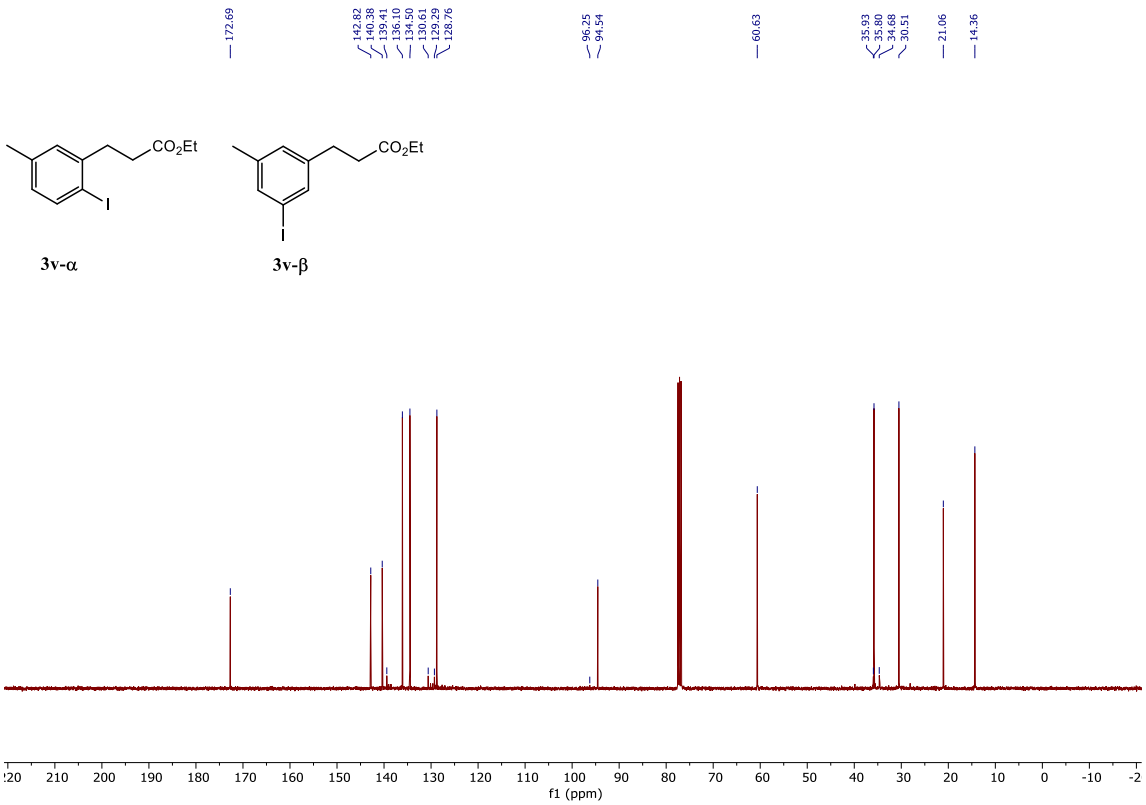
HRMS (ESI pos) m/z: Calcd for $C_{12}H_{15}O_2INa^+$ 341.0009, Found 341.0007.

IR (cm^{-1}): 1730, 1559, 1507, 1457, 1374, 1244, 1180, 1155, 849, 552.

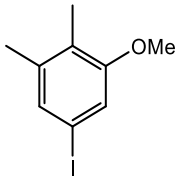
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



5-iodo-1-methoxy-2,3-dimethylbenzene (3w)



Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), 1-methoxy-2,3-dimethylbenzene (**1w**) (27.2 mg, 0.200 mmol), and purification via silica column chromatography using pentane:CH_2Cl_2 = 9:1 as the eluent, the target compound **3w** was obtained as a colorless liquid (32.5 mg, 62%).

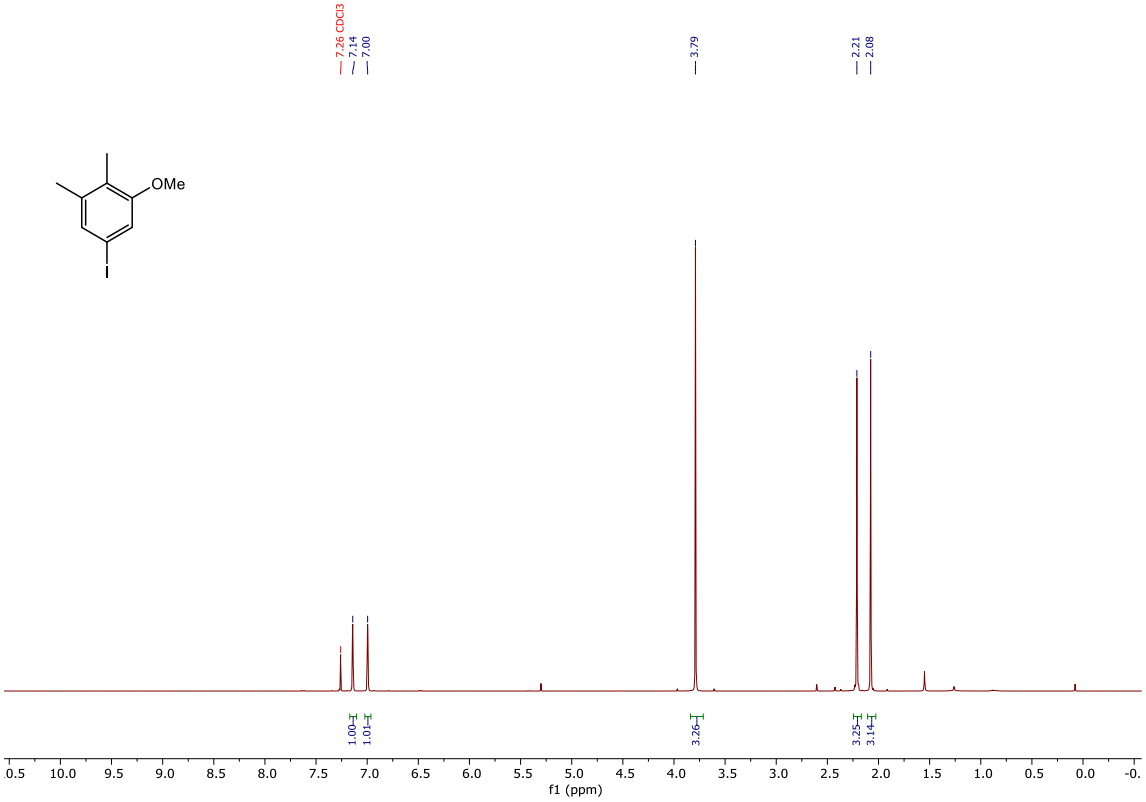
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.14 (s, 1H), 7.00 (s, 1H), 3.79 (s, 3H), 2.21 (s, 3H), 2.08 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 158.2, 139.9, 131.2, 125.1, 117.3, 90.0, 55.9, 19.7, 11.6 ppm.

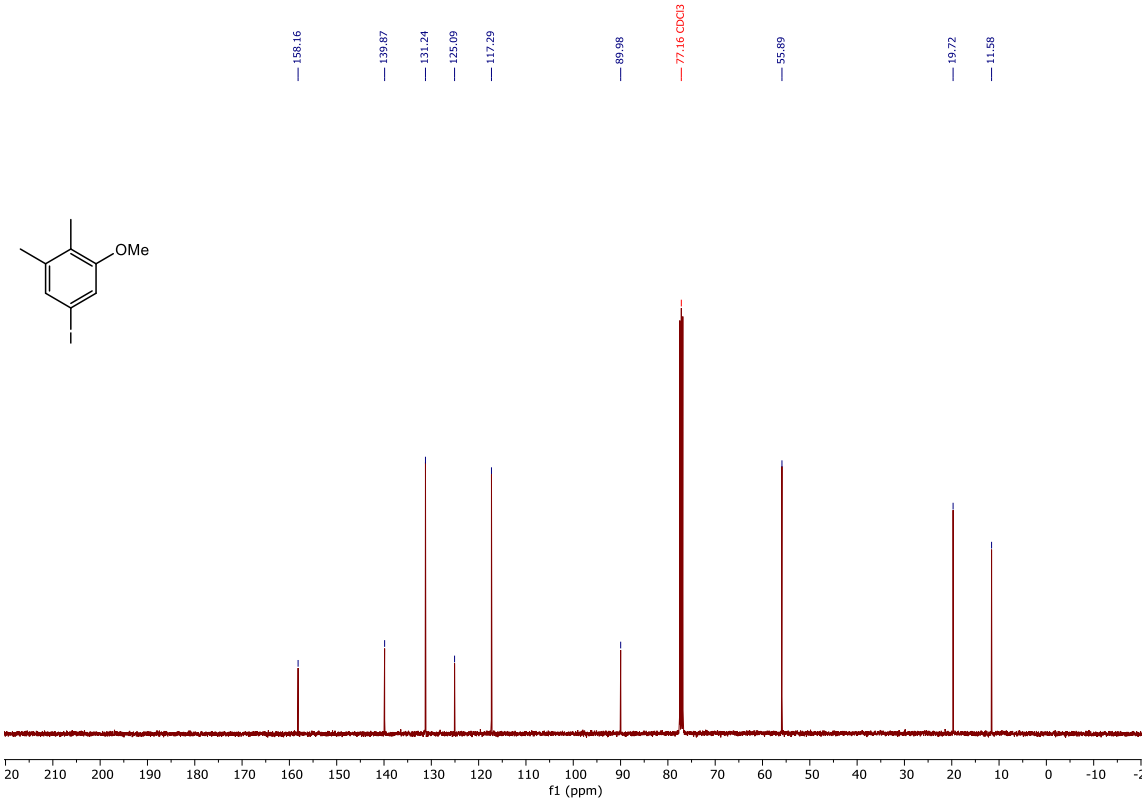
HRMS (EI pos) m/z: Calcd for $C_9H_{11}OI^+$ 261.9849, Found 261.9847.

IR (cm^{-1}): 2981, 1570, 1473, 1457, 1397, 1299, 1258, 1113, 827, 560.

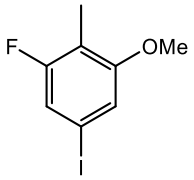
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



1-fluoro-5-iodo-3-methoxy-2-methylbenzene (3x)



Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), 1-fluoro-3-methoxy-2-methylbenzene (**1x**) (28.0 mg, 0.200 mmol), and purification via silica column chromatography using pentane:CH_2Cl_2 = 19:1 as the eluent, the target compound **3x** was obtained as a colorless liquid (22.3 mg, 42%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.04 (d, *J* = 8.2 Hz, 1H), 6.92 (s, 1H), 3.81 (s, 3H), 2.06 (s, 3H) ppm.

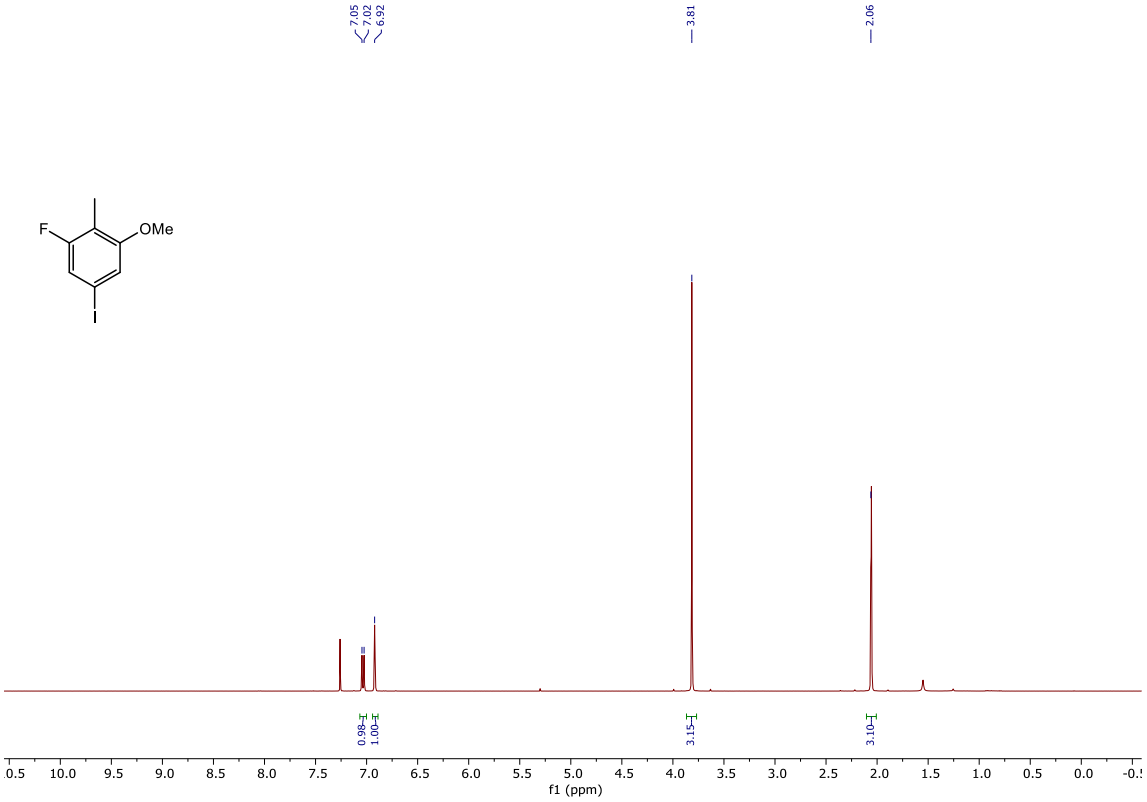
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 161.4 (d, *J* = 247.1 Hz), 159.4 (d, *J* = 9.5 Hz), 117.4 (d, *J* = 26.2 Hz), 115.5 (d, *J* = 3.0 Hz), 114.1 (d, *J* = 19.3 Hz), 88.7 (d, *J* = 11.6 Hz) , 56.2, 7.7 (d, *J* = 4.8 Hz) ppm.

^{19}F NMR ($CDCl_3$, 375 MHz): δ = –115.1 ppm.

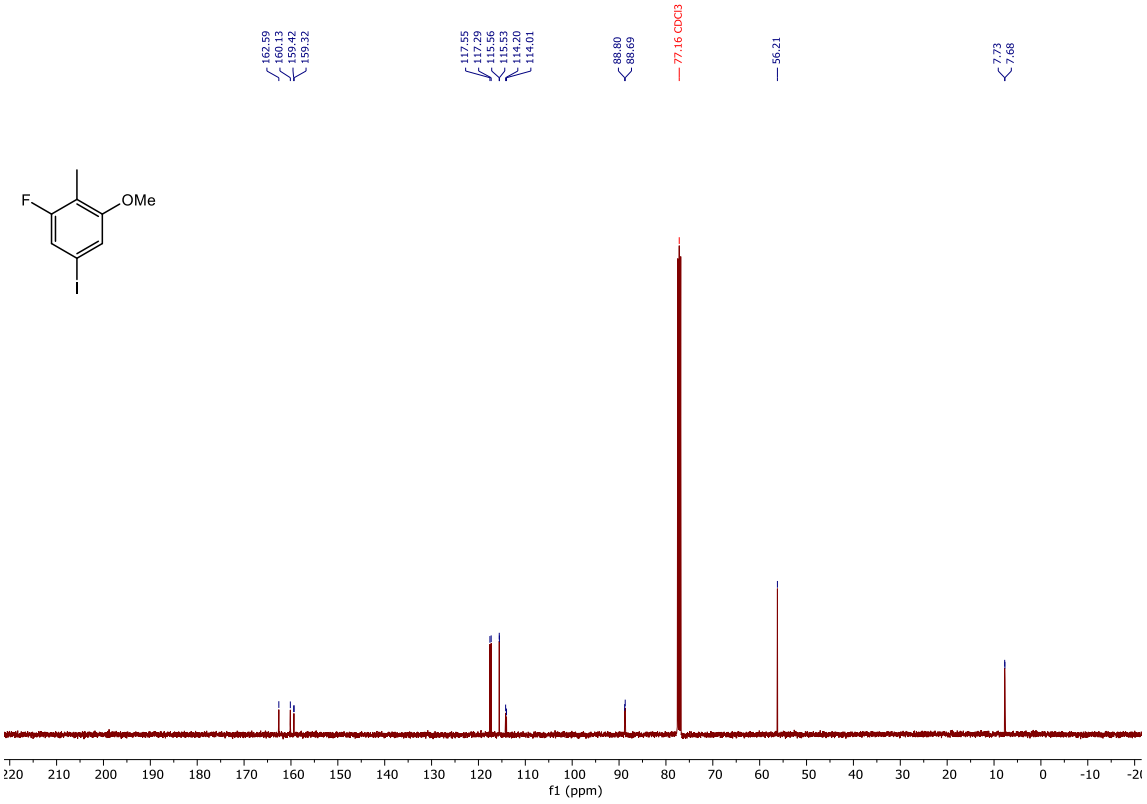
HRMS (EI pos) m/z: Calcd for $C_8H_8OFI^+$ 265.9598, Found 265.9598.

IR (cm^{-1}): 1600, 1576, 1482, 1404, 1276, 1115, 833, 823, 557.

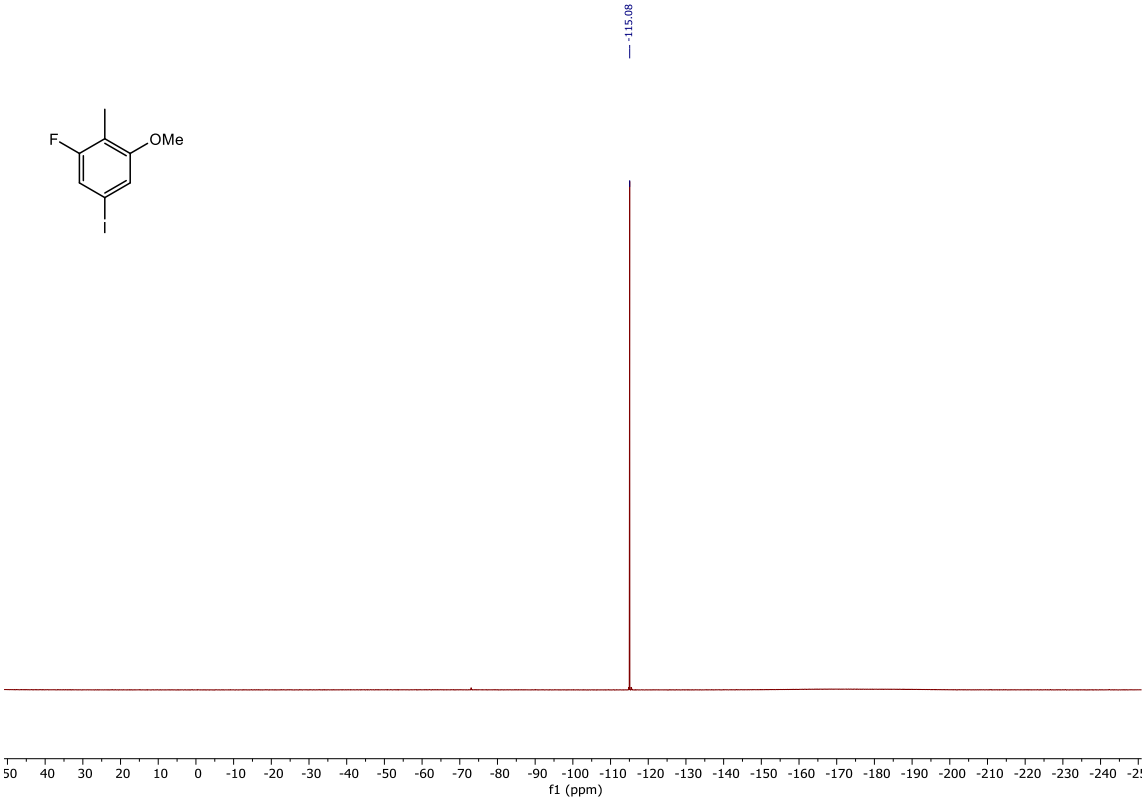
^{1}H NMR spectrum in $CDCl_3$:



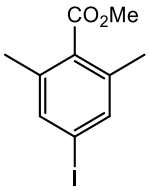
^{13}C NMR spectrum in $CDCl_3$:



^{19}F NMR spectrum in $CDCl_3$:



methyl 4-iodo-2,6-dimethylbenzoate (3y)



Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), methyl 2,6-dimethylbenzoate (**1y**) (32.8 mg, 0.200 mmol), and purification via silica column chromatography using pentane:CH_2Cl_2 = 1:1 as the eluent, the target compound **3y** was obtained as a colorless liquid (32.5 mg, 56%).

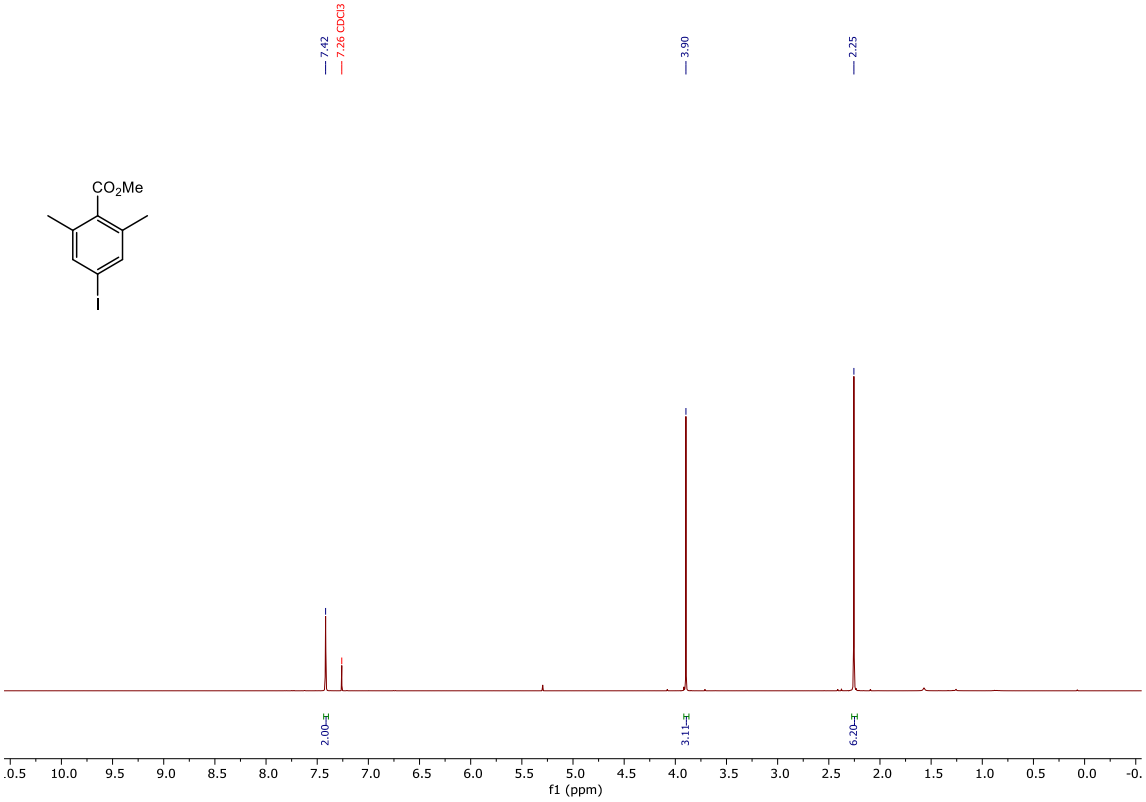
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.42 (s, 2H), 3.90 (s, 3H), 2.25 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.9, 137.2, 136.6, 133.5, 95.9, 52.2, 19.5 ppm.

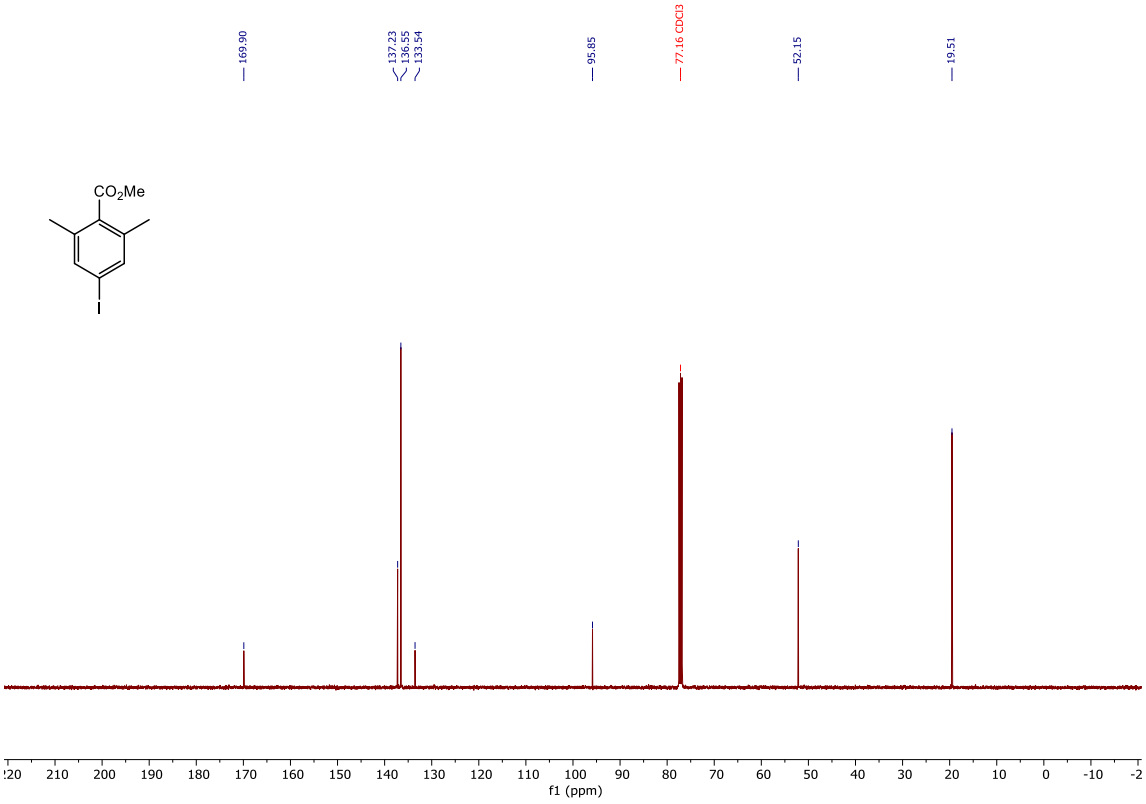
HRMS (ESI pos) m/z: Calcd for $C_{10}H_{11}O_2INa^+$ 312.9696, Found 312.9696.

IR (cm^{-1}): 1726, 1576, 1457, 1262, 1122, 1081, 855, 835, 576.

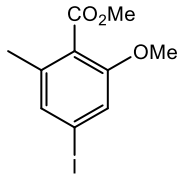
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



methyl 4-iodo-2-methoxy-6-methylbenzoate (3z)



Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), methyl 2-methoxy-6-methylbenzoate (**1z**) (36.0 mg, 0.200 mmol), and purification via silica column chromatography using pentane:CH_2Cl_2 = 1:1 as the eluent, the target compound **3z** was obtained as a colorless liquid (23.3 mg, 38%).

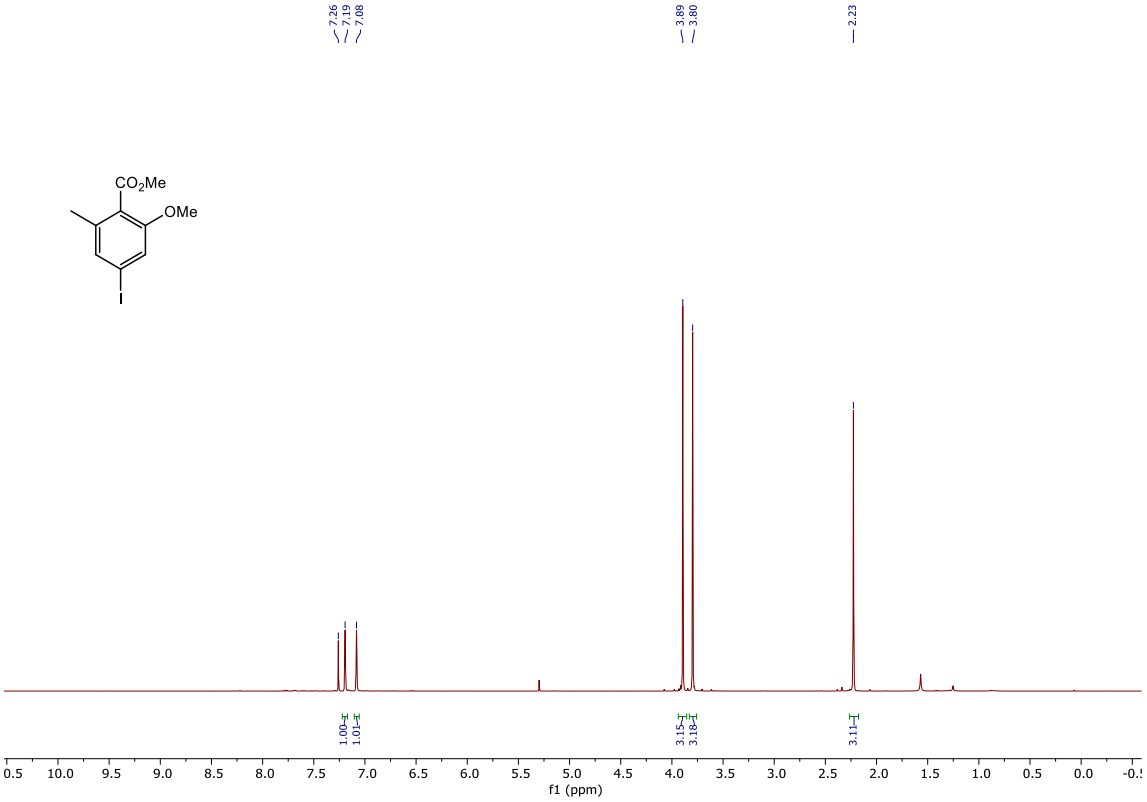
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.19 (s, 1H), 7.08 (s, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 2.23 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.3, 156.8, 138.3, 131.6, 123.6, 118.1, 95.8, 56.3, 52.4, 19.0 ppm.

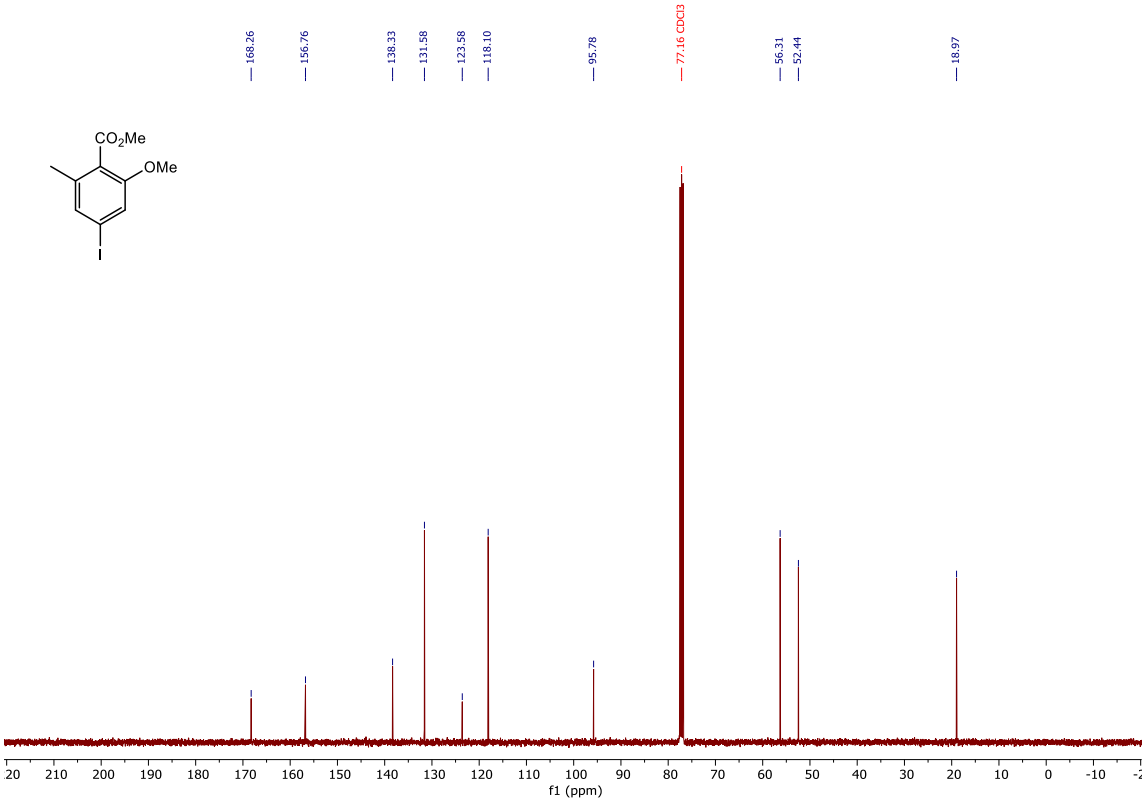
HRMS (EI pos) m/z: Calcd for $C_{10}H_{11}O_3I^+$ 305.9747, Found 305.9744.

IR (cm^{-1}): 1730, 1570, 1457, 1264, 1121, 1080, 835, 556.

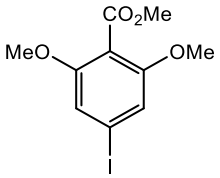
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



methyl 4-iodo-2,6-dimethoxybenzoate (3aa)



Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), methyl 2,6-dimethoxybenzoate (**1aa**) (39.2 mg, 0.200 mmol), and purification via silica column chromatography using pentane:CH_2Cl_2 = 1:4 as the eluent, the target compound **3aa** was obtained as a colorless liquid (14.2 mg, 22%).

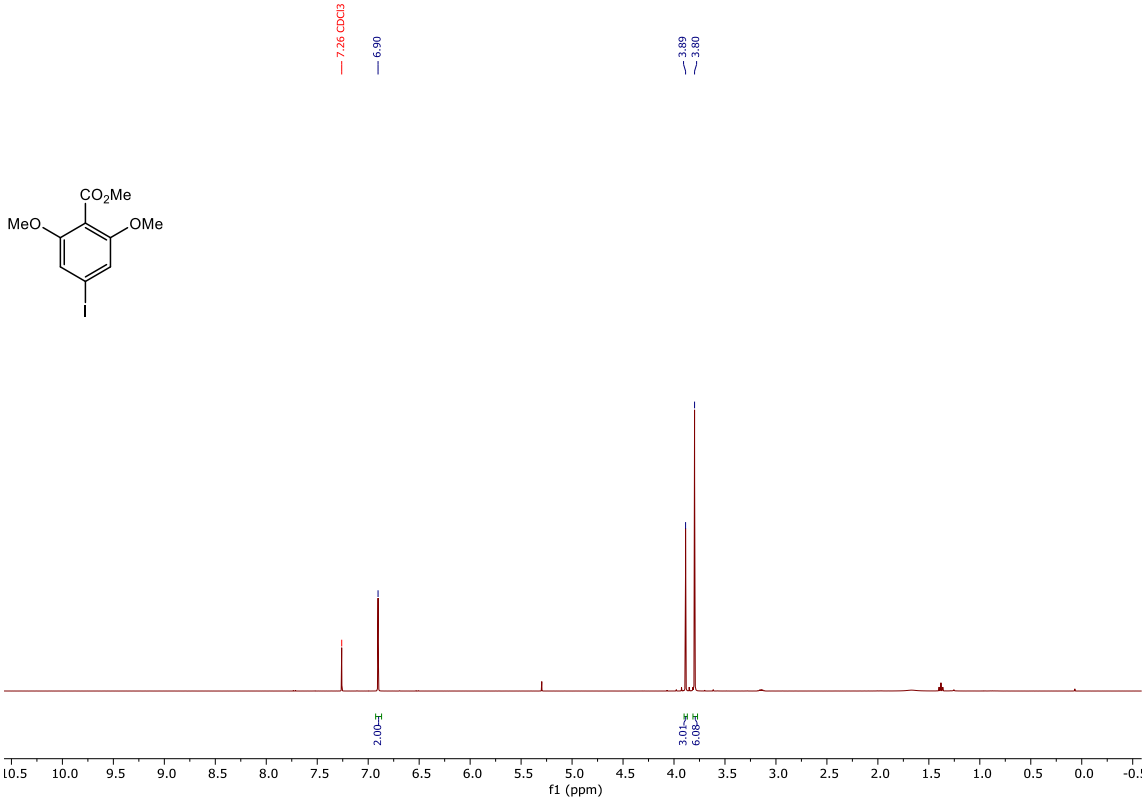
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.90 (s, 2H), 3.89 (s, 3H), 3.80 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.4, 157.6, 114.0, 113.1, 95.9, 56.5, 52.7 ppm.

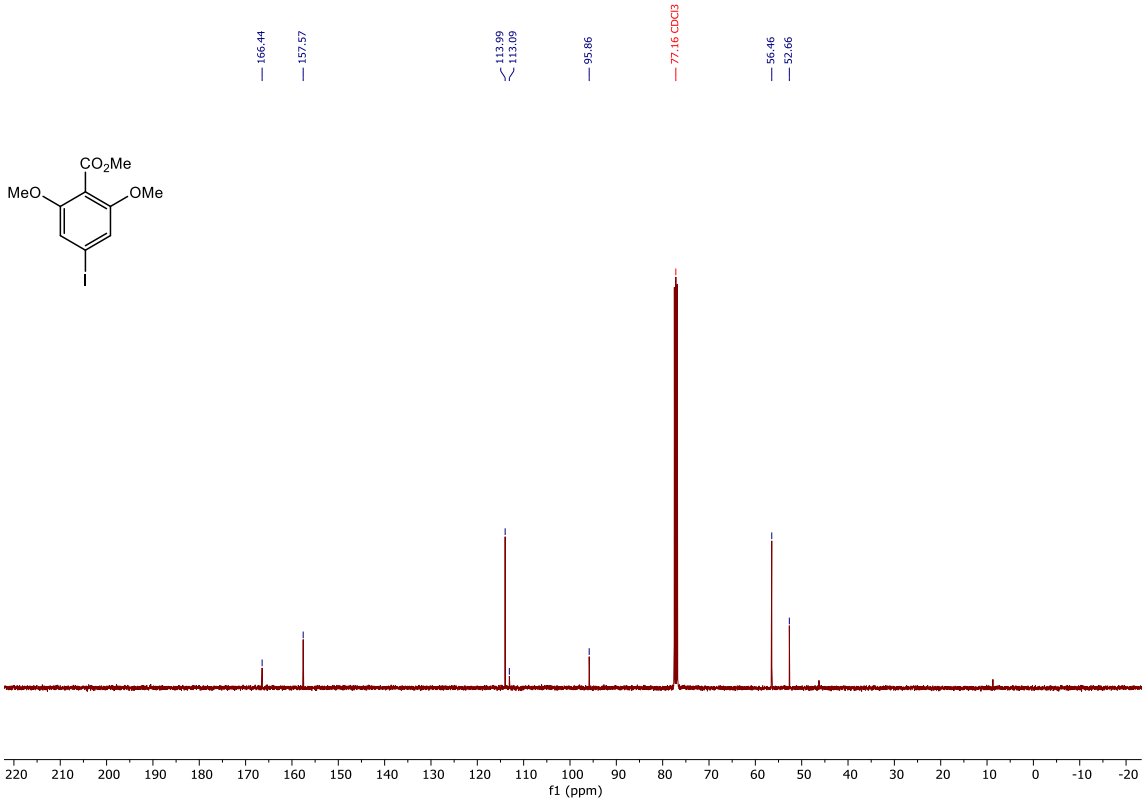
HRMS (ESI pos) m/z: Calcd for $C10H11O4INa^+$ 344.9594, Found 344.9592.

IR (cm^{-1}): 1729, 1576, 1507, 1399, 1302, 1261, 1262, 1125, 1081, 835, 580.

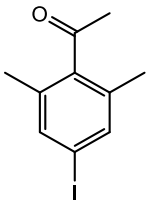
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



1-(4-iodo-2,6-dimethylphenyl)ethan-1-one (3ab)

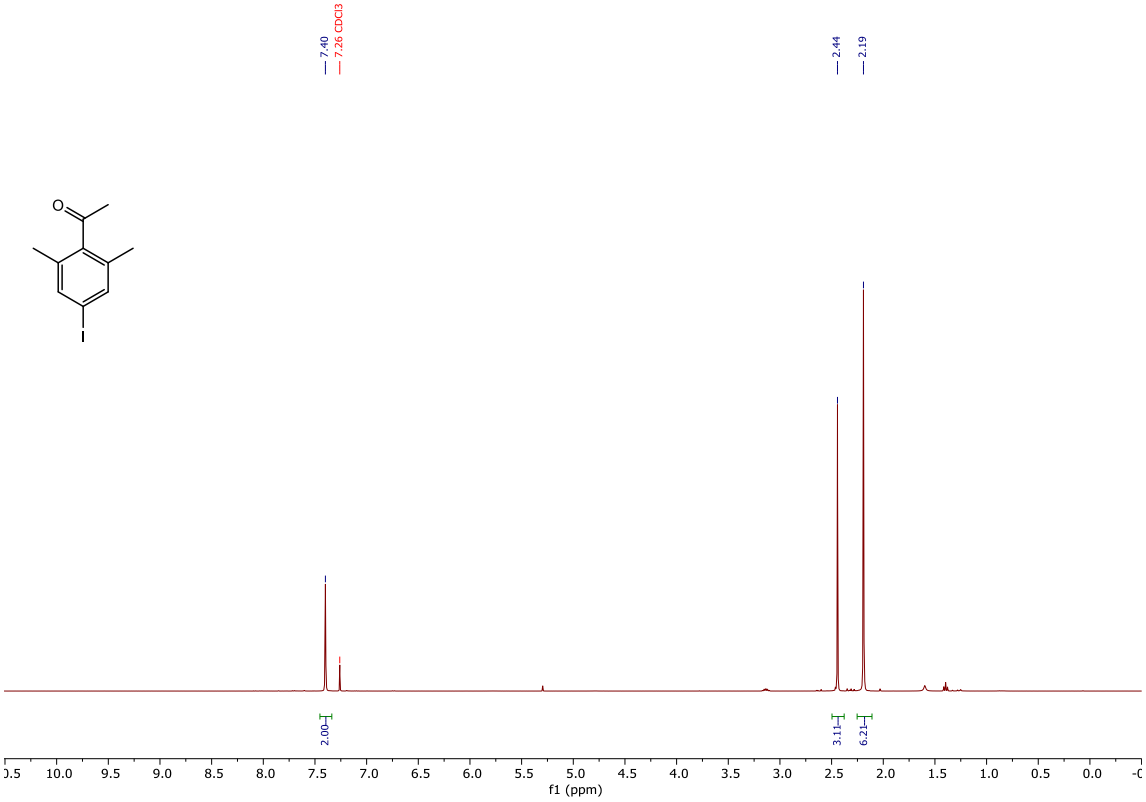


Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), 1-(2,6-dimethylphenyl)ethan-1-one (**1ab**) (29.6 mg, 0.200 mmol), and purification via silica column chromatography using pentane:CH_2Cl_2 = 1:4 as the eluent, the target compound **3ab** was obtained as a colorless liquid (28.5 mg, 52%). The assignment of the compound was achieved by comparison with the literature.[11]

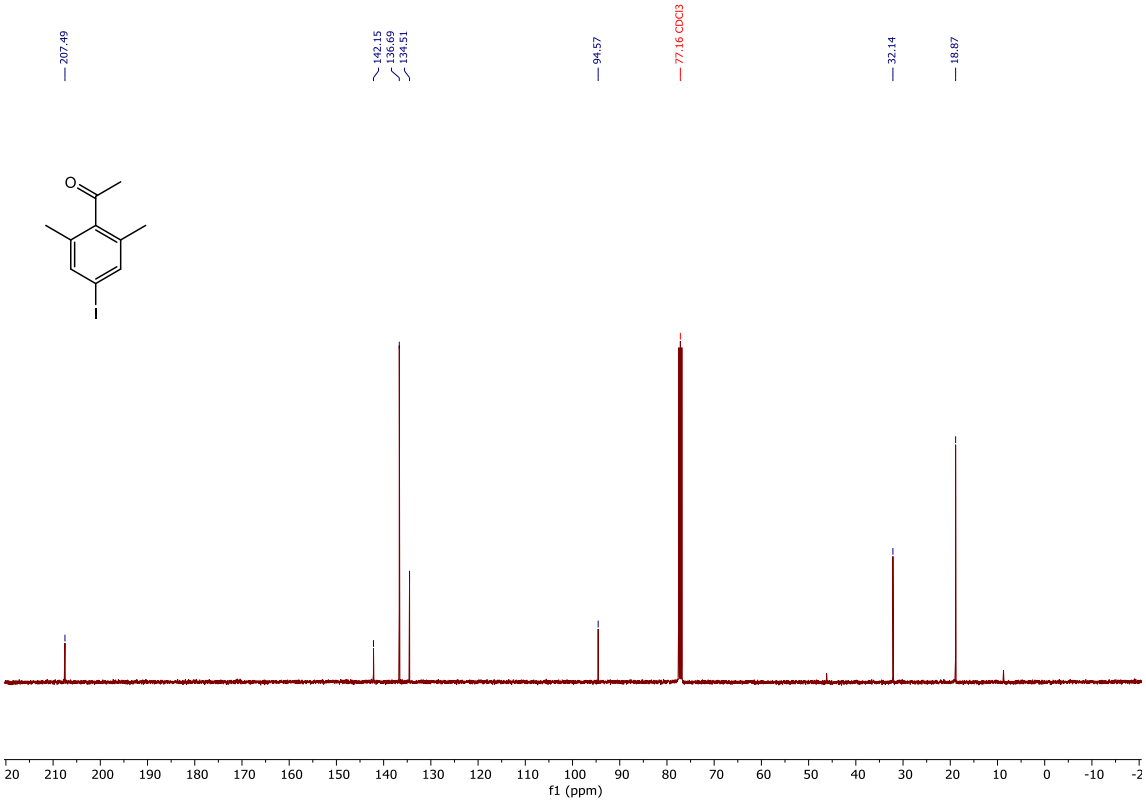
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.40 (s, 2H), 2.44 (s, 3H), 2.19 (s, 6H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 207.5, 142.2, 136.7, 134.5, 94.6, 32.1, 18.9 ppm.

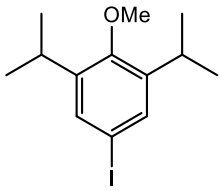
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



5-iodo-1,3-diisopropyl-2-methoxybenzene (3ac)



Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), 1,3-diisopropyl-2-methoxybenzene (**1ac**) (38.5 mg, 0.200 mmol), and purification via silica column chromatography using pentane:CH_2Cl_2 = 9:1 as the eluent, the target compound **3ac** was obtained as a colorless liquid (52.3 mg, 82%).

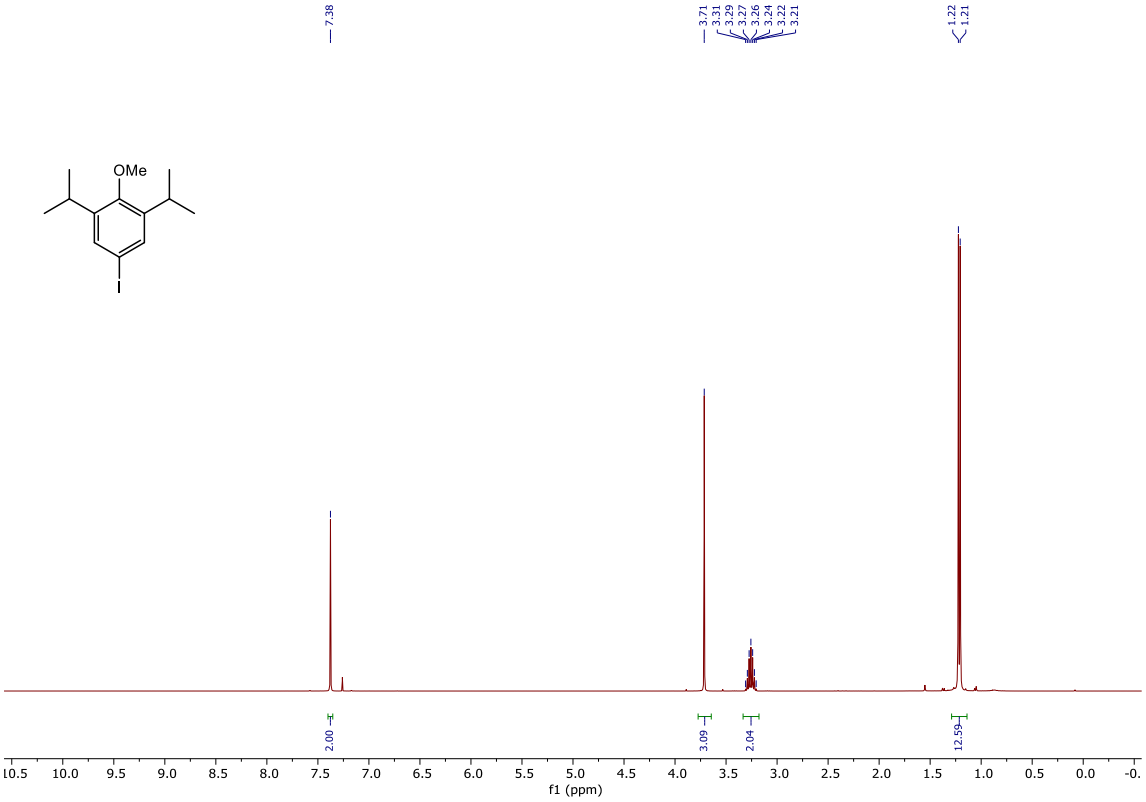
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.38 (s, 2H), 3.71 (s, 3H), 3.26 (hept, *J* = 6.9 Hz, 2H), 1.21 (d, *J* = 6.9 Hz, 12H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.7, 144.7, 133.6, 89.4, 62.4, 26.7, 24.1 ppm.

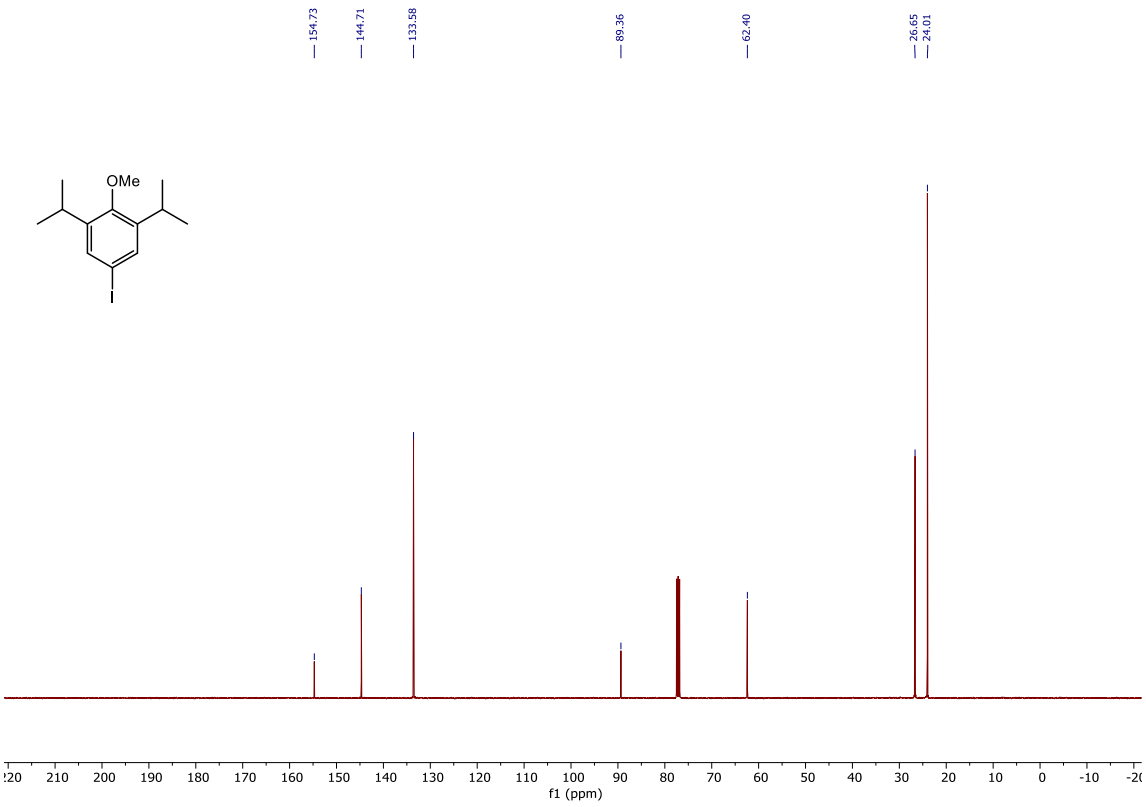
HRMS (EI pos) m/z: Calcd for $C_{13}H_{19}OI^+$ 318.0475, Found 318.0473.

IR (cm^{-1}): 2962, 2931, 1458, 1425, 1325, 1199, 1167, 1010, 865, 817, 788, 700, 552.

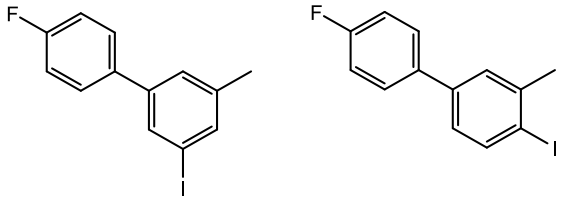
^{1}H NMR spectrum in $CDCl_3$:



^{1}H NMR spectrum in $CDCl_3$:



4'-fluoro-3-iodo-5-methyl-1,1'-biphenyl (3ad-β) and 4'-fluoro-4-iodo-3-methyl-1,1'-biphenyl (3ad-γ)



3ad-β **3ad-γ**

Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), 4'-fluoro-3-methyl-1,1'-biphenyl (**1ad**) (37.2 mg, 0.200 mmol), and purification via silica column chromatography using pentane as the eluent, the target compound **3ad** was obtained as a colorless liquid (19.9 mg, 32%, β:γ = 93:7).

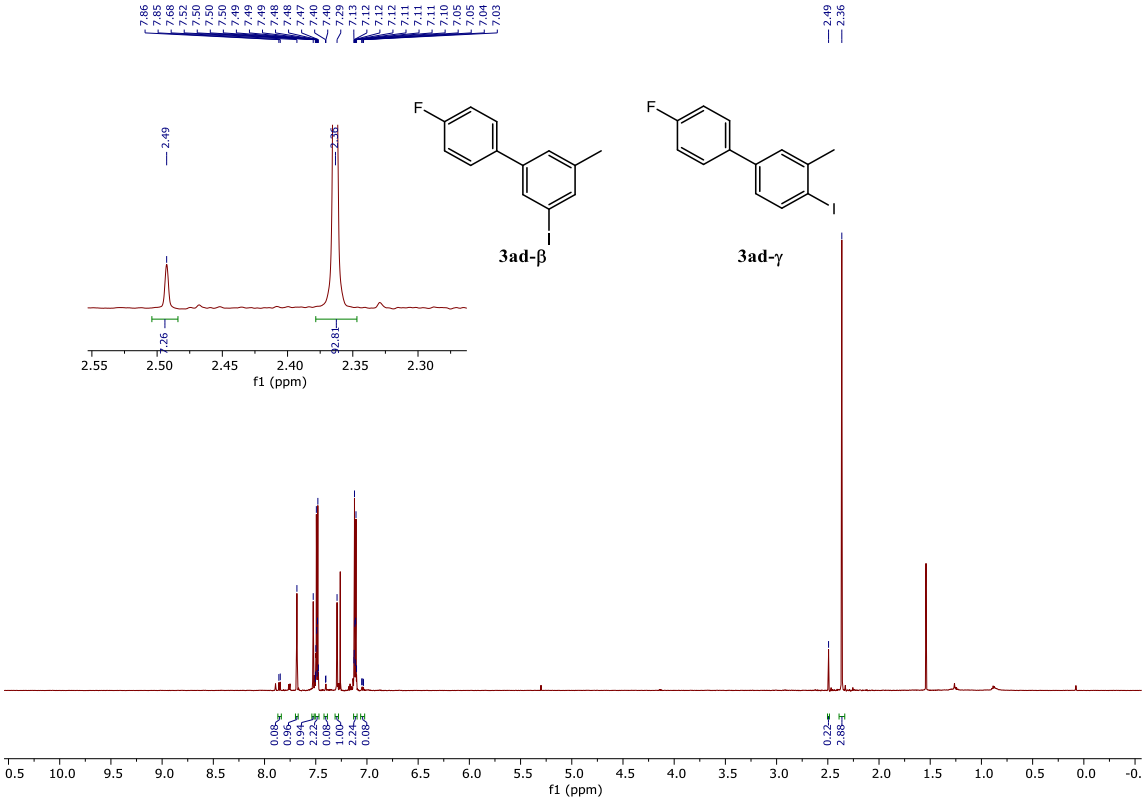
^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.85 (d, *J* = 8.1 Hz, $1H^{\gamma}$), 7.68 (s, $1H^{\beta}$), 7.52 (s, $1H^{\beta}$), 7.52-7.46 (m, $2H^{\beta}$+$2H^{\gamma}$), 7.40 (d, *J* = 2.3 Hz, $1H^{\gamma}$), 7.29 (s, $1H^{\beta}$), 7.14-7.09 (m, $2H^{\beta}$+$2H^{\gamma}$), 7.04 (dd, *J* = 8.1, 2.3 Hz, $1H^{\gamma}$), 2.49 (s, $3H^{\gamma}$), 2.36 (s, $3H^{\beta}$) ppm.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 162.8 (d, *J* = 247.2 Hz), 142.4, 140.7, 137.0, 136.0 (d, *J* = 3.3 Hz), 133.3, 128.9 (d, *J* = 8.1 Hz), 127.4, 115.9 (d, *J* = 21.5 Hz), 94.9, 21.2 ppm.

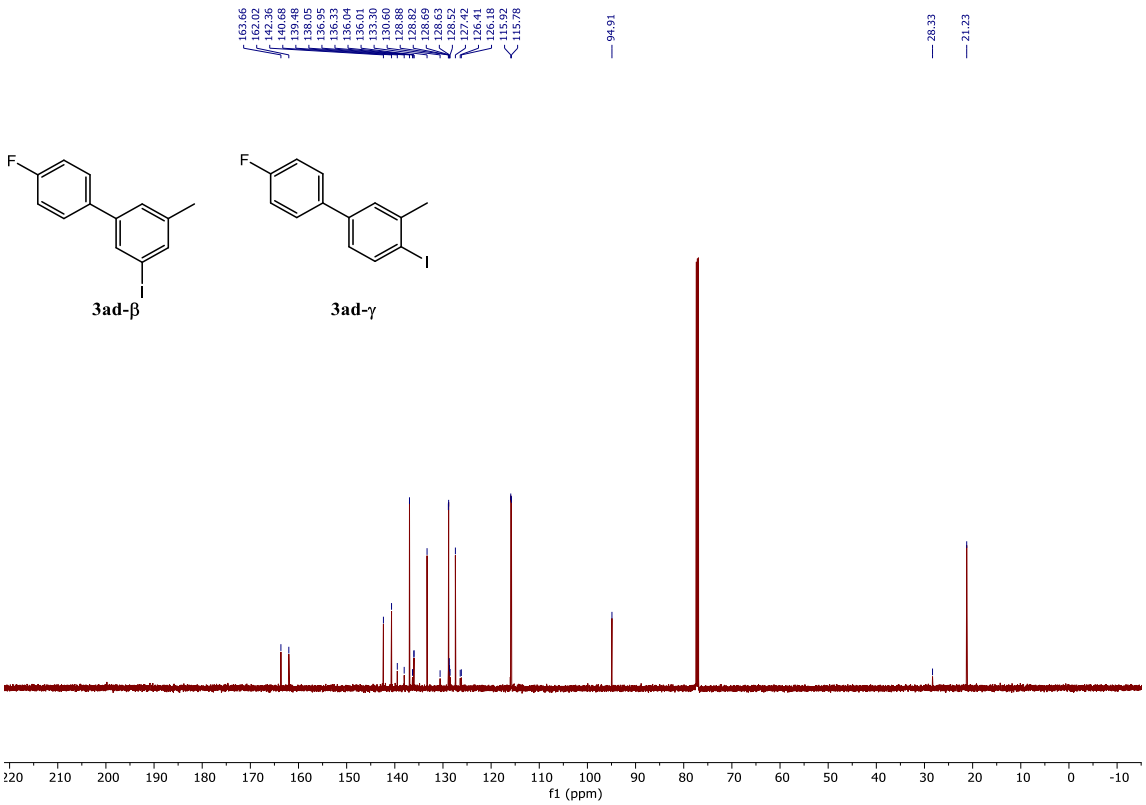
^{19}F NMR ($CDCl_3$, 564 MHz): δ = –114.92, –115.14 ppm.

HRMS (EI pos) m/z: Calcd for $C_{13}H_{10}FI^{+}$ 311.9811, Found 311.9813.

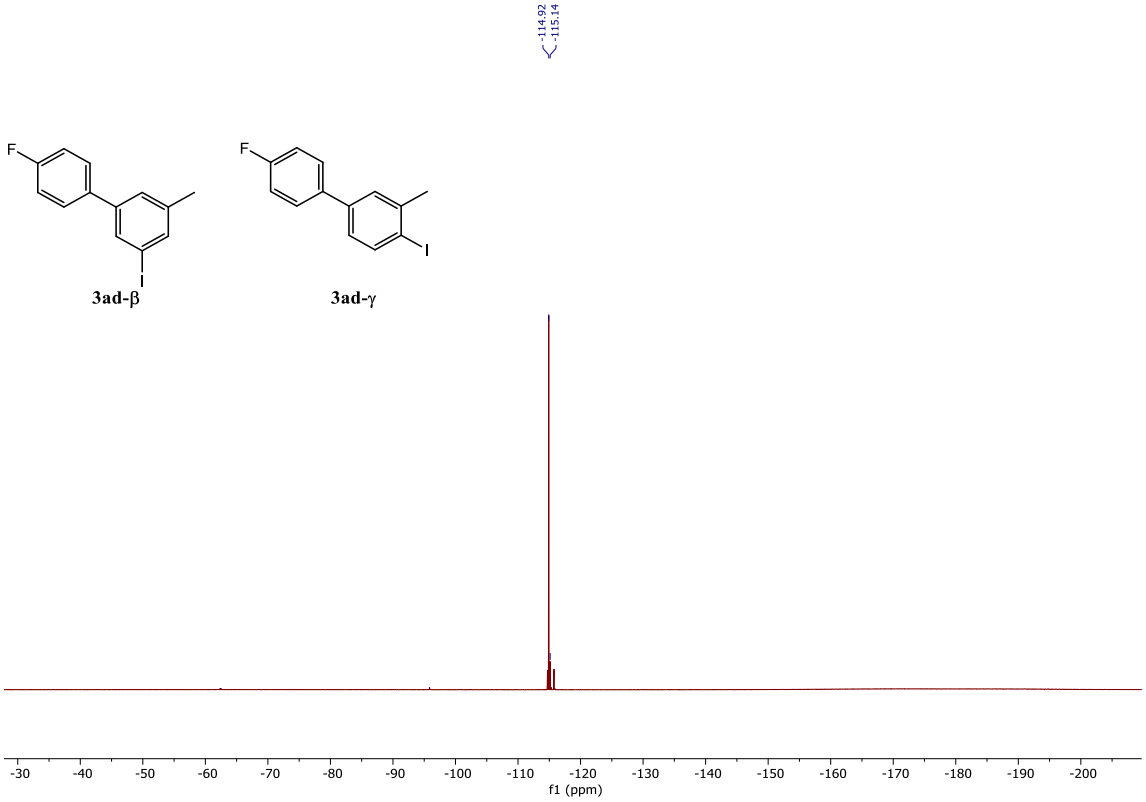
^{1}H NMR spectrum in $CDCl_3$:



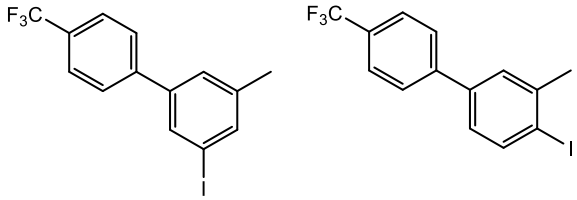
^{13}C NMR spectrum in $CDCl_3$:



^{19}F NMR spectrum in $CDCl_3$:



3-iodo-5-methyl-4'-(trifluoromethyl)-1,1'-biphenyl (3ae-β) and 4-iodo-3-methyl-4'-(trifluoromethyl)-1,1'-biphenyl (3ae-γ)



3ae-β **3ae-γ**

Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), 3-methyl-4'-(trifluoromethyl)-1,1'-biphenyl (**1ae**) (47.2 mg, 0.200 mmol), and purification via silica column chromatography using pentane as the eluent, the target compound **3ae** was obtained as a colorless liquid (21.7 mg, 30%, β:γ = 96:4).

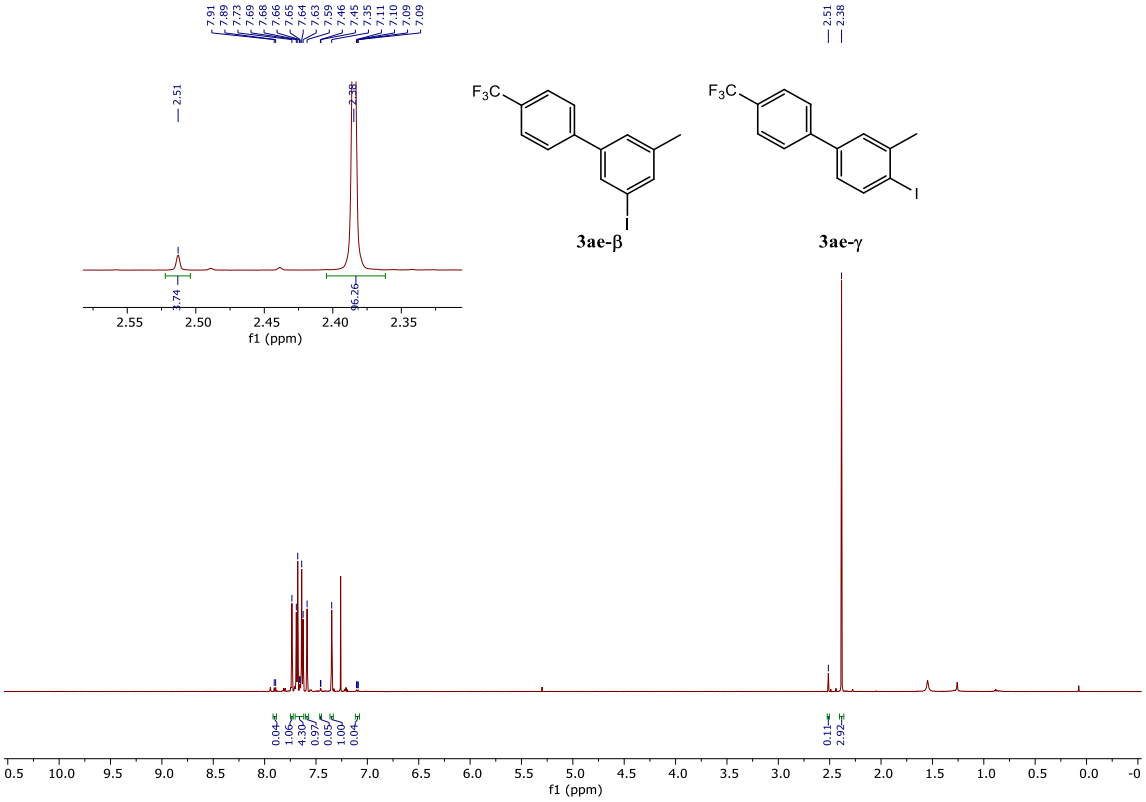
^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.90 (d, *J* = 8.1 Hz, 1H$^{\gamma}$), 7.73 (s, 1H$^{\beta}$), 7.71-7.61 (m, 4H$^{\beta}$+4H$^{\gamma}$), 7.59 (s, 1H$^{\beta}$), 7.45 (d, *J* = 2.3 Hz, 1H$^{\gamma}$), 7.35 (s, 1H$^{\beta}$), 7.10 (dd, *J* = 8.1, 2.3 Hz, 1H$^{\gamma}$), 2.51 (s, 3H$^{\gamma}$), 2.38 (s, 3H$^{\beta}$) ppm.

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 143.4 (q, *J* = 1.2 Hz), 141.9, 140.9, 138.5 (q, *J* = 370.3 Hz), 137.9, 133.5, 130.0 (q, *J* = 32.6 Hz), 127.7, 127.6, 125.9 (q, *J* = 3.8 Hz), 95.0, 21.2 ppm.

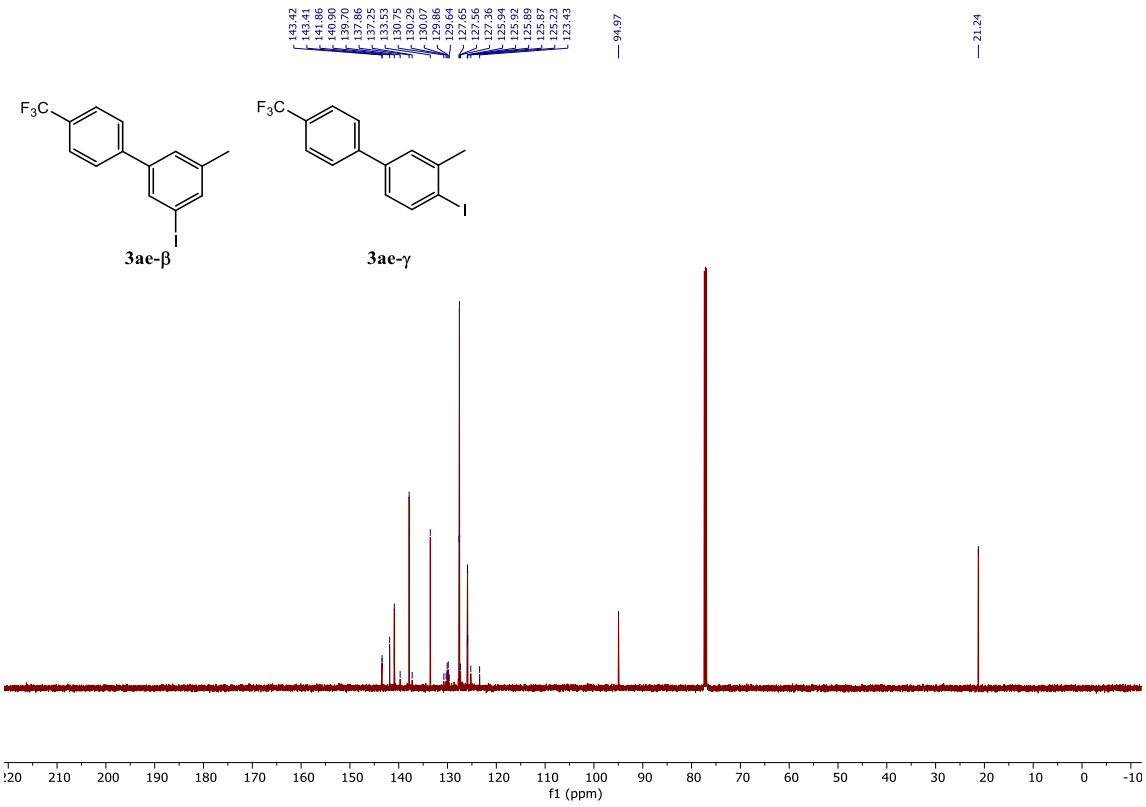
^{19}F NMR ($CDCl_3$, 564 MHz): δ = –62.5(0), –62.5(3) ppm.

HRMS (EI pos) m/z: Calcd for $C_{14}H_{10}F_3I^+$ 361.9779, Found 361.9778.

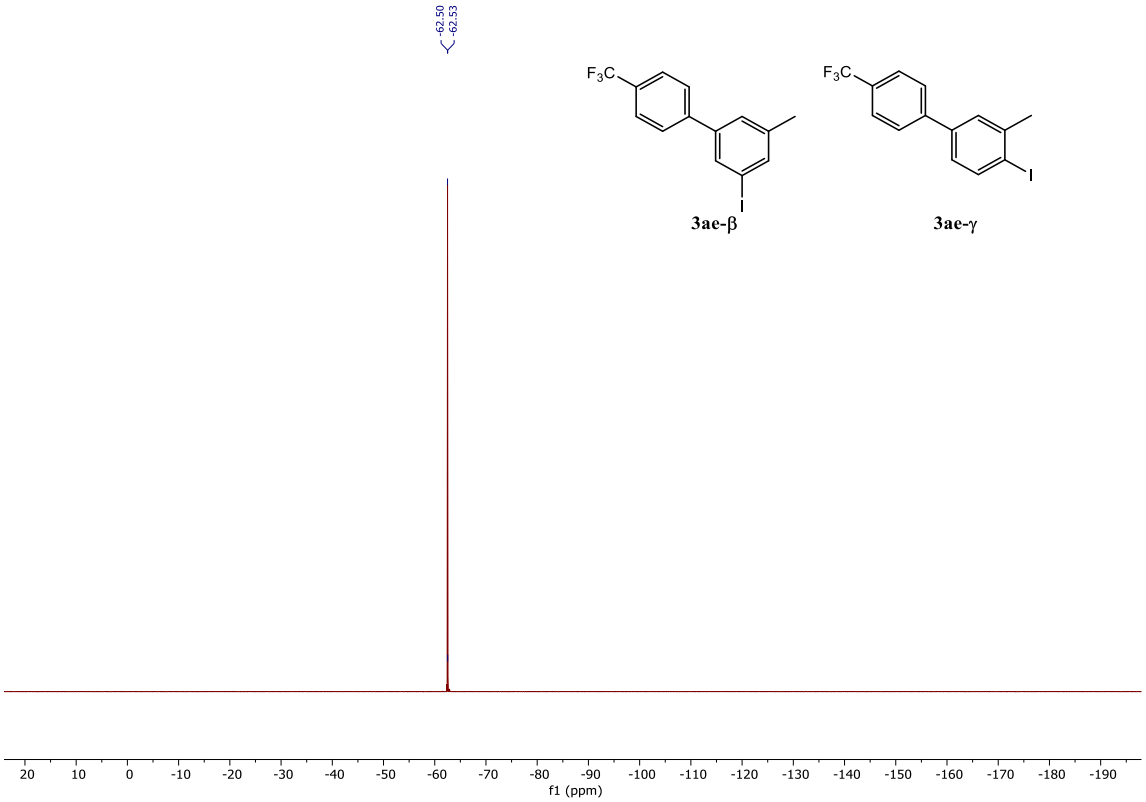
^{1}H NMR spectrum in $CDCl_3$:



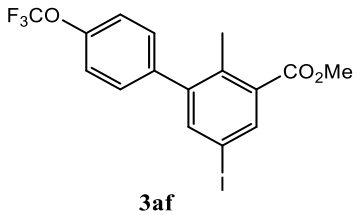
^{13}C NMR spectrum in $CDCl_3$:



^{19}F NMR spectrum in $CDCl_3$:



methyl 5-iodo-2-methyl-4'-(trifluoromethoxy)-[1,1'-biphenyl]-3-carboxylate (3af)



3af

Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), methyl 2-methyl-4'-(trifluoromethoxy)-[1,1'-biphenyl]-3-carboxylate (**1af**) (62.1 mg, 0.200 mmol), and purification via silica column chromatography using pentane:CH_2Cl_2 = 3:2 as the eluent, the target compound **3af** was obtained as a colorless liquid (26.0 mg, 30%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.14 (d, *J* = 1.9 Hz, 1H), 7.67 (d, *J* = 1.9 Hz, 1H), 7.28 (s, 4H), 3.92 (s, 3H), 2.33 (s, 3H) ppm.

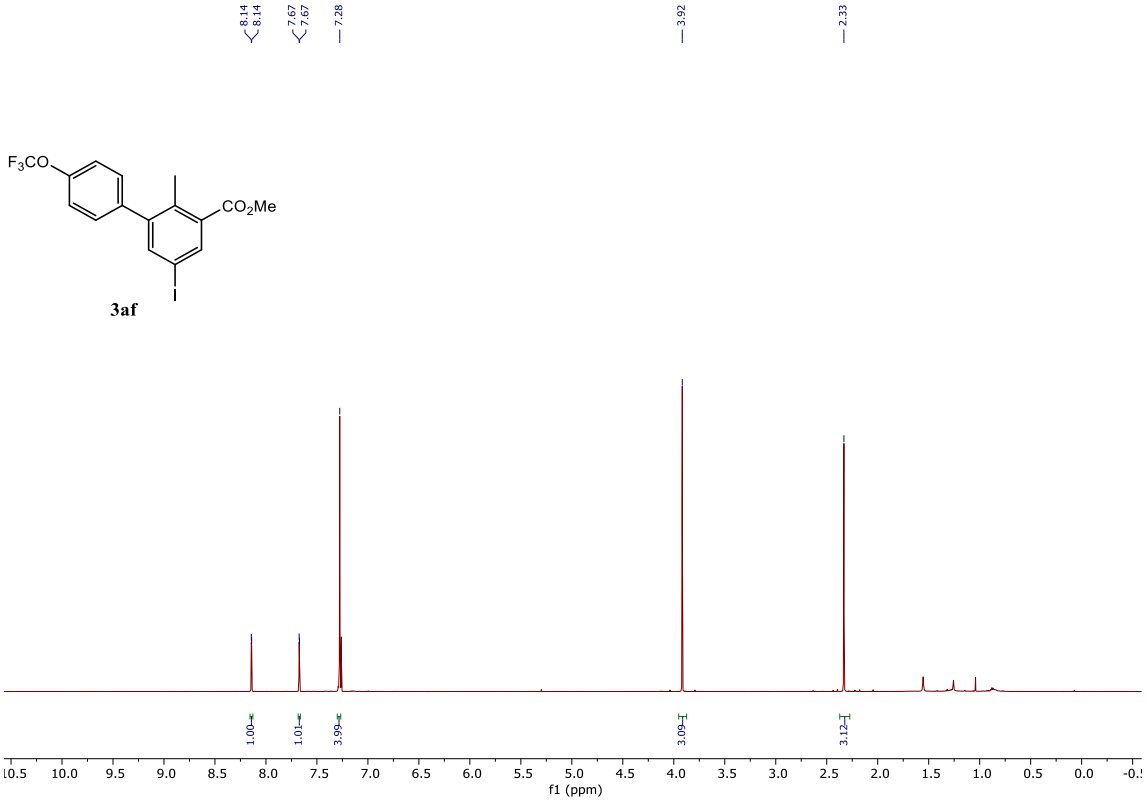
^{13}C NMR ($CDCl_3$, 150 MHz): δ = 167.2, 148.9, 144.5, 141.7, 138.7, 138.3, 136.7, 133.3, 130.8, 121.0, 120.6 (d, *J* =257.5 Hz), 89.8, 52.5, 18.3 ppm.

^{19}F NMR ($CDCl_3$, 564 MHz): δ = –57.80 ppm.

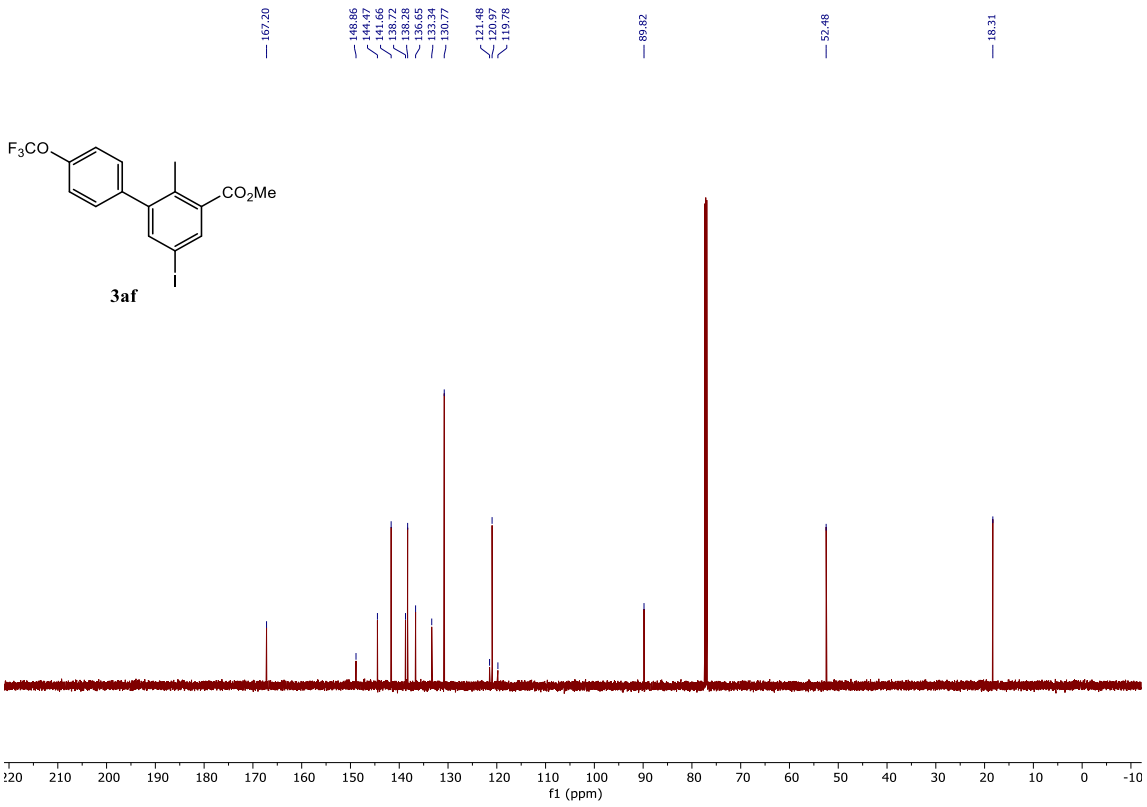
HRMS (ESI pos) m/z: Calcd for $C_{16}H_{12}O_3F_3INa^+$ 458.9675, Found 458.9675.

IR (cm^{-1}): 1730, 1559, 1507, 1257, 1206, 1165, 1079, 565.

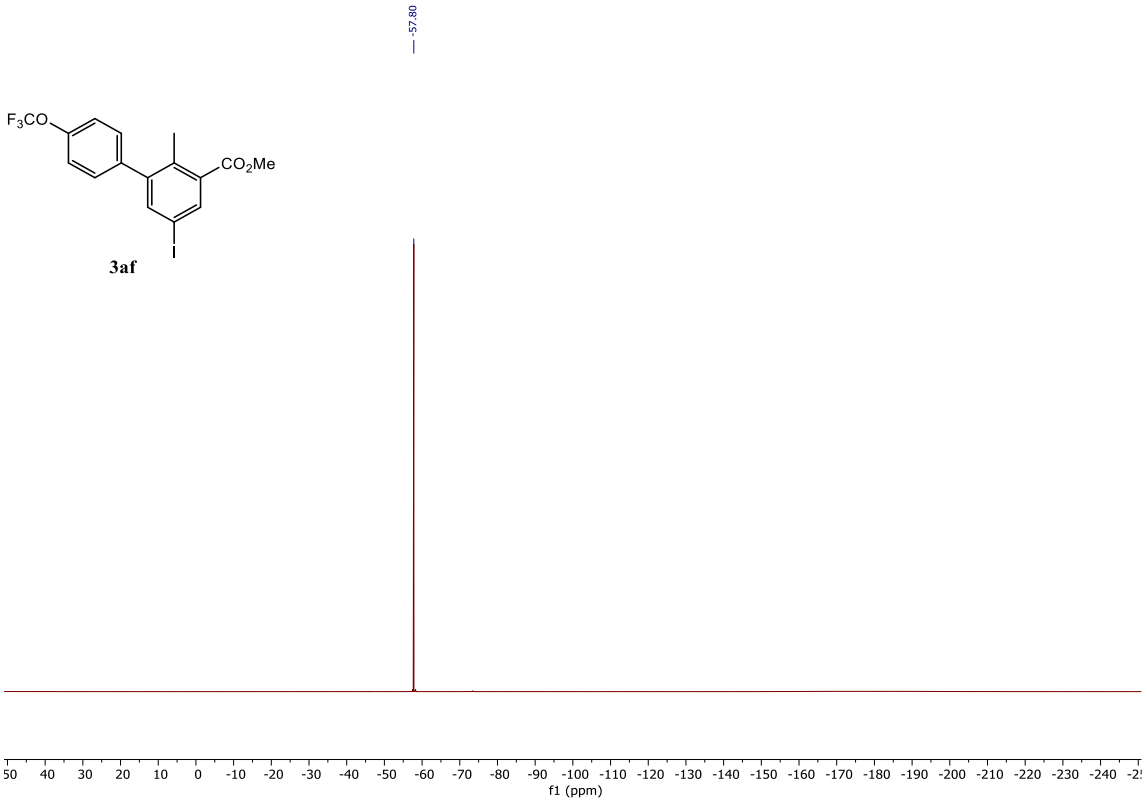
^{1}H NMR spectrum in $CDCl_3$:



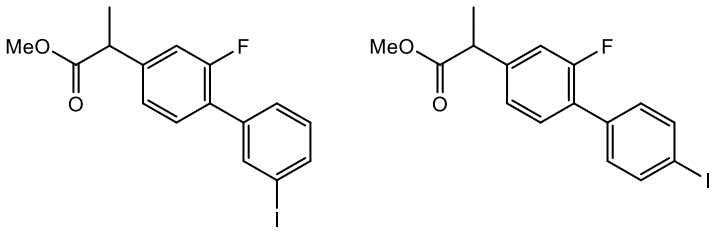
^{13}C NMR spectrum in $CDCl_3$:



^{19}F NMR spectrum in $CDCl_3$:



methyl 2-(2-fluoro-3'-iodo-[1,1'-biphenyl]-4-yl)propanoate (3ag-meta) and methyl 2-(2-fluoro-4'-iodo-[1,1'-biphenyl]-4-yl)propanoate (3ag-para)



3ag-meta **3ag-para**

Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), methyl 2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanoate (**1ag**) (51.7 mg, 0.200 mmol), and purification via silica column chromatography using pentane:CH_2Cl_2 = 2:1 as the eluent, the target compound **3ag** was obtained as a colorless oil (36.9 mg, 48%, m:p =69:31).

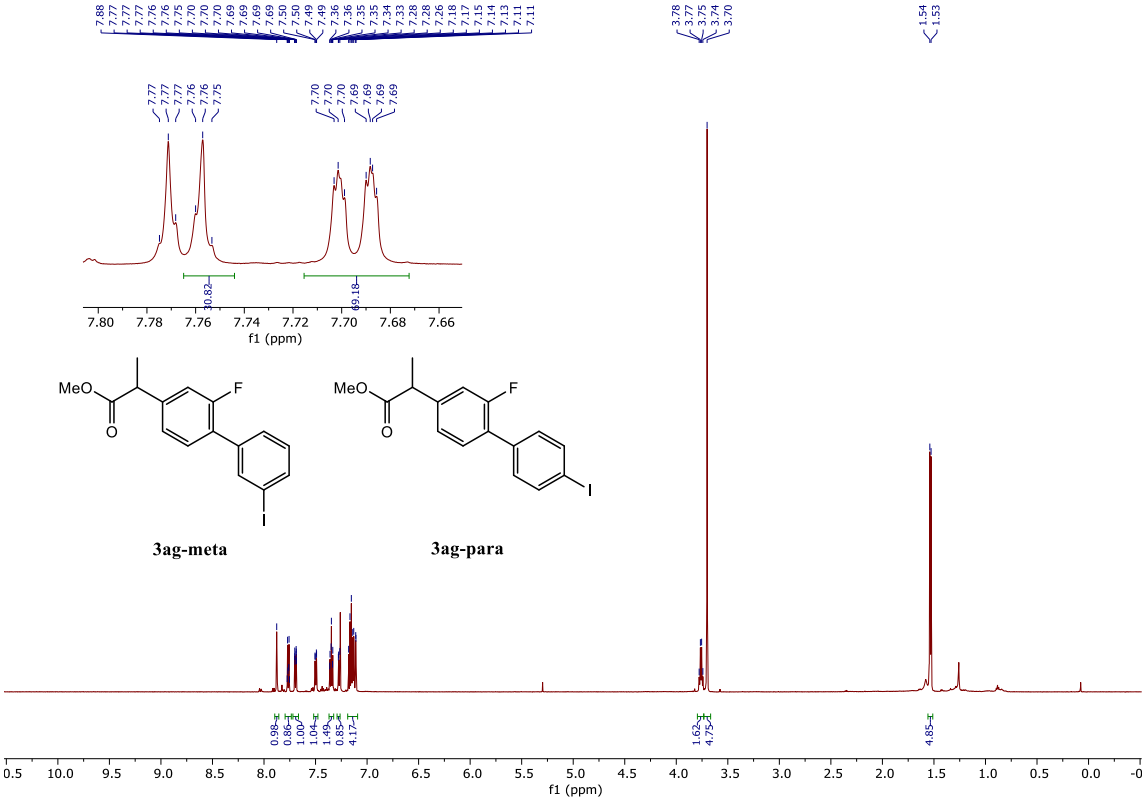
^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.88 (s, 1H^m), 7.78-7.75 (m, 2H^p), 7.71-7.68 (m, 1H^m), 7.51-7.48 (m, 1H^m), 7.37-7.33 (m, 1H^m+1H^p), 7.28-7.25 (m, 2H^p), 7.19-7.09 (m, 3H^m+2H^p), 3.76 (q, *J* = 7.2 Hz, 1H^m+1H^p), 3.70 (s, 3H^m+3H^p), 1.53 (d, *J* = 7.2 Hz, 3H^m+3H^p) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.5, 174.4, 159.6(8) (d, *J* = 249.0 Hz), 159.6(7) (d, *J* = 248.8 Hz), 142.7 (d, *J* = 7.7 Hz), 142.5 (d, *J* = 7.8 Hz), 137.9 (d, *J* = 2.9 Hz), 137.7(4), 137.7(2) (d, *J* = 1.2 Hz), 136.8, 130.9 (d, *J* = 3.1 Hz), 130.8 (d, *J* = 3.7 Hz), 130.6 (d, *J* = 3.7 Hz), 130.2, 129.1 (d, *J* = 2.9 Hz), 128.3 (d, *J* = 3.1 Hz), 126.9 (d, *J* = 13.4 Hz), 126.4 (d, *J* = 13.5 Hz), 123.8(3) (d, *J* = 3.4 Hz), 123.8(0) (d, *J* = 3.4 Hz), 115.5(3) (d, *J* = 23.5 Hz), 115.4(9) (d, *J* = 23.5 Hz), 94.4, 93.7, 52.4, 45.0(8), 45.0(7), 18.5 ppm.

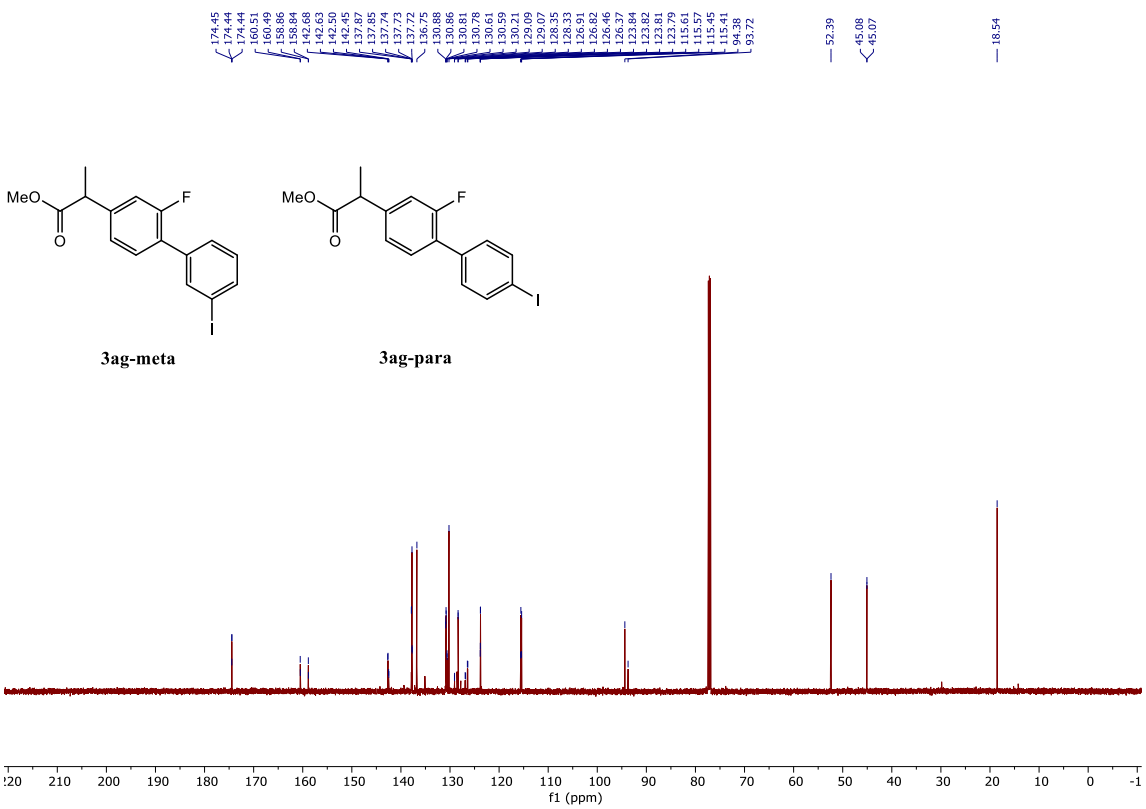
^{19}F NMR ($CDCl_3$, 564 MHz): δ = –117.3, –117.4 ppm.

HRMS (ESI pos) m/z: Calcd for $C_{16}H_{14}O_2FINa^+$ 406.9915, Found 406.9914.

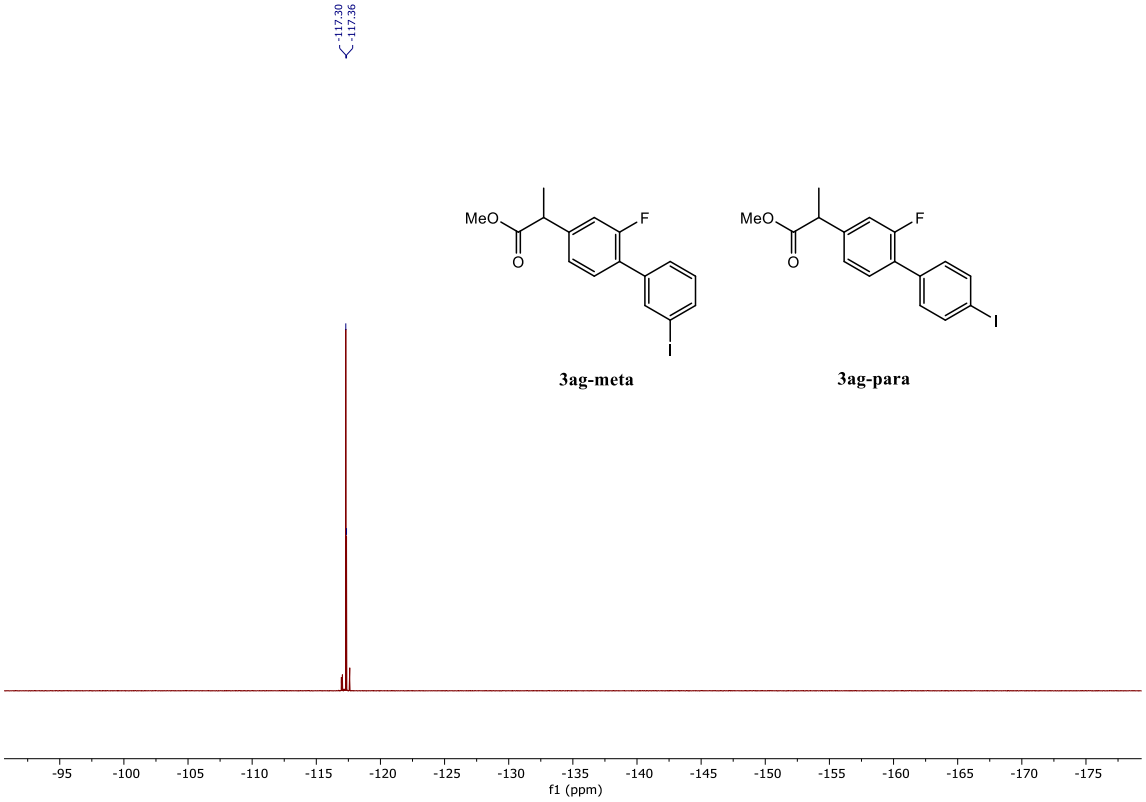
^{1}H NMR spectrum in $CDCl_3$:



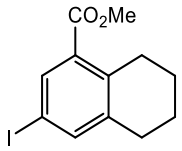
^{13}C NMR spectrum in $CDCl_3$:



^{19}F NMR spectrum in $CDCl_3$:



methyl 3-iodo-5,6,7,8-tetrahydronaphthalene-1-carboxylate (3ah)



Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), methyl 5,6,7,8-tetrahydronaphthalene-1-carboxylate (**1ah**) (38.0 mg, 0.200 mmol), and purification via silica column chromatography using pentane:CH_2Cl_2 = 1:4 as the eluent, the target compound **3ah** was obtained as a colorless liquid (20.2 mg, 32%).

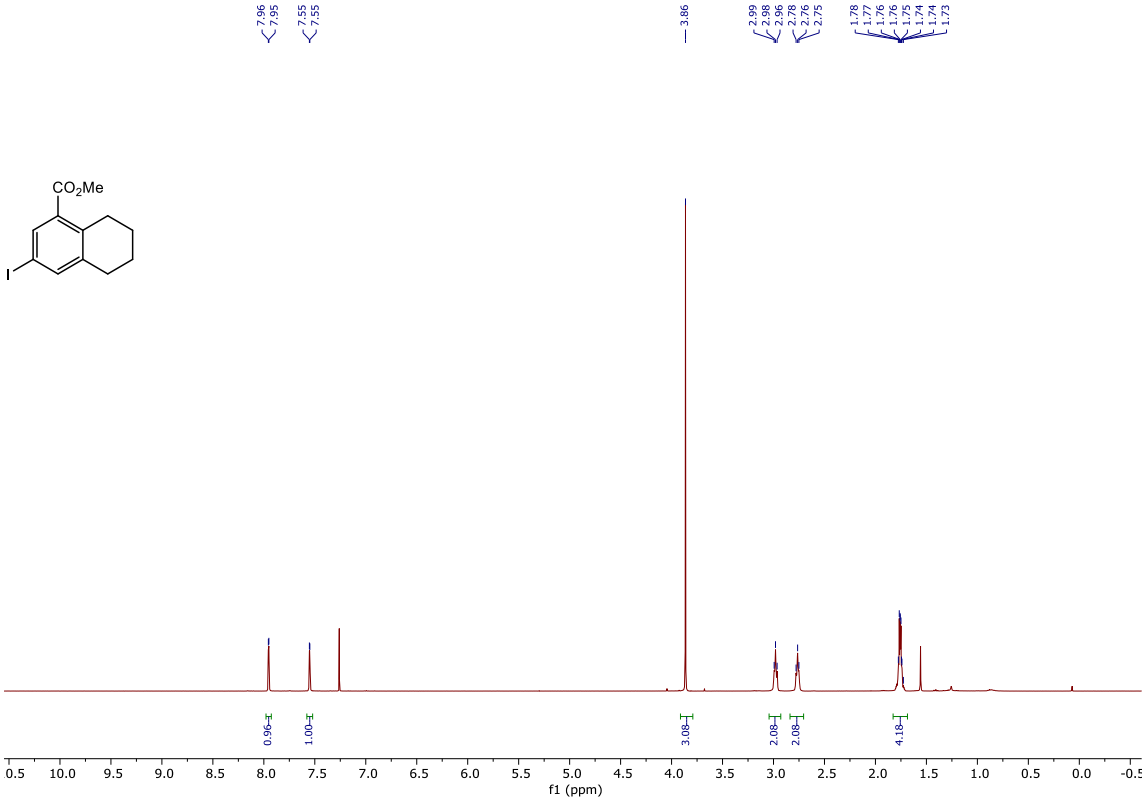
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.95 (d, *J* = 1.8 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 3.86 (s, 3H), 2.98 (t, *J* = 5.7 Hz, 2H), 2.76 (t, *J* = 5.7 Hz, 2H), 1.84-1.66 (m, 4H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.1, 141.6, 141.1, 138.5, 136.5, 132.2, 89.7, 52.2, 30.0, 27.6, 22.9, 22.3 ppm.

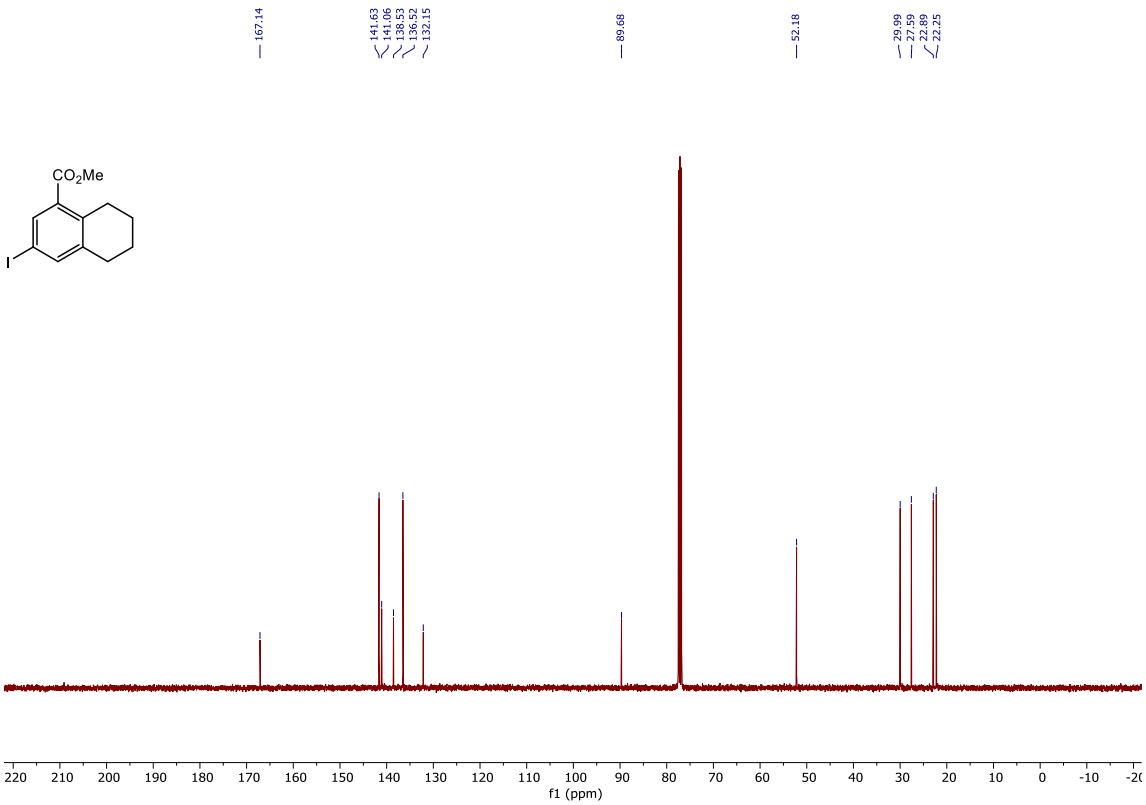
HRMS (ESI pos) m/z: Calcd for $C_{12}H_{13}O_2INa^+$ 338.9852, Found 338.9854.

IR (cm^{-1}): 2933, 1723, 1559, 1456, 1433, 1274, 1256, 1193, 1148, 1021, 819, 778, 556.

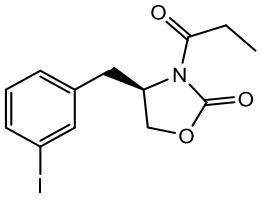
^{1}H NMR spectrum in $CDCl_3$:



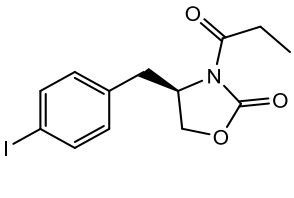
^{13}C NMR spectrum in $CDCl_3$:



4-(3-iodobenzyl)-3-propionyloxazolidin-2-one (3ai-meta) and 4-(4-iodobenzyl)-3-propionyloxazolidin-2-one (3ai-para)



3ai-meta



3ai-para

Following the general procedure B[a], using 1-iodo-2-nitrobenzene (**2**) (100 mg, 0.400 mmol, 2.0 equiv.), 4-benzyl-3-propionyloxazolidin-2-one (**1ai**) (46.7 mg, 0.200 mmol), and purification via silica column chromatography using pentane:EtOAc = 4:1 as the eluent, the target compound **3ai** was obtained as a colorless oil (30.3 mg, 42%, m:p =65:35).

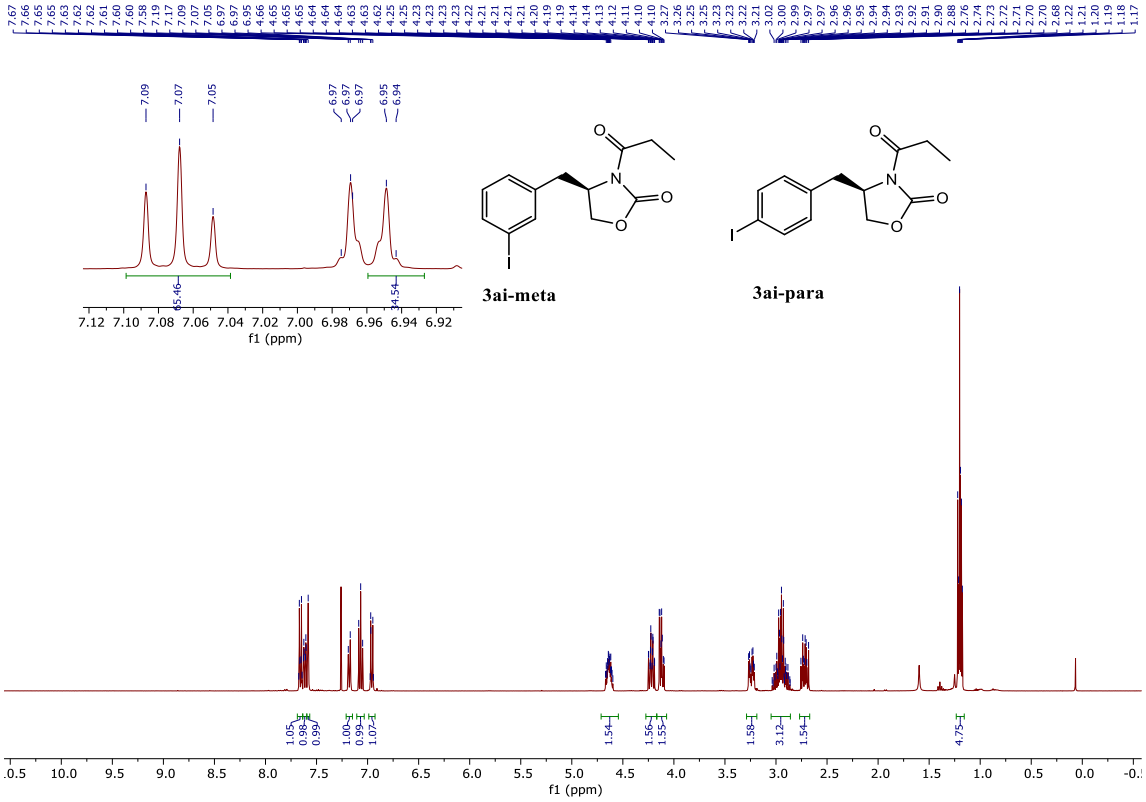
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.68-7.64 (m, 2H^p), 7.61 (dt, *J* = 7.8, 1.2 Hz, 1H^m), 7.58 (s, 1H^m), 7.18 (d, *J* = 7.8 Hz, 1H^m), 7.07 (t, *J* = 7.8 Hz, 1H^m), 6.99-6.93 (m, 2H^p), 4.68-4.59 (m, 1H^m+1H^p), 4.26-4.18 (m, 1H^m+1H^p), 4.16-4.09 (m, 1H^m+1H^p), 3.28-3.20 (m, 1H^m+1H^p), 3.05-2.85 (m, 2H^m+2H^p), 2.77-2.67 (m, 1H^m+1H^p), 1.24-1.17 (m, 3H^m+3H^p) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 174.2(3), 174.2(1), 153.5, 153.4, 138.5, 138.2, 137.9, 136.6, 135.1, 131.5, 130.8, 128.7, 95.0, 93.0, 66.2(9), 66.2(5), 55.1(0), 55.0(5), 37.6(3), 37.6(0), 29.3(2), 29.3(1), 8.4(3), 8.4(1) ppm.

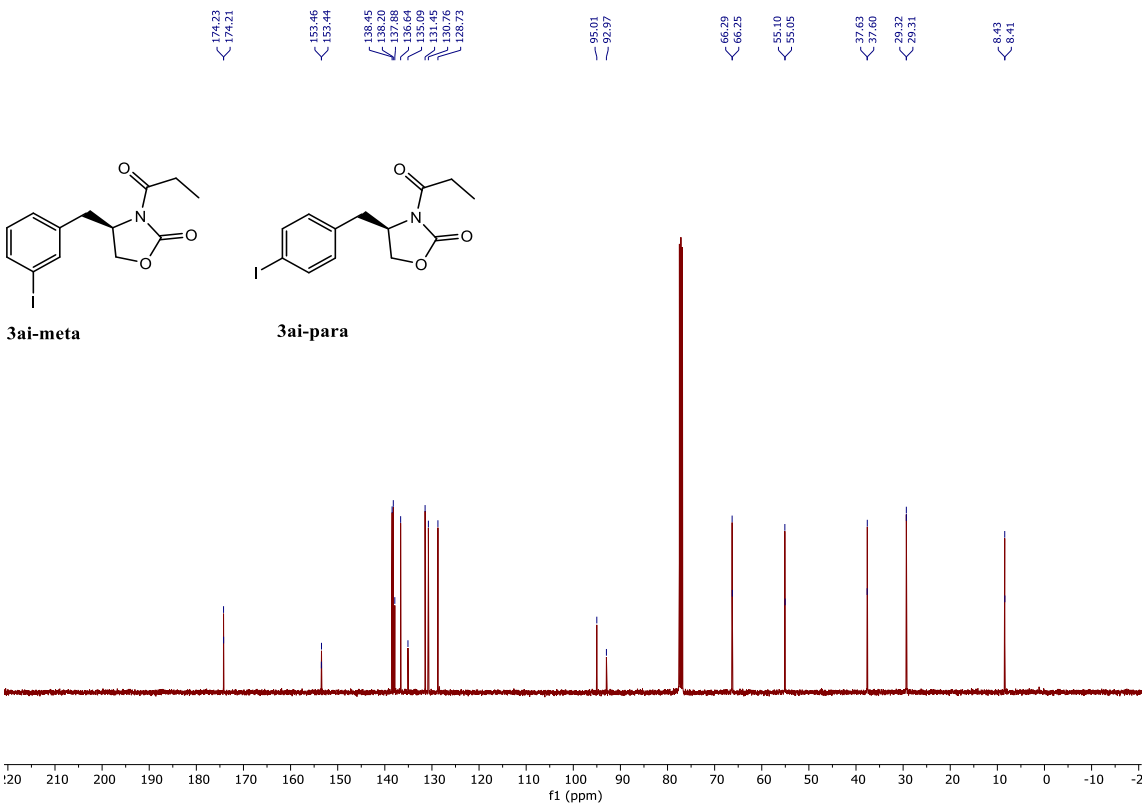
HRMS (ESI pos) m/z: Calcd for $C_{13}H_{14}NO_3INa^+$ 381.9911, Found 381.9908.

[a] Reaction was performed at 70 °C and 48 h reaction time.

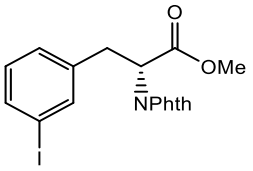
^{1}H NMR spectrum in $CDCl_3$:



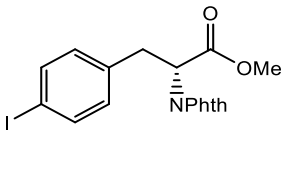
^{13}C NMR spectrum in $CDCl_3$:



methyl (*R*)-2-(1,3-dioxoisoindolin-2-yl)-3-(3-iodophenyl)propanoate (3aj-meta) methyl (*R*)-2-(1,3-dioxoisoindolin-2-yl)-3-(4-iodophenyl)propanoate (3aj-para)



3aj-meta



3aj-para

Following the general procedure B[a], using 1-iodo-2-nitrobenzene (**2**) (100 mg, 0.400 mmol, 2.0 equiv.), methyl (*R*)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoate (**1aj**) (61.9 mg, 0.200 mmol), and purification via silica column chromatography using pentane:CH_2Cl_2 = 1:4 as the eluent, the target compound **3aj** was obtained as a colorless oil (39.2 mg, 45%, m:p =64:36).

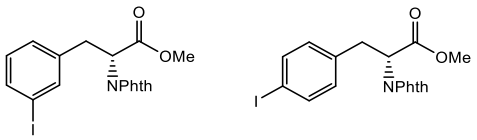
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.84-7.77 (m, $2H^m$+$2H^p$), 7.74-7.68 (m, $2H^m$+$2H^p$), 7.53-7.49 (m, $1H^m$+$2H^p$), 7.47 (d, *J* = 7.8 Hz, $1H^m$), 7.14 (d, *J* = 7.8, $1H^m$), 6.96-6.89 (m, $1H^m$+$2H^p$), 5.16-5.07 (m, $1H^m$+$1H^p$), 3.79-3.74 (m, $3H^m$+$3H^p$), 3.60-3.41 (m, $2H^m$+$2H^p$) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.2(2), 169.1(5), 167.6, 167.5, 139.3, 138.1, 137.8, 136.5, 136.2, 134.4, 131.7, 131.6, 131.0, 130.4, 128.2, 123.7, 94.5, 92.5, 53.1(1), 53.0(7), 53.0, 34.4, 34.3 ppm.

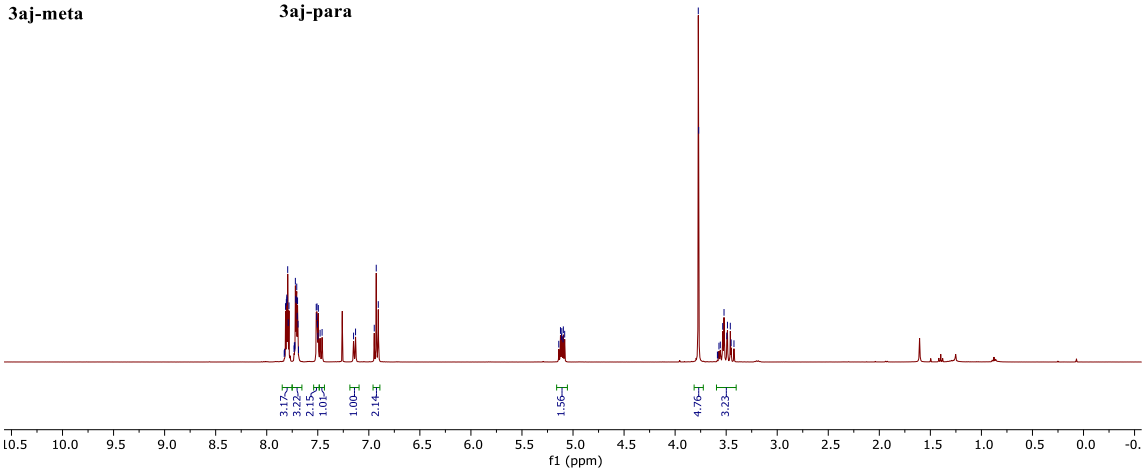
HRMS (ESI pos) m/z: Calcd for $C_{18}H_{14}NO_4INa^+$ 457.9860, Found 457.9853.

[a] Reaction was performed at 70 °C and 48 h reaction time.

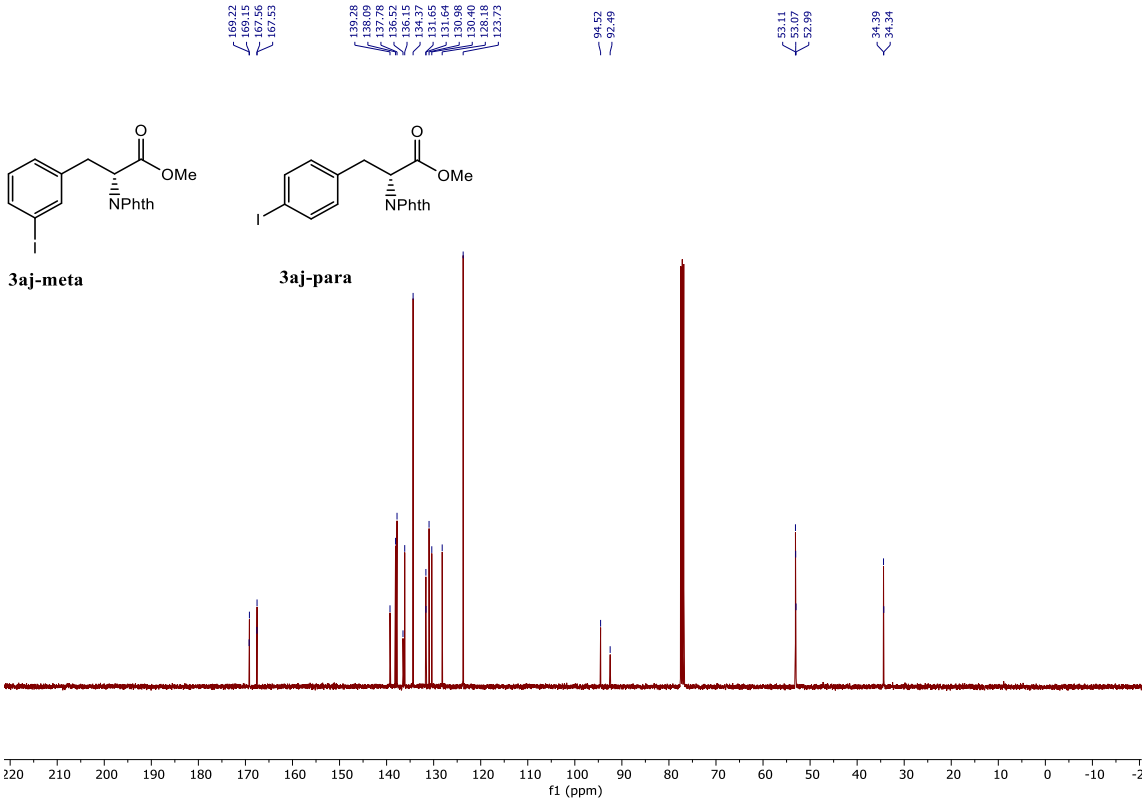
^{1}H NMR spectrum in $CDCl_3$:



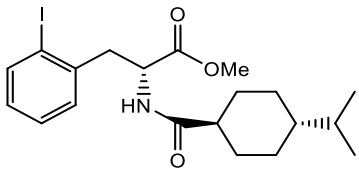
3aj-meta **3aj-para**



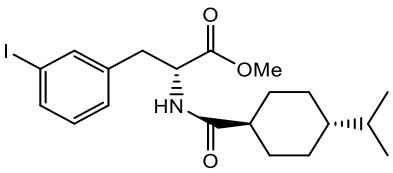
^{13}C NMR spectrum in $CDCl_3$:



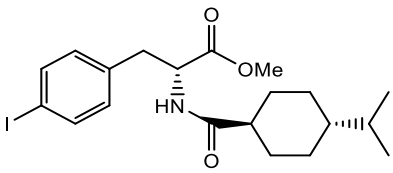
methyl (*R*)-3-(2-iodophenyl)-2-((1*r*,4*R*)-4-isopropylcyclohexane-1-carboxamido)propanoate (3ak-ortho), methyl (*R*)-3-(3-iodophenyl)-2-((1*r*,4*R*)-4-isopropylcyclohexane-1-carboxamido)propanoate (3ak-meta) and methyl (*R*)-3-(4-iodophenyl)-2-((1*r*,4*R*)-4-isopropylcyclohexane-1-carboxamido)propanoate (3ak-para)



3ak-ortho



3ak-meta



3ak-para

Following the general procedure B[a], using 1-iodo-2-nitrobenzene (**2**) (100 mg, 0.400 mmol, 2.0 equiv.), methyl ((1*r*,4*R*)-4-isopropylcyclohexane-1-carbonyl)-D-phenylalaninate (**1ak**) (66.3 mg, 0.200 mmol), and purification via silica column chromatography using pentane:EtOAc = 4:1 as the eluent, the target compound **3ak** was obtained as a colorless solid (37.0 mg, 40%, o:m:p =7:54:39).

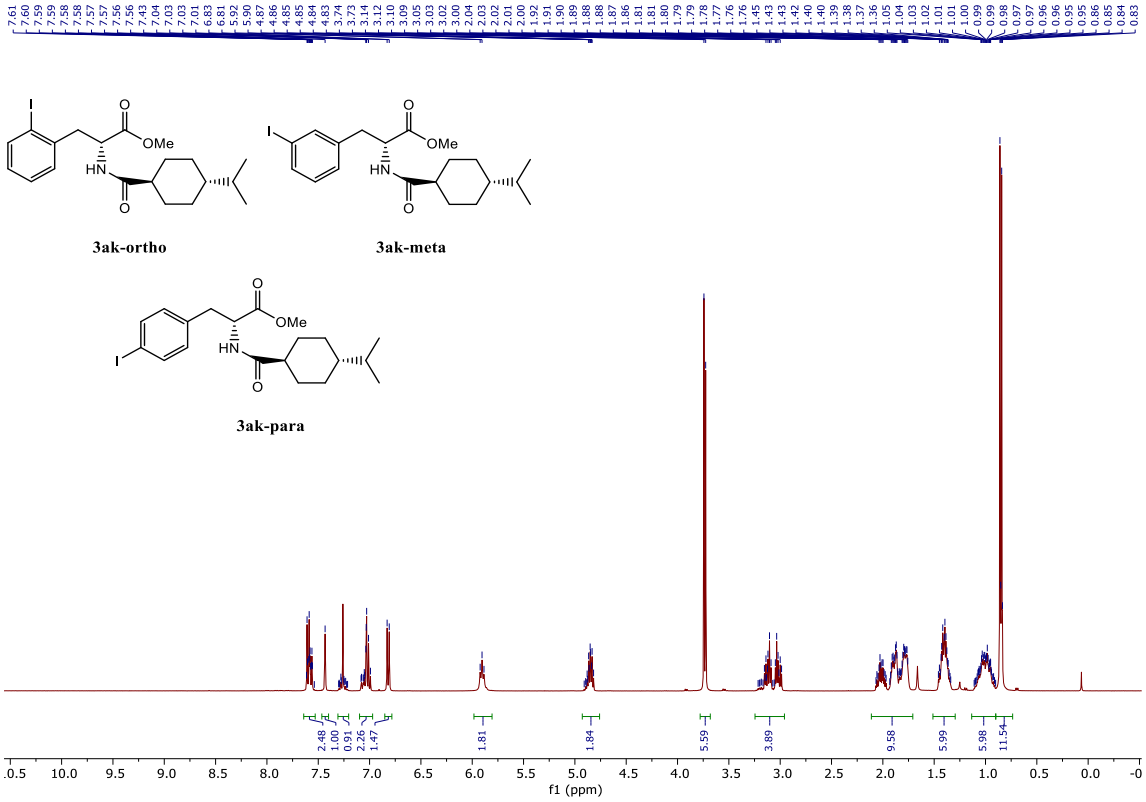
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.63-7.53 (m, $1H^m$+$2H^p$), 7.43 (s, $1H^m$), 7.31-7.20 (m, $2H^o$), 7.10-6.98 (m, $2H^m$+$2H^o$), 6.84-6.79 (m, $2H^p$), 5.96-5.85 (m, $1NH^o$+$1NH^m$+$1NH^p$), 4.92-4.78 (m, $1H^o$+$1H^m$+$1H^p$), 3.78-3.68 (m, $3H^o$+$3H^m$+$3H^p$), 3.25-2.95 (m, $2H^o$+$2H^m$+$2H^p$), 2.09-1.71 (m, $5H^o$+$5H^m$+$5H^p$), 1.51-1.30 (m, $3H^o$+$3H^m$+$3H^p$), 1.15-0.90 (m, $3H^o$+$3H^m$+$3H^p$), 0.89-0.79 (m, $6H^o$+$6H^m$+$6H^p$) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 175.7(4), 175.6(9), 172.1, 172.0, 138.7, 138.5, 137.7, 136.2, 135.8, 131.5, 130.3, 129.5, 128.6(4), 128.6(0), 127.2, 94.5, 92.7, 52.8(3), 52.7(9), 52.7, 52.6, 52.5, 52.4, 45.7, 45.6, 43.4, 43.3, 38.0, 37.5, 37.4, 32.9, 30.1, 29.9(4), 29.9(1), 29.6(4), 29.6(1), 29.1(4), 29.1(0), 29.0, 19.9 ppm.

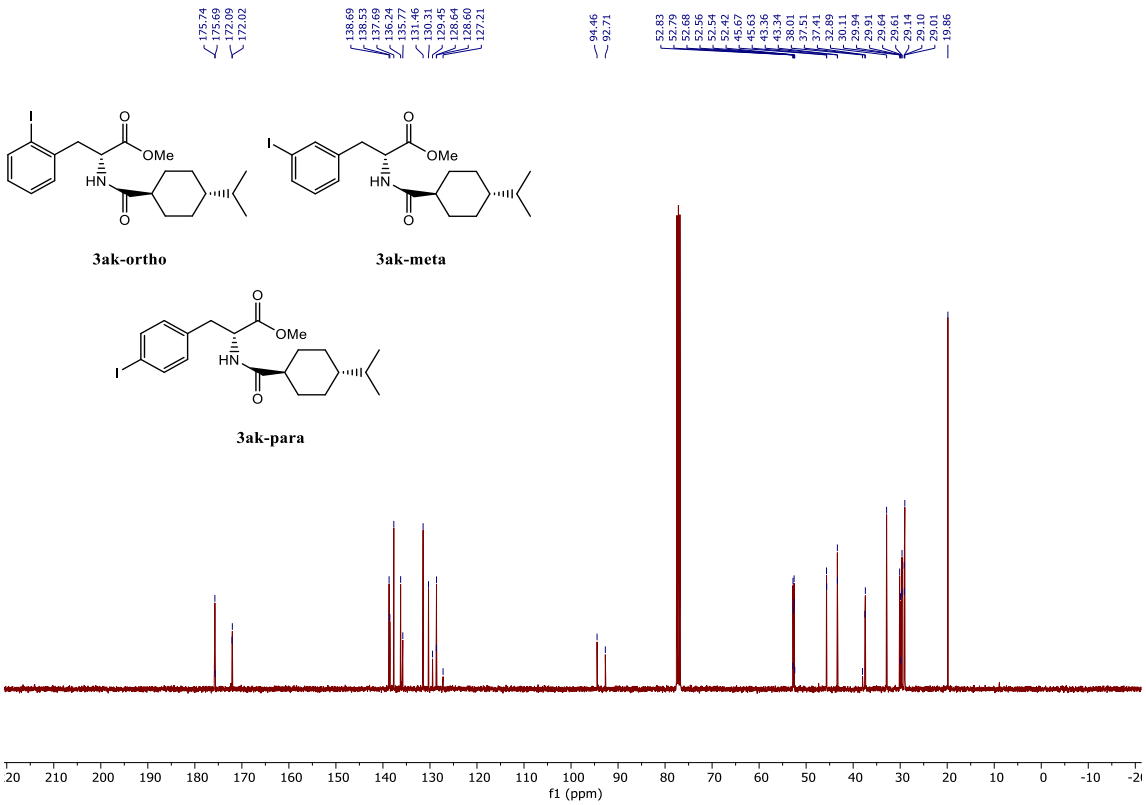
HRMS (ESI pos) m/z: Calcd for $C_{20}H_{28}NO_3INa^+$ 480.1006, Found 480.1002.

[a] Reaction was performed at 70 °C and 48 h reaction time.

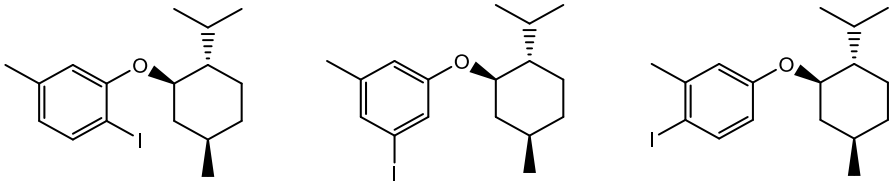
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



1-iodo-2-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)-4-methylbenzene (3al-α), 1-iodo-3-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)-5-methylbenzene (3al-β) and 1-iodo-4-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)-2-methylbenzene (3al-γ)



3al-α **3al-β** **3al-γ**

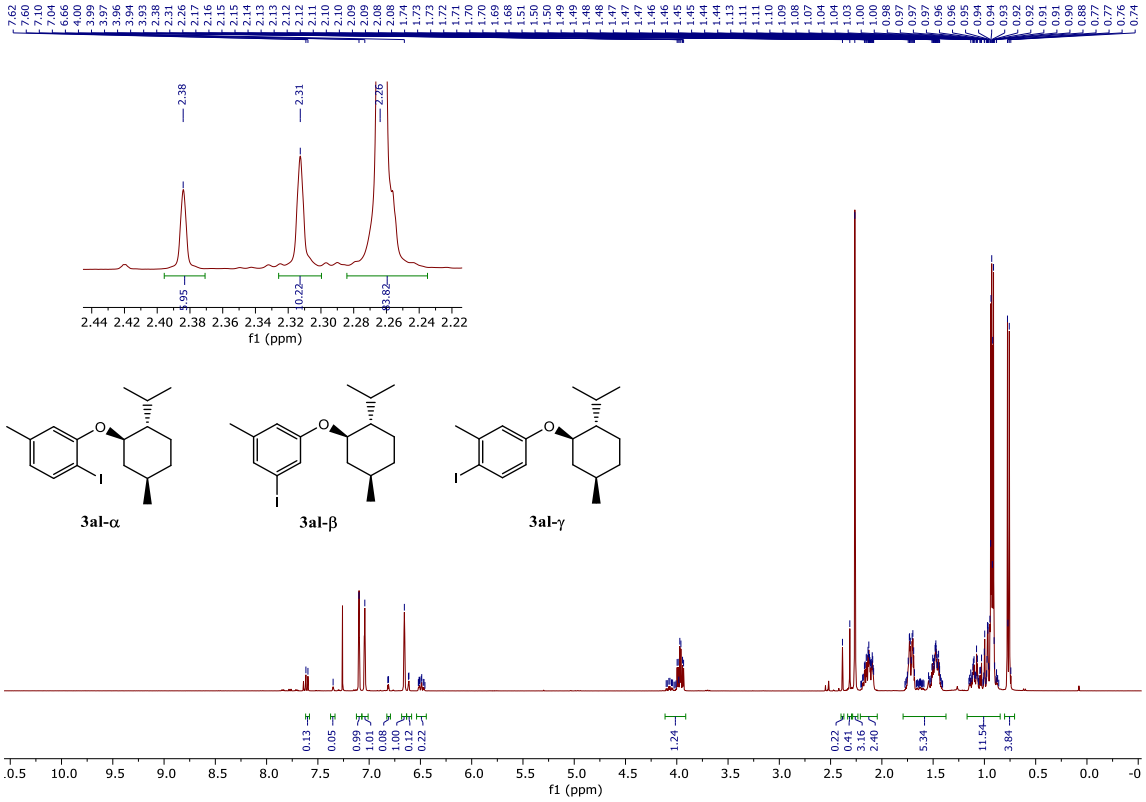
Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), 1-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)-3-methylbenzene (**1al**) (49.3 mg, 0.200 mmol), and purification via silica column chromatography using pentane:CH_2Cl_2 = 9:1 as the eluent, the target compound **3al** was obtained as a colorless liquid (43.2 mg, 58%, α:β:γ =10:84:6).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.61(d, *J* =7.9 Hz, 1H$^{\alpha}$), 7.35 (s, 1H$^{\gamma}$), 7.10 (s, 1H$^{\beta}$), 7.04 (s, 1H$^{\beta}$), 6.81 (d, *J* = 2.8 Hz, 1H$^{\gamma}$), 6.66 (s, 1H$^{\beta}$), 6.61 (d, *J* = 1.7 Hz, 1H$^{\alpha}$), 6.54-6.44 (m, 1H$^{\alpha}$+1H$^{\gamma}$), 4.13-3.89 (m, 1H$^{\alpha}$+1H$^{\beta}$+1H$^{\gamma}$), 2.38 (s, 3H$^{\gamma}$), 2.31 (s, 3H$^{\alpha}$), 2.26 (s, 3H$^{\beta}$), 2.22-2.05 (m, 2H$^{\alpha}$+2H$^{\beta}$+2H$^{\gamma}$), 1.80-1.39 (m, 4H$^{\alpha}$+4H$^{\beta}$+4H$^{\gamma}$), 1.17-0.84 (m, 9H$^{\alpha}$+9H$^{\beta}$+9H$^{\gamma}$), 0.81-0.73 (m, 3H$^{\alpha}$+3H$^{\beta}$+3H$^{\gamma}$) ppm.

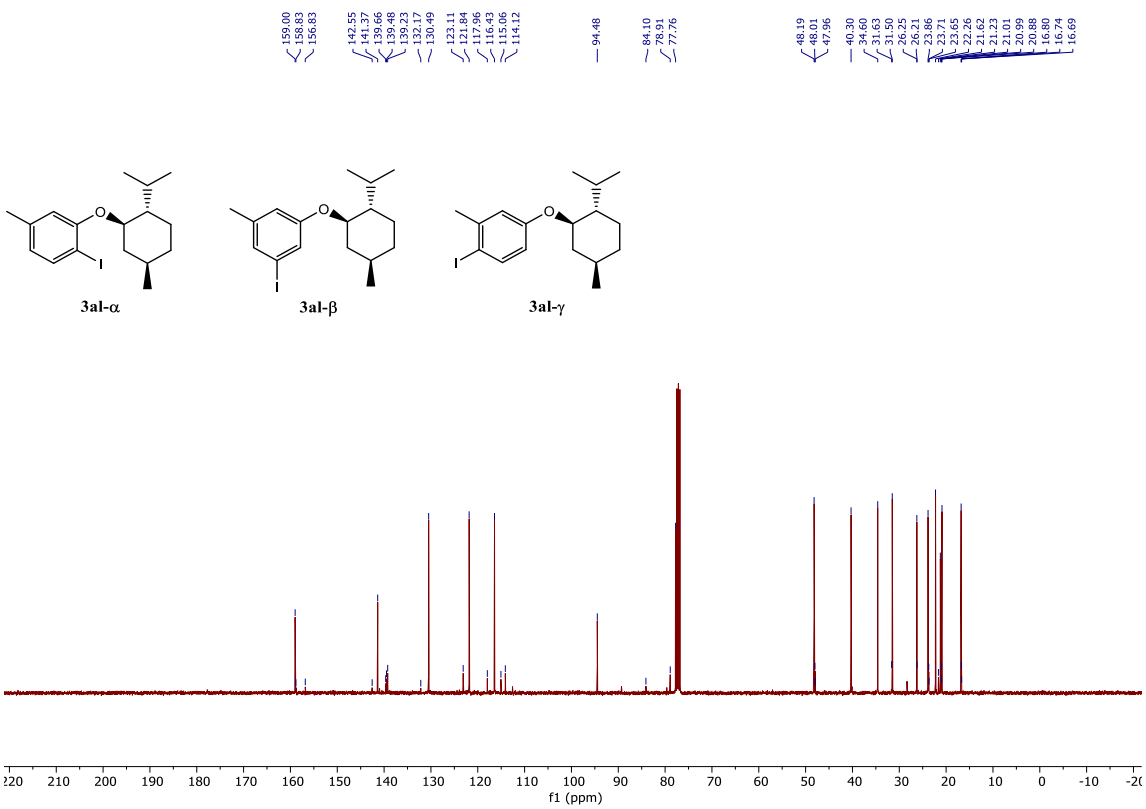
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.0, 159.8, 156.8, 142.6, 141.4, 139.7, 139.5, 139.2, 130.5, 123.1, 121.8, 118.0, 116.4, 115.1, 114.1, 94.5, 84.1, 78.9, 77.8, 48.2, 48.0, 47.0, 40.3, 34.6, 31.6, 31.5, 26.3, 26.2, 23.9, 23.7(1), 23.6(5), 22.3, 21.6, 21.2, 21.0(1), 20.9(9), 20.9, 16.8, 16.7(4), 16.6(9) ppm.

HRMS (EI pos) m/z: Calcd for $C_{17}H_{25}OI^+$ 372.0945, Found 372.0945.

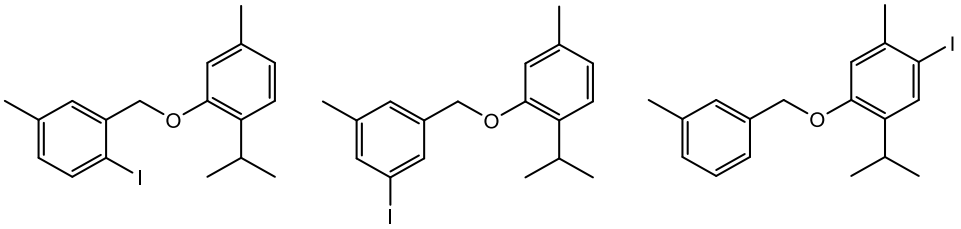
^{1}H NMR spectrum in $CDCl_3$:



^{13}C NMR spectrum in $CDCl_3$:



1-iodo-2-((2-isopropyl-5-methylphenoxy)methyl)-4-methylbenzene (3am-α), 2-((3-iodo-5-methylbenzyl)oxy)-1-isopropyl-4-methylbenzene (3am-β) and 1-iodo-5-isopropyl-2-methyl-4-((3-methylbenzyl)oxy)benzene (3am-α´)



3am-α 3am-β 3am-α´

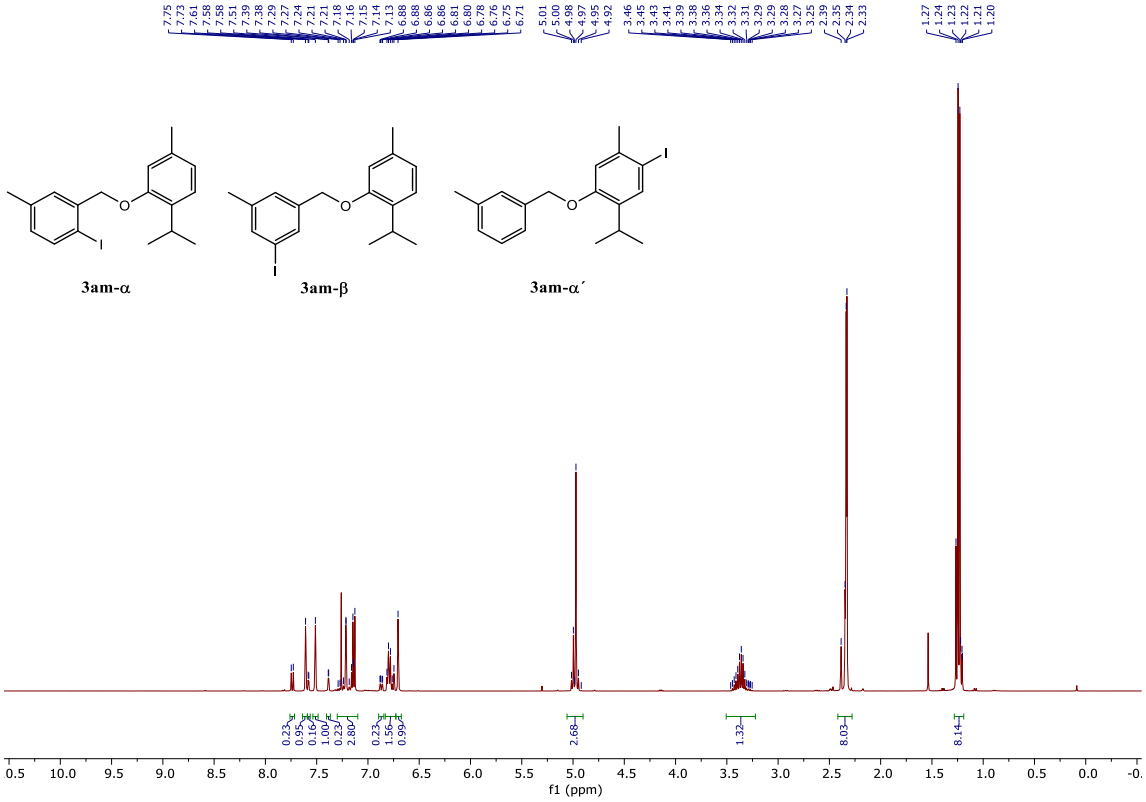
Following the general procedure B, using 1-iodo-2-nitrobenzene (**2**) (150 mg, 0.600 mmol, 3.0 equiv.), 1-isopropyl-4-methyl-2-((3-methylbenzyl)oxy)benzene (**1am**) (50.9 mg, 0.200 mmol), and purification via silica column chromatography using pentane:CH_2Cl_2 = 9:1 as the eluent, the target compound **3am** was obtained as a colorless oil (30.4 mg, 40%, α:β:α´ =18:75:7).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.74 (d, *J* = 8.0 Hz, 1H$^{\alpha}$), 7.61 (s, 1H$^{\beta}$), 7.59-7.56 (m, 2H$^{\alpha'}$), 7.51 (s, 1H$^{\beta}$), 7.41-7.37 (m, 1H$^{\alpha}$), 7.31-7.10 (m, 1H$^{\alpha}$+2H$^{\beta}$+3H$^{\alpha'}$), 6.87 (d, *J* = 8.0, 2.1 Hz, 1H$^{\alpha}$), 6.83-6.73 (m, 2H$^{\alpha}$+1H$^{\beta}$+1H$^{\alpha'}$), 6.71 (s, 1H$^{\beta}$), 5.03-4.91 (m, 2H$^{\alpha}$+2H$^{\beta}$+2H$^{\alpha'}$), 3.49-3.23 (m, 1H$^{\alpha}$+1H$^{\beta}$+1H$^{\alpha'}$), 2.41-2.29 (m, 6H$^{\alpha}$+6H$^{\beta}$+6H$^{\alpha'}$), 1.29-1.18 (m, 6H$^{\alpha}$+6H$^{\beta}$+6H$^{\alpha'}$) ppm.

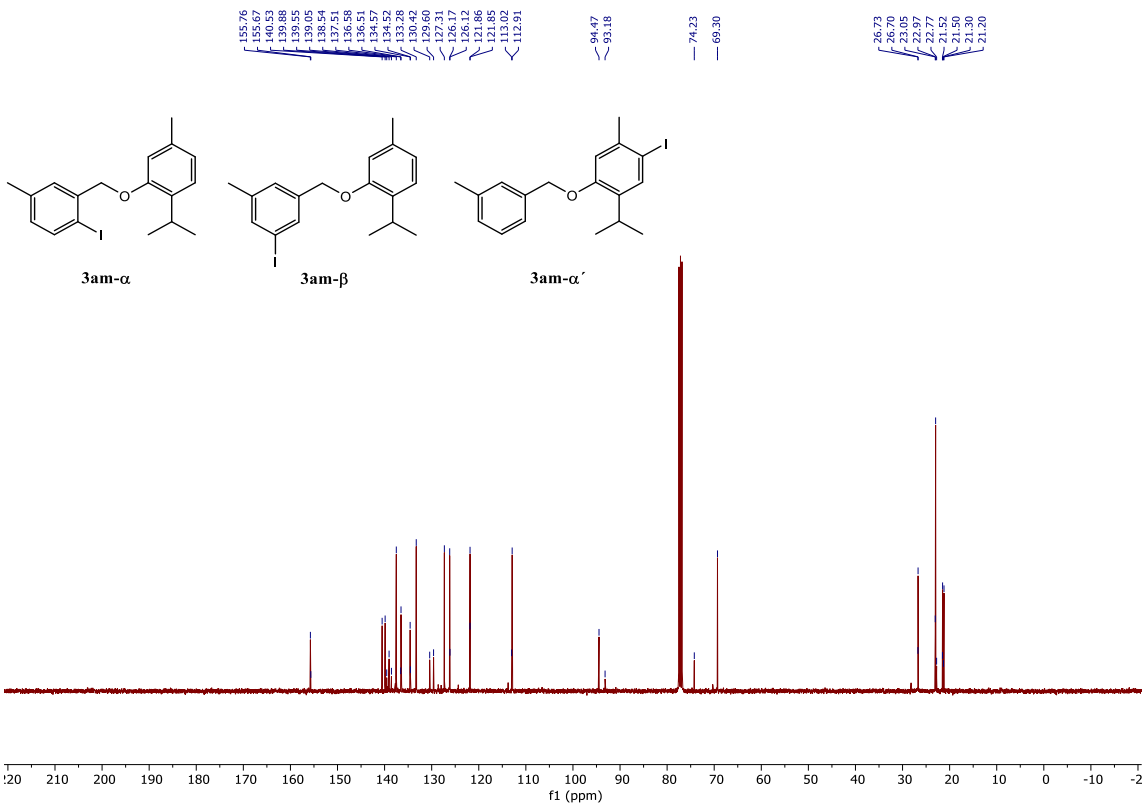
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.8, 155.7, 140.5, 139.9, 139.6, 139.1, 138.5, 137.5, 136.6, 136.5, 134.6, 134.5, 133.3, 130.4, 129.6, 127.3, 126.2, 126.1, 121.8(6), 121.8(5), 113.0, 112.9, 94.5, 93.2, 74.2, 69.3, 26.7(3), 26.7(0), 23.1, 23.0, 22.8, 21.5(2), 21.5(0), 21.3, 21.2 ppm.

HRMS (ESI pos) m/z: Calcd for $C_{18}H_{21}OINa^+$ 403.0529, Found 403.0530.

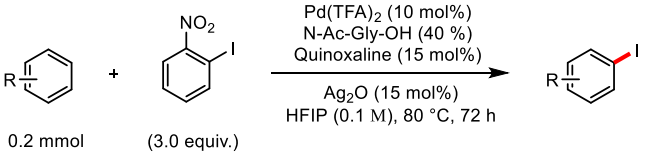
^{1}H NMR spectrum in $CDCl_3$:

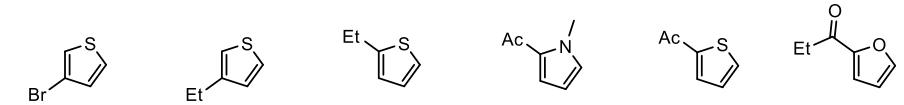


^{13}C NMR spectrum in $CDCl_3$:

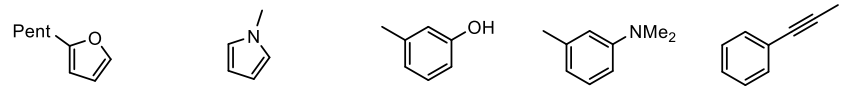


Scheme S43: Unsuccessful Entries of the C–H Iodination

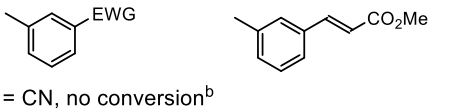




no conversion | no conversion[a] | no conversion[a] | traces | no conversion | traces

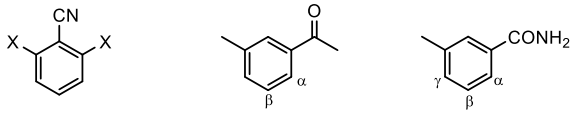


decomposition | decomposition[a] | traces | no reaction[a] | decomposition[a]



EWG = CN, no conversion[b]
EWG = NO_2, no conversion[b]
EWG = CF_3, traces[b]
EWG = COH, traces[b]

traces[b] | traces | 12%[c] β-only



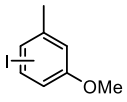
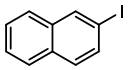
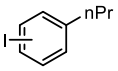
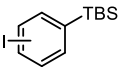
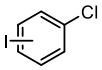
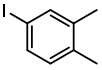
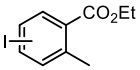
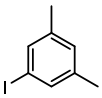
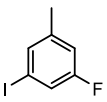
X = Me, traces
X = OMe, traces

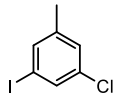
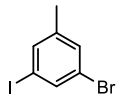
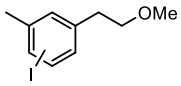
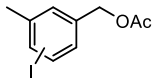
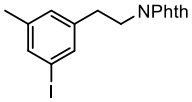
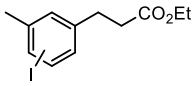
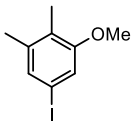
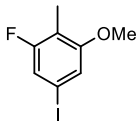
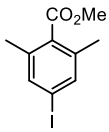
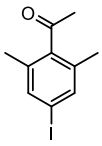
18%[c]
α:β = 32:68

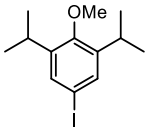
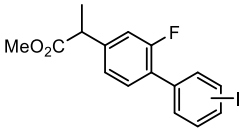
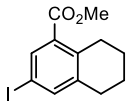
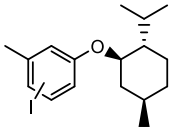
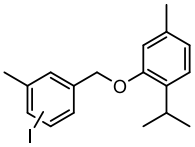
16%[b,c]
α:β = 59:41

[a]I-Reagent = 2.0 equiv.; 70 °C, 48 h
[b]I-Reagent = 4.0 equiv.;$AgNO_3$ (30 mol%), 100 °C
[c]Isolated Yield

5 Comparison of Isolated Selectivity and Selectivity of Crude Reaction Mixture (Selected Examples)

Code	Structure	Selectivity of Isolated Compound	Selectivity from Crude Reaction Mixture
3a		β-only	α:β:γ = 12:85:3
3b		β-only	β-only
3c		m:p = 68:32	m:p = 69:31
3d		m:p = 72:28	m:p = 73:27
3e		m:p = 82:18	m:p = 78:22
3f		m:p = 62:38	m:p = 59:41
3i		β-only	β-only
3k		β:β´ = 38:62	β:β´ = 37:63
3l		β-only	β-only
3m		β-only	β-only

Code	Structure	Selectivity of Isolated Compound	Selectivity from Crude Reaction Mixture
3n		β-only	β-only
3o		β-only	β-only
3r		α:β = 20:80	α:β = 23:77
3s		α:β = 8:92	α:β = 8:92
3t		β-only	β-only
3v		α:β = 6:94	α:β = 5:95
3w		β-only	β-only
3x		β-only	β-only
3y		β-only	β-only
3ab		β-only	β-only

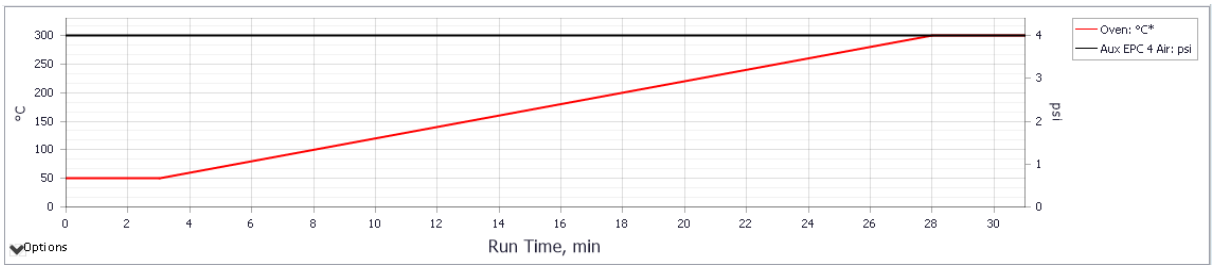
Code	Structure	Selectivity of Isolated Compound	Selectivity from Crude Reaction Mixture
3ac		β-only	β-only
3ag		m:p = 69:31	m:p = 68:32
3ah		β-only	β-only
3al		α:β:γ = 10:84:6	α:β:γ = 4:92:4
3am		α:β:α′ = 18:75:7	α:β:α′ = 19:79:3

A comparison of the regioselectivities resulting from the iodination reaction (crude reaction mixture) and the regioselectivities obtained after isolation of the iodinated product determined by GC-FID analysis confirms that the values are nearly identical to one another. No influence or change has been caused by solely isolating/removing one isomer during the purification procedure leading to falsely good regioselectivities. Hence, the regioselectivities shown for the respective scope entries can be considered direct and intrinsic results produced by the reaction conditions.

GC-data of selected examples

Method Information:

1) Standard method

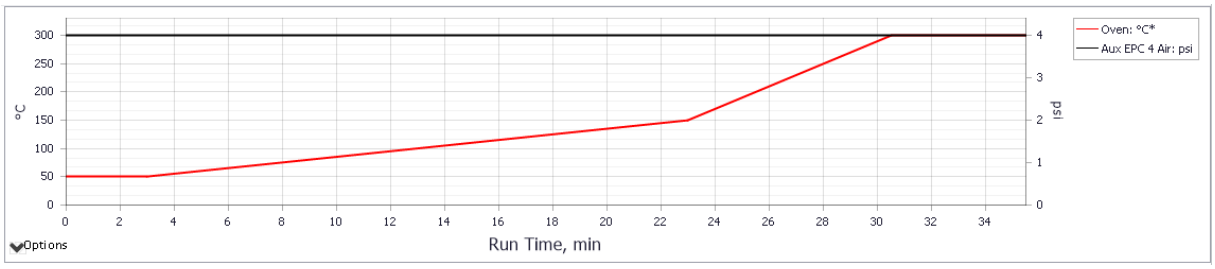


	Rate °C/min	Value °C	Hold Time min	Run Time min
(Initial)		50	3	3
Ramp 1	10	300	3	31
*				

Post Run: 50 °C

Post Run Time: 0 min

2) Method for separation of compound **3a**

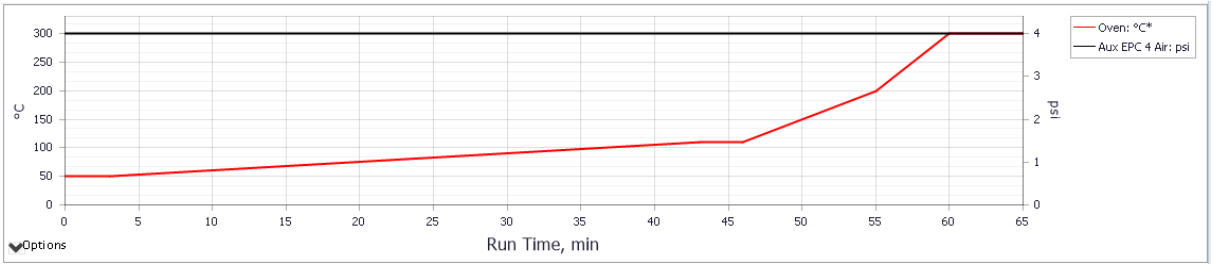


	Rate °C/min	Value °C	Hold Time min	Run Time min
(Initial)		50	3	3
Ramp 1	5	150	0	23
Ramp 2	20	300	5	35.5
*				

Post Run: 50 °C

Post Run Time: 0 min

3) Method for separation of compound **3c**

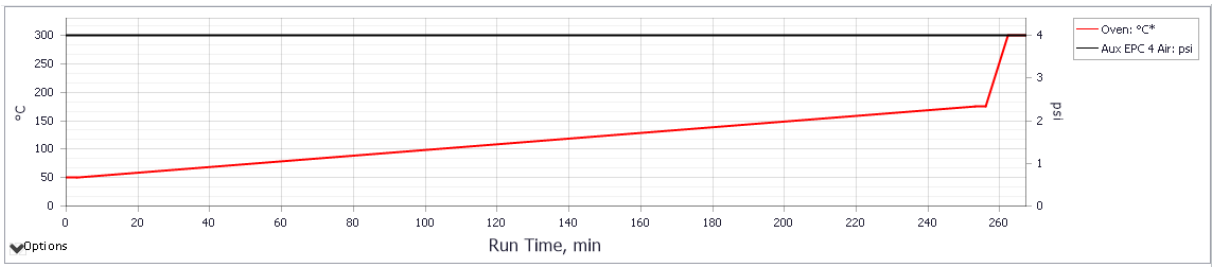


	Rate °C/min	Value °C	Hold Time min	Run Time min
(Initial)		50	3	3
Ramp 1	1.5	110	3	46
Ramp 2	10	200	0	55
Ramp 3	20	300	5	65
*				

Post Run: 50 °C

Post Run Time: 0 min

4) Method for the separation of compound **3f**

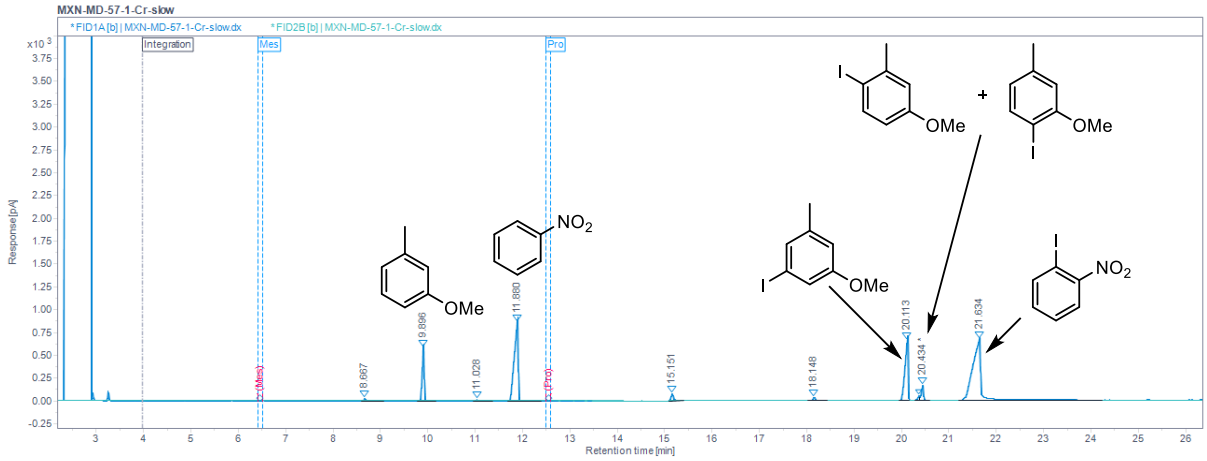


	Rate °C/min	Value °C	Hold Time min	Run Time min
(Initial)		50	3	3
Ramp 1	0.5	175	3	256
Ramp 2	20	300	5	267.25
*				

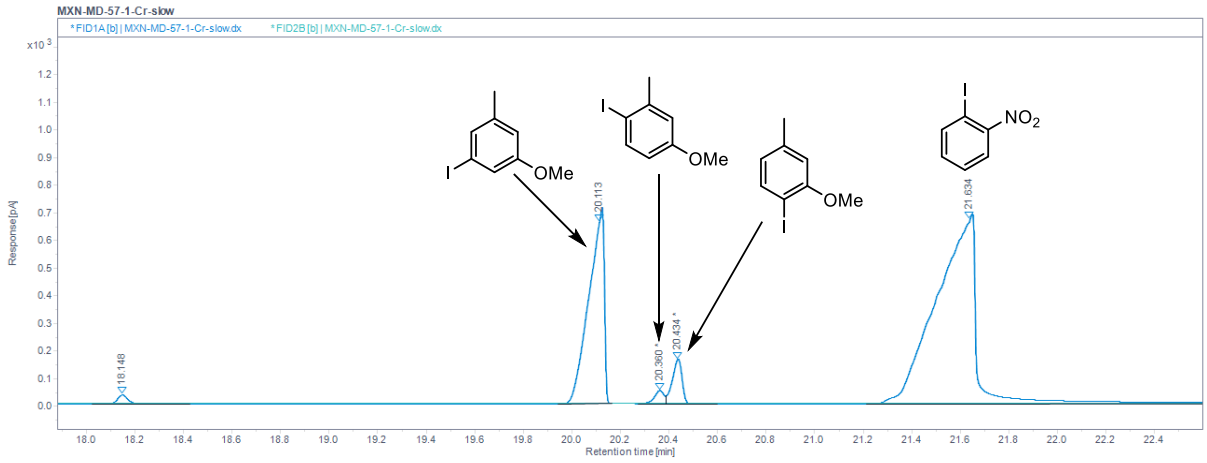
Post Run: 50 °C

Post Run Time: 0 min

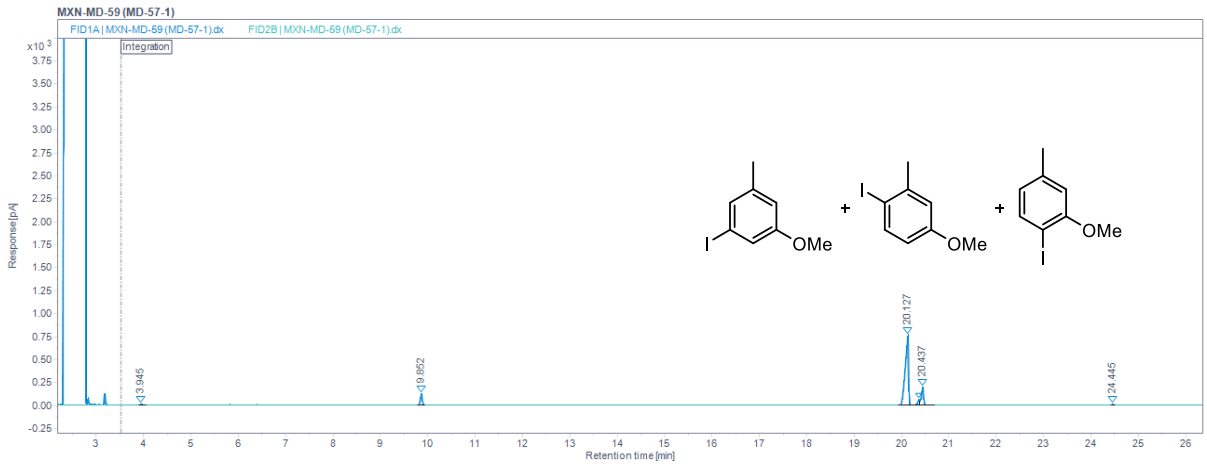
1-iodo-2-methoxy-4-methylbenzene (3a-α), 1-iodo-3-methoxy-5-methylbenzene (3a-β) and 1-iodo-4-methoxy-2-methylbenzene (3a-γ): GC-FID trace of crude reaction mixture



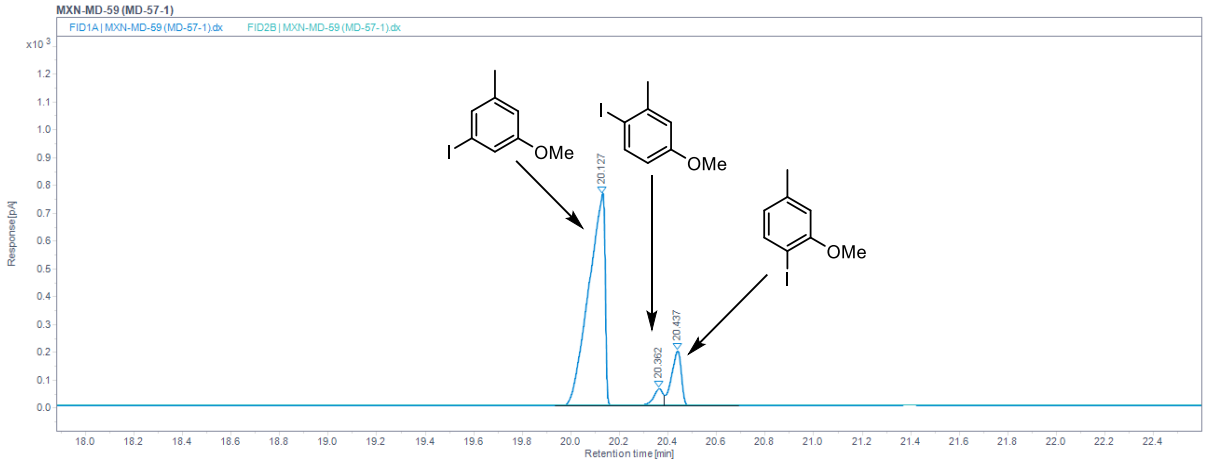
1-iodo-2-methoxy-4-methylbenzene (3a-α), 1-iodo-3-methoxy-5-methylbenzene (3a-β) and 1-iodo-4-methoxy-2-methylbenzene (3a-γ): GC-FID trace of crude reaction mixture (close-up)



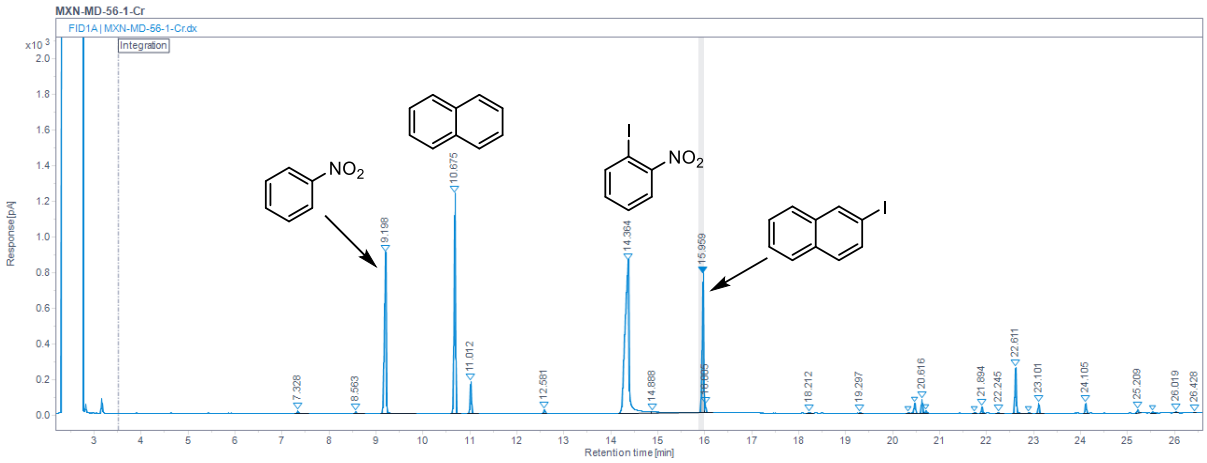
1-iodo-2-methoxy-4-methylbenzene (3a-α), 1-iodo-3-methoxy-5-methylbenzene (3a-β) and 1-iodo-4-methoxy-2-methylbenzene (3a-γ): GC-FID trace of isolated compound



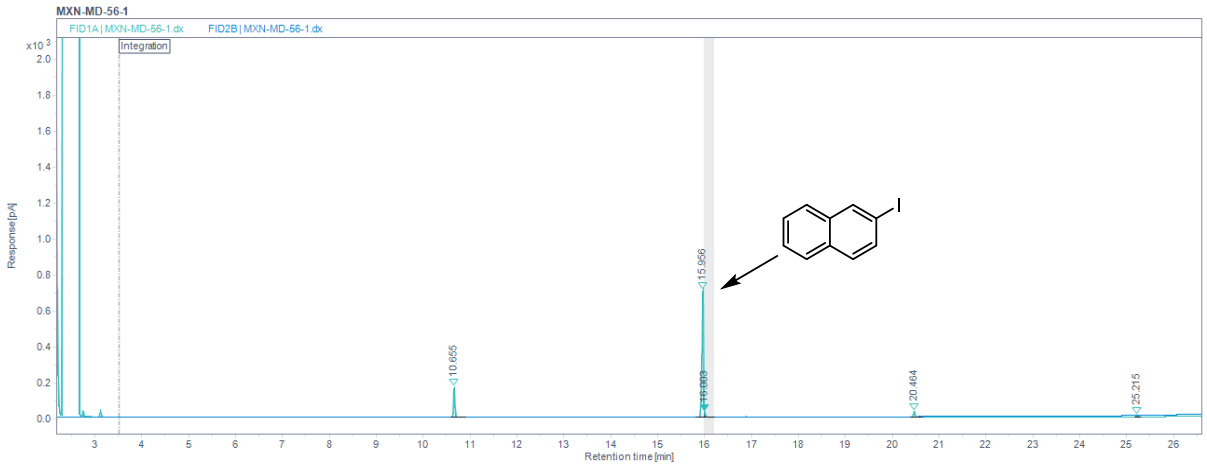
1-iodo-2-methoxy-4-methylbenzene (3a-α), 1-iodo-3-methoxy-5-methylbenzene (3a-β) and 1-iodo-4-methoxy-2-methylbenzene (3a-γ): GC-FID trace of isolated compound (close-up)



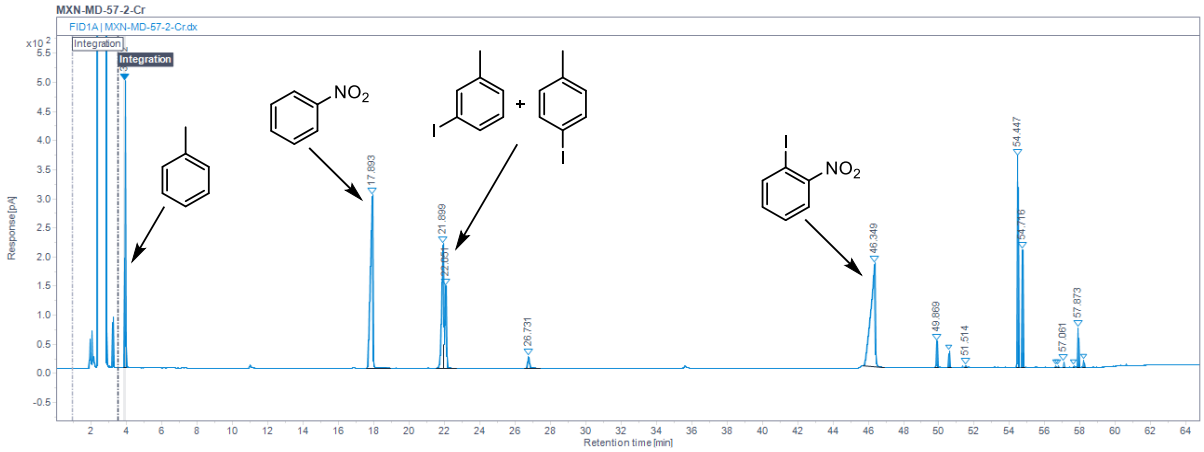
2-iodonaphthalene (3b): GC-FID trace of crude reaction mixture



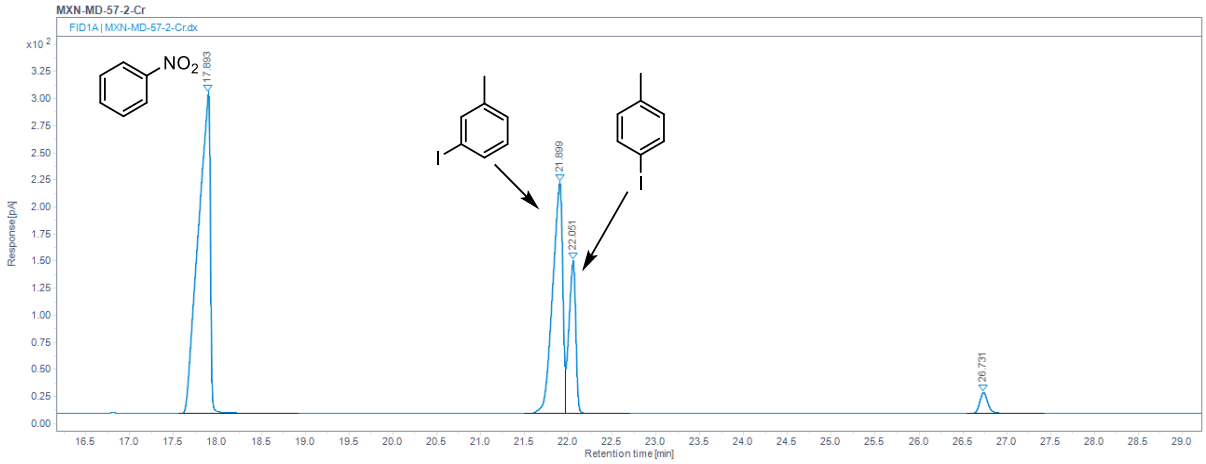
2-iodonaphthalene (3b): GC-FID trace of isolated compound



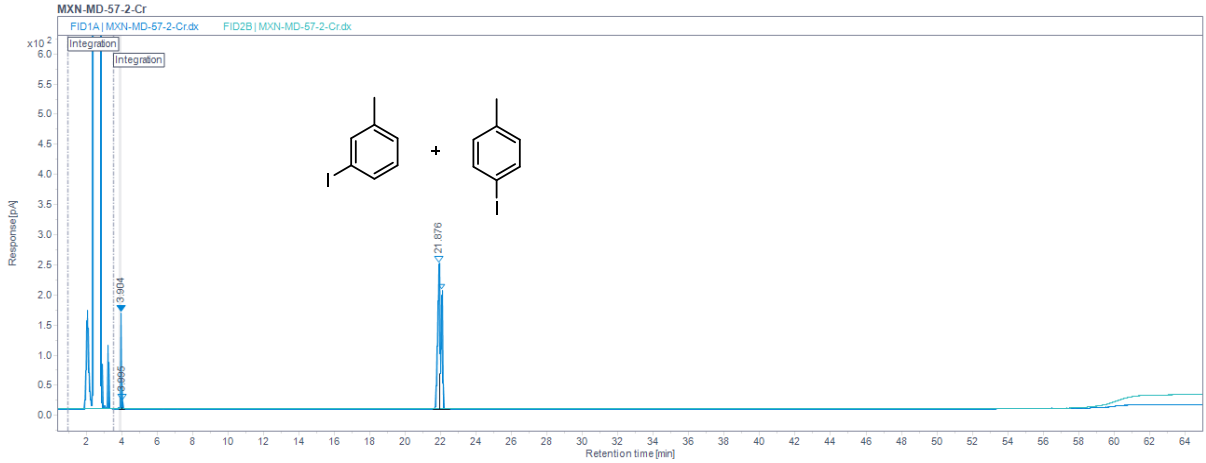
1-iodo-3-methylbenzene (3c-meta) and 1-iodo-4-methylbenzene (3c-para): GC-FID trace of crude reaction mixture



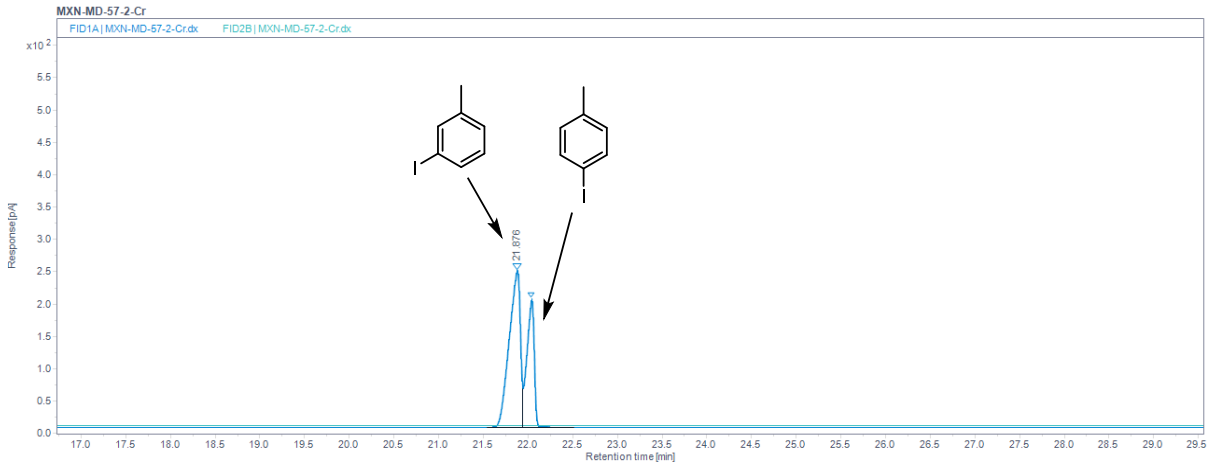
1-iodo-3-methylbenzene (3c-meta) and 1-iodo-4-methylbenzene (3c-para): GC-FID trace of crude reaction mixture (close-up)



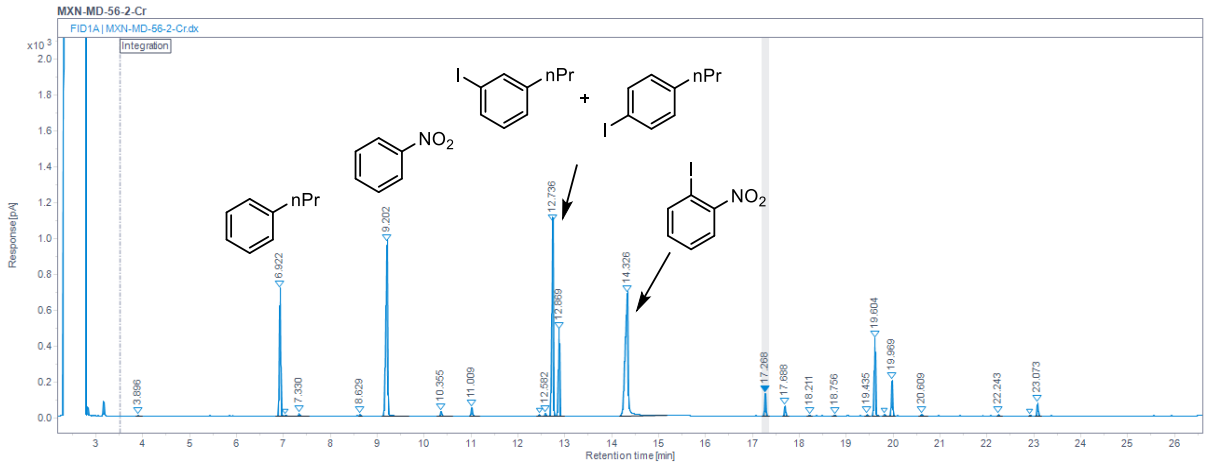
1-iodo-3-methylbenzene (3c-meta) and 1-iodo-4-methylbenzene (3c-para): GC-FID trace of isolated compound



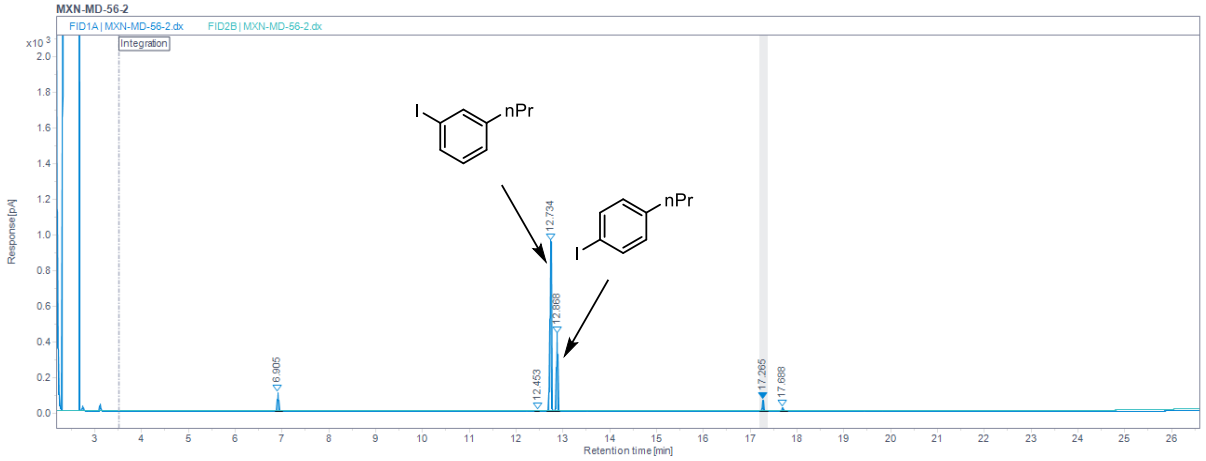
1-iodo-3-methylbenzene (3c-meta) and 1-iodo-4-methylbenzene (3c-para): GC-FID trace of isolated compound (close-up)



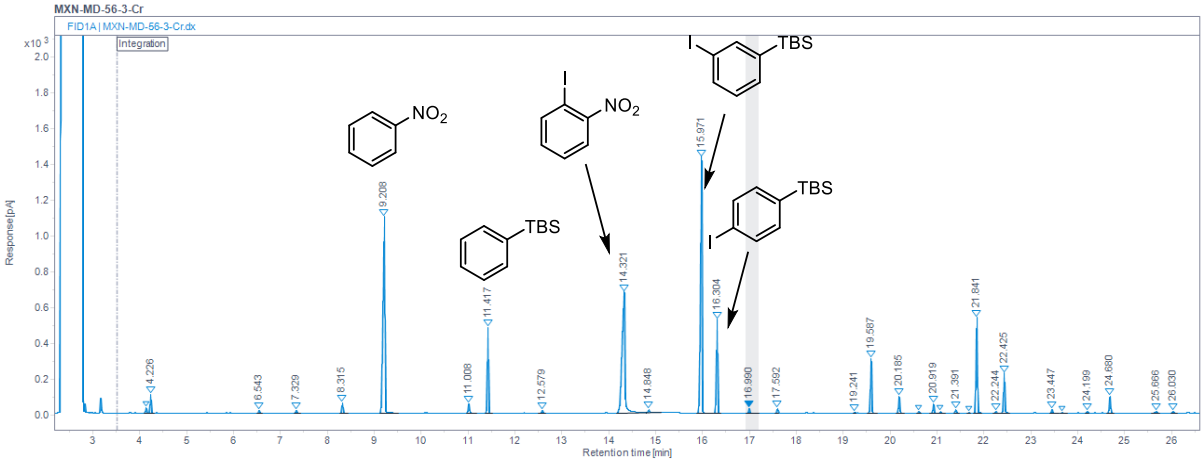
1-iodo-3-propylbenzene (3d-meta) and 1-iodo-4-propylbenzene (3d-para): GC-FID trace of crude reaction mixture



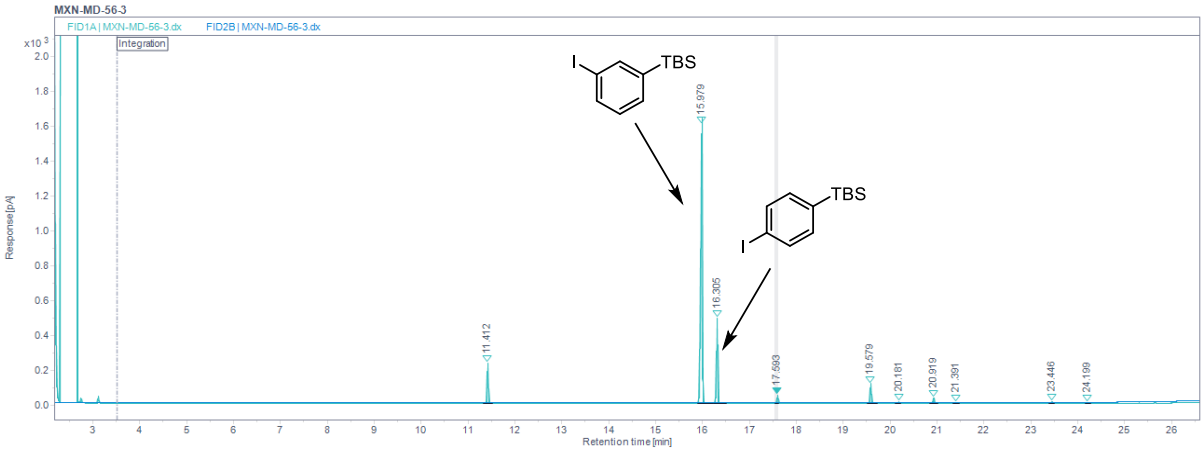
1-iodo-3-propylbenzene (3d-meta) and 1-iodo-4-propylbenzene (3d-para): GC-FID trace of isolated compound



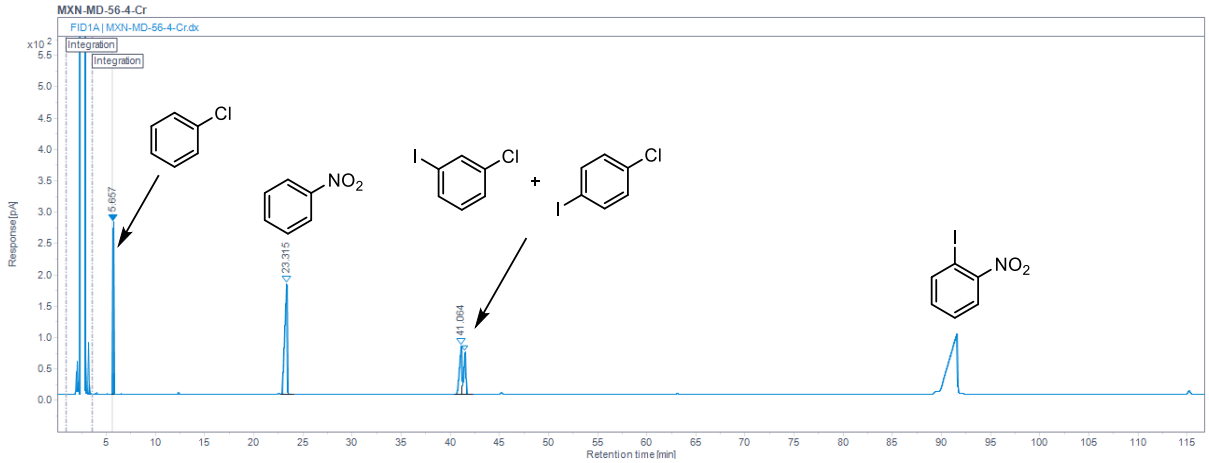
***tert*-butyl(3-iodophenyl)dimethylsilane (3e-meta) and *tert*-butyl(4-iodophenyl)dimethylsilane (3e-para): GC-FID trace of crude reaction mixture**



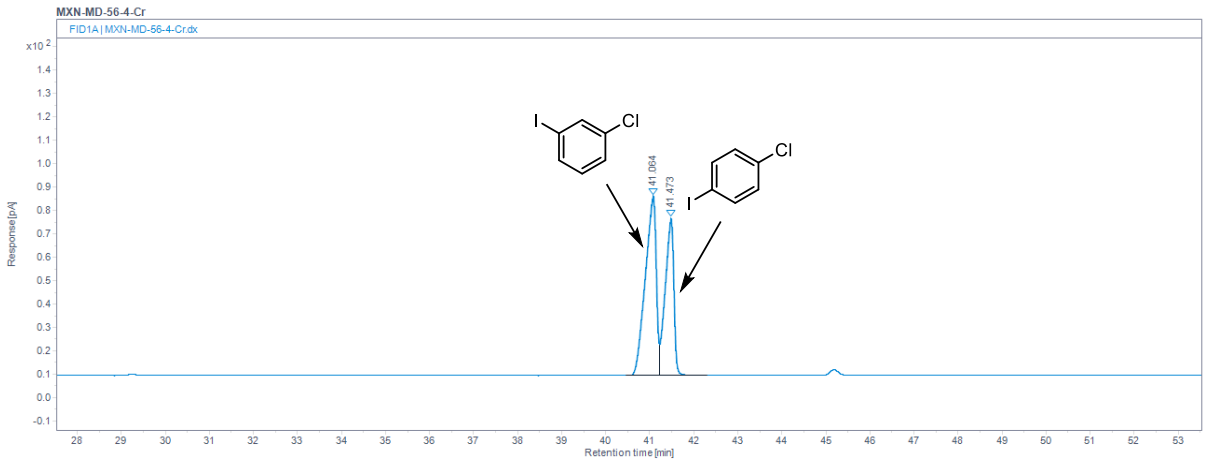
***tert*-butyl(3-iodophenyl)dimethylsilane (3e-meta) and *tert*-butyl(4-iodophenyl)dimethylsilane (3e-para): GC-FID trace of isolated compound**



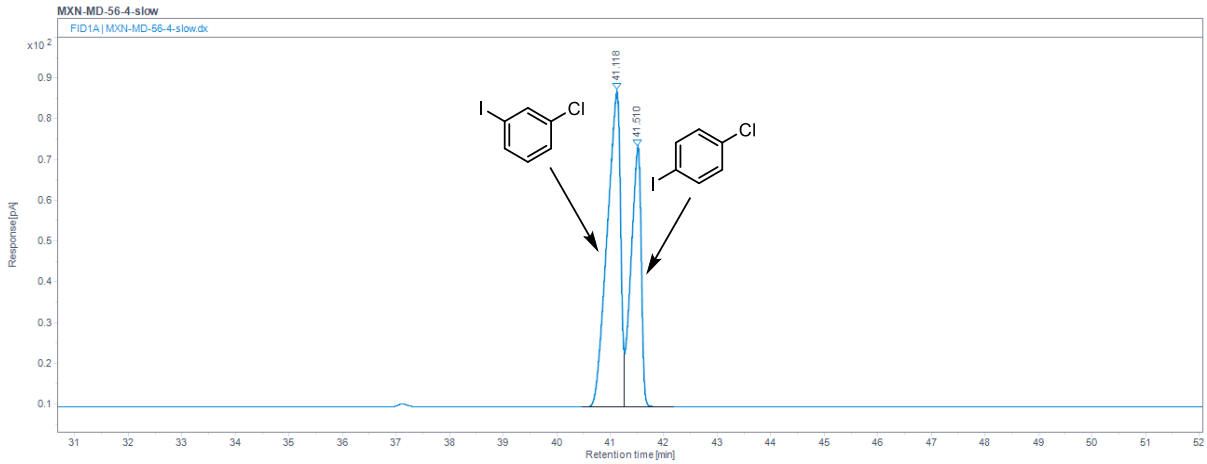
1-chloro-3-iodobenzene (3f-meta) and 1-chloro-4-iodobenzene (3f-para): GC-FID trace of crude reaction mixture



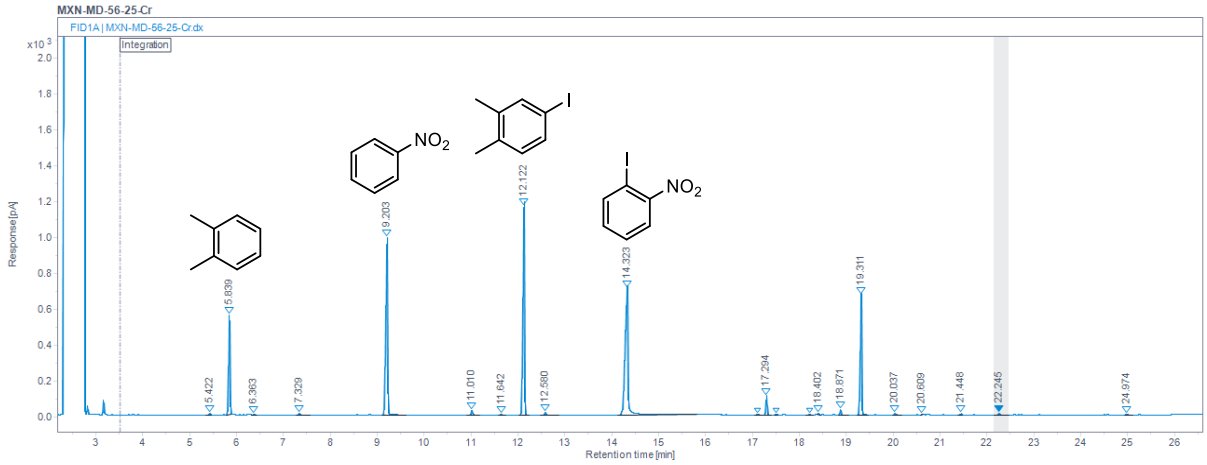
1-chloro-3-iodobenzene (3f-meta) and 1-chloro-4-iodobenzene (3f-para): GC-FID trace of crude reaction mixture (close-up).



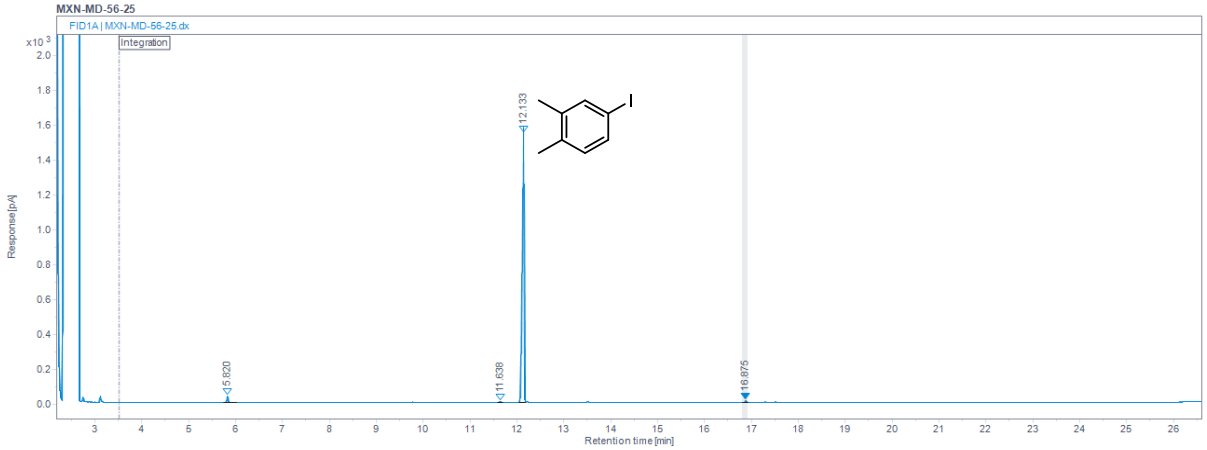
1-chloro-3-iodobenzene (3f-meta) and 1-chloro-4-iodobenzene (3f-para): GC-FID trace of isolated compound (close-up).



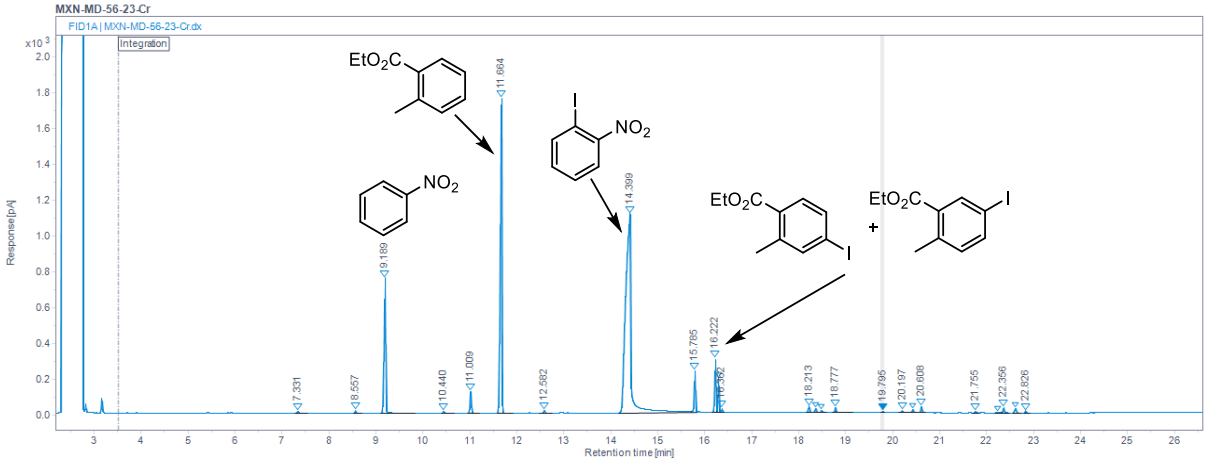
4-iodo-1,2-dimethylbenzene (3i): GC-FID trace of crude reaction mixture



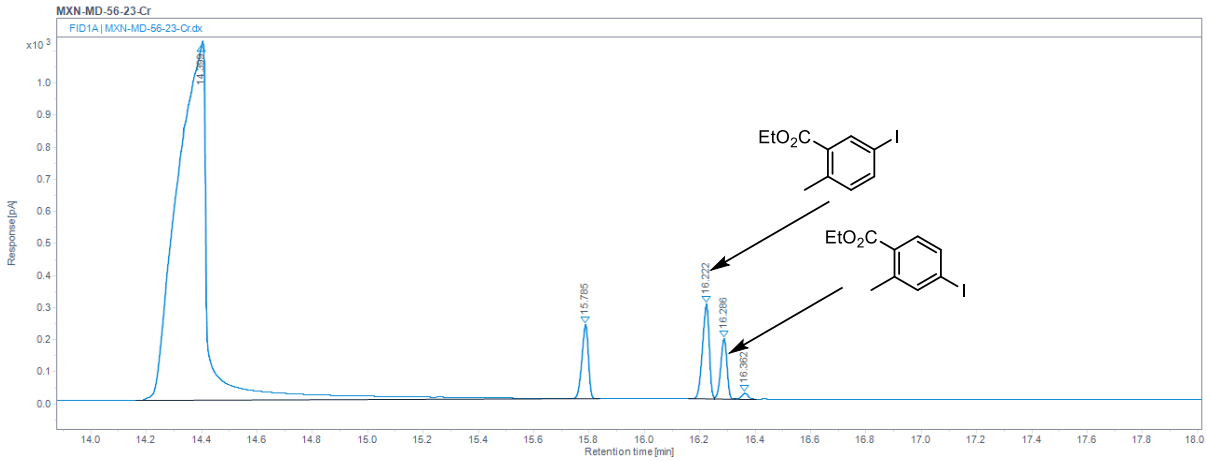
4-iodo-1,2-dimethylbenzene (3i): GC-FID trace of isolated compound



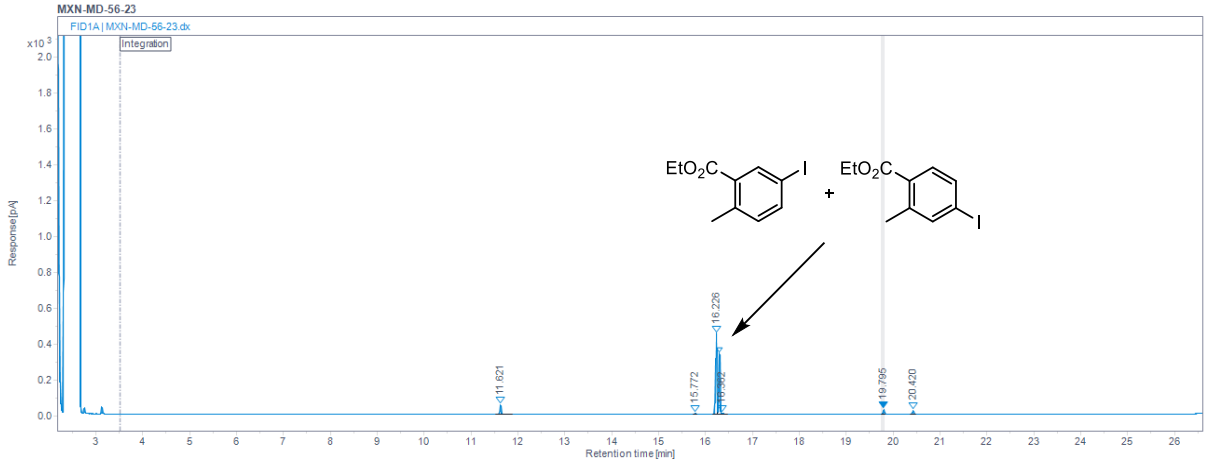
ethyl 4-iodo-2-methylbenzoate (3k-β) and ethyl 5-iodo-2-methylbenzoate (3k-β´): GC-FID trace of crude reaction mixture



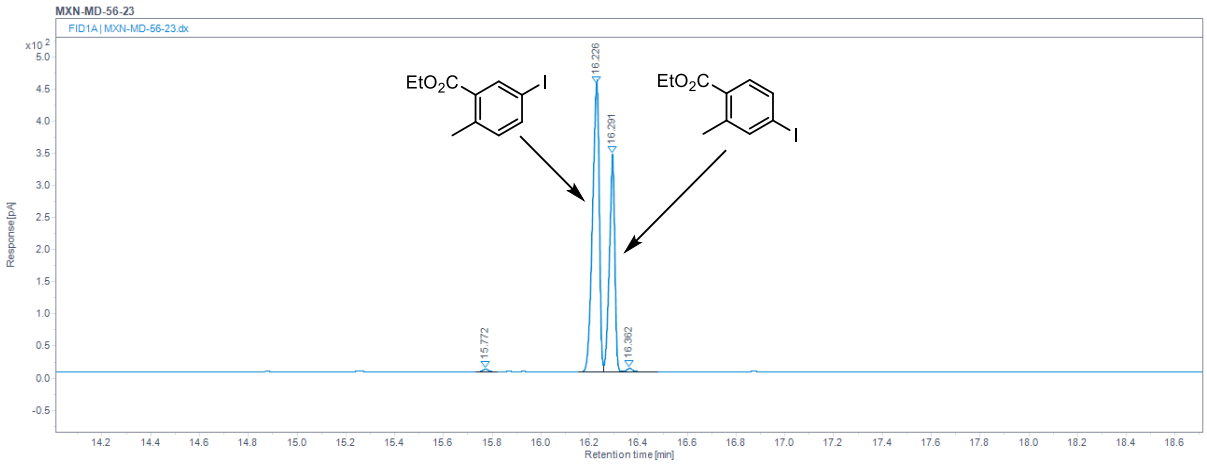
ethyl 4-iodo-2-methylbenzoate (3k-β) and ethyl 5-iodo-2-methylbenzoate (3k-β´): GC-FID trace of crude reaction mixture (close-up)



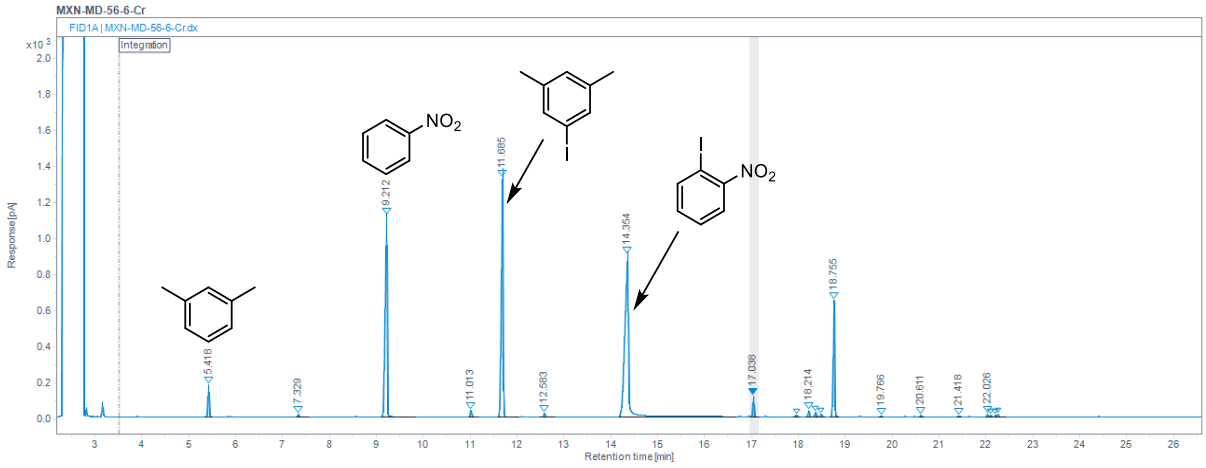
ethyl 4-iodo-2-methylbenzoate (3k-β) and ethyl 5-iodo-2-methylbenzoate (3k-β´): GC-FID trace of isolated compound



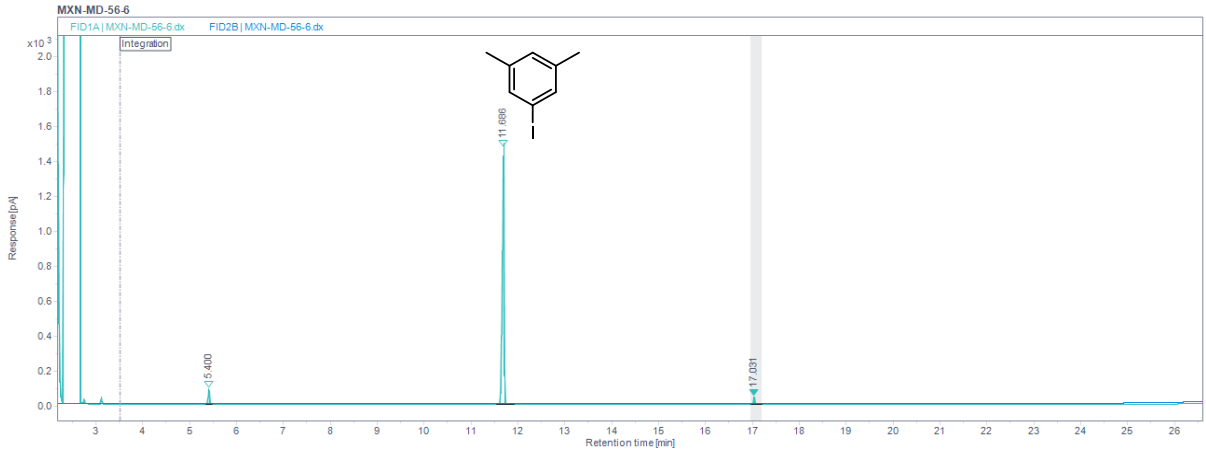
ethyl 4-iodo-2-methylbenzoate (3k-β) and ethyl 5-iodo-2-methylbenzoate (3k-β´): GC-FID trace of isolated compound (close-up)



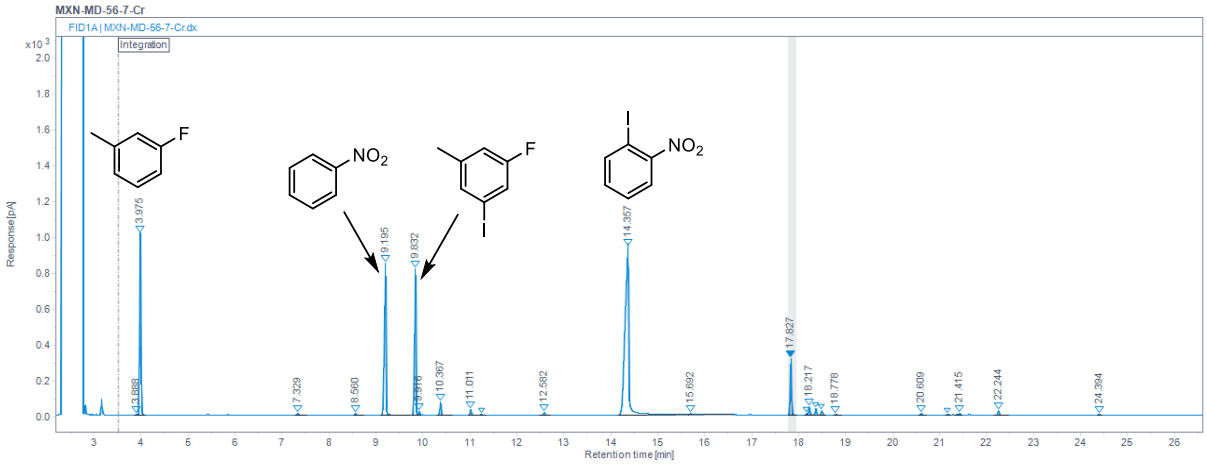
1-iodo-3,5-dimethylbenzene (3l): GC-FID trace of crude reaction mixture



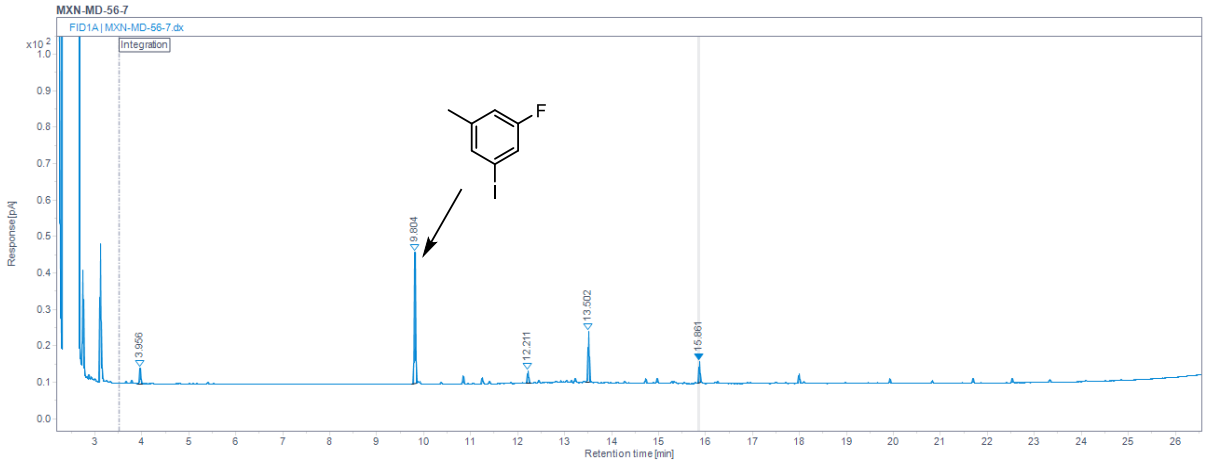
1-iodo-3,5-dimethylbenzene (3l): GC-FID trace of isolated compound



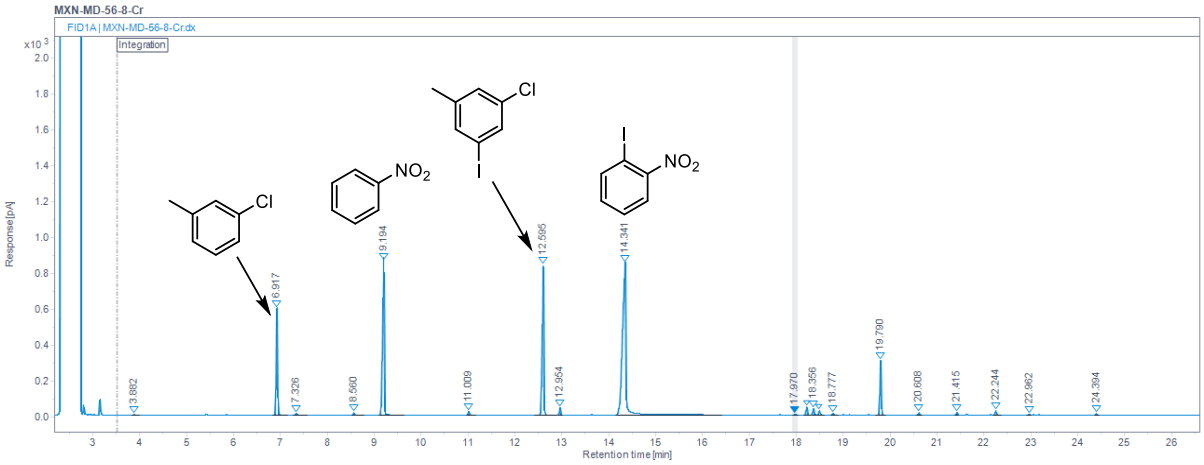
1-fluoro-3-iodo-5-methylbenzene (3m): GC-FID trace of crude reaction mixture



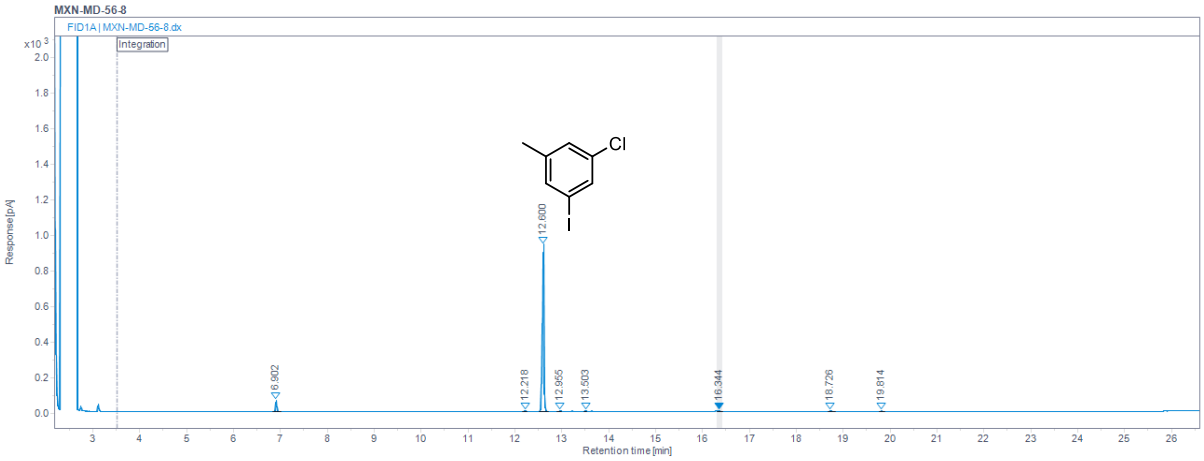
1-fluoro-3-iodo-5-methylbenzene (3m): GC-FID trace of isolated compound



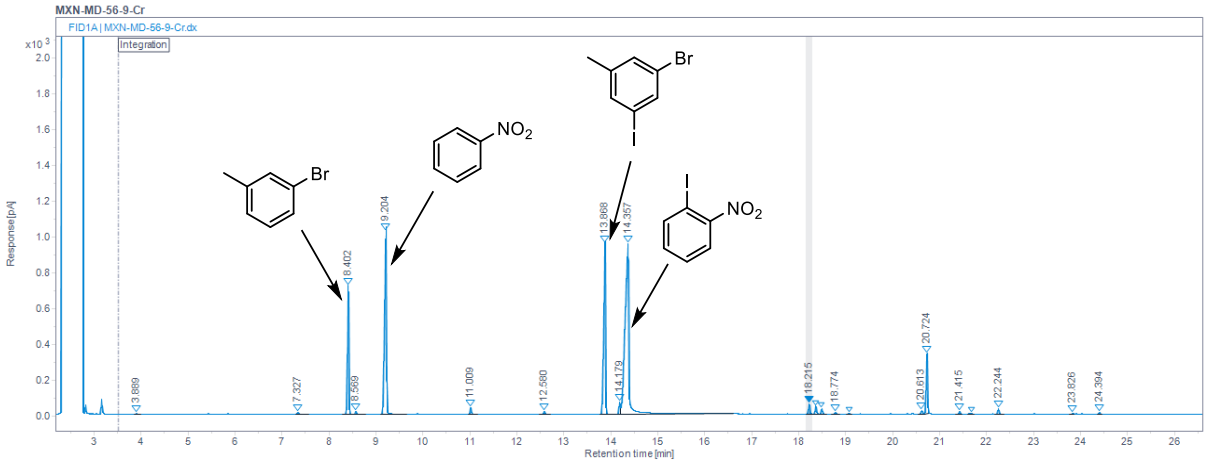
1-chloro-3-iodo-5-methylbenzene (3n): GC-FID trace of crude reaction mixture



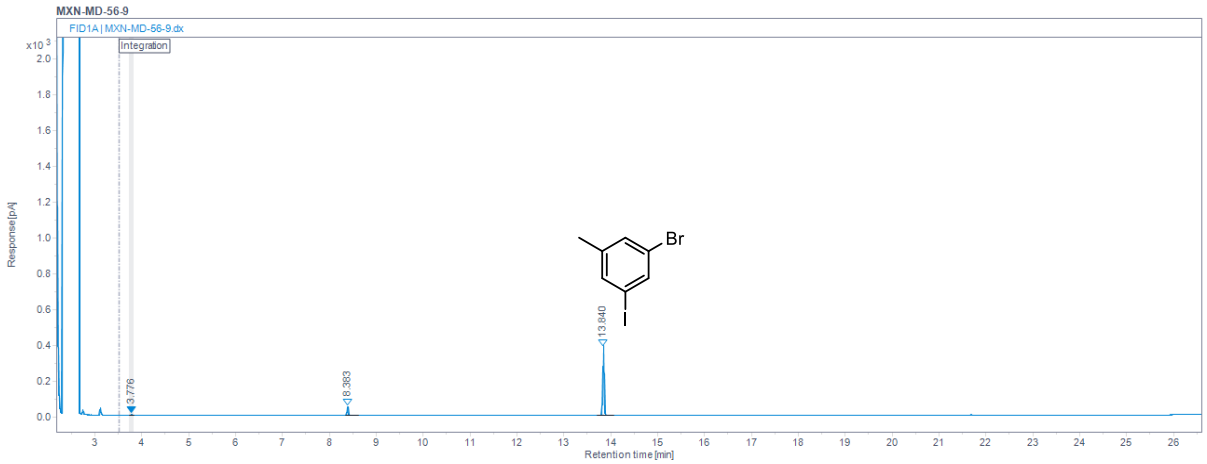
1-chloro-3-iodo-5-methylbenzene (3n): GC-FID trace of isolated compound



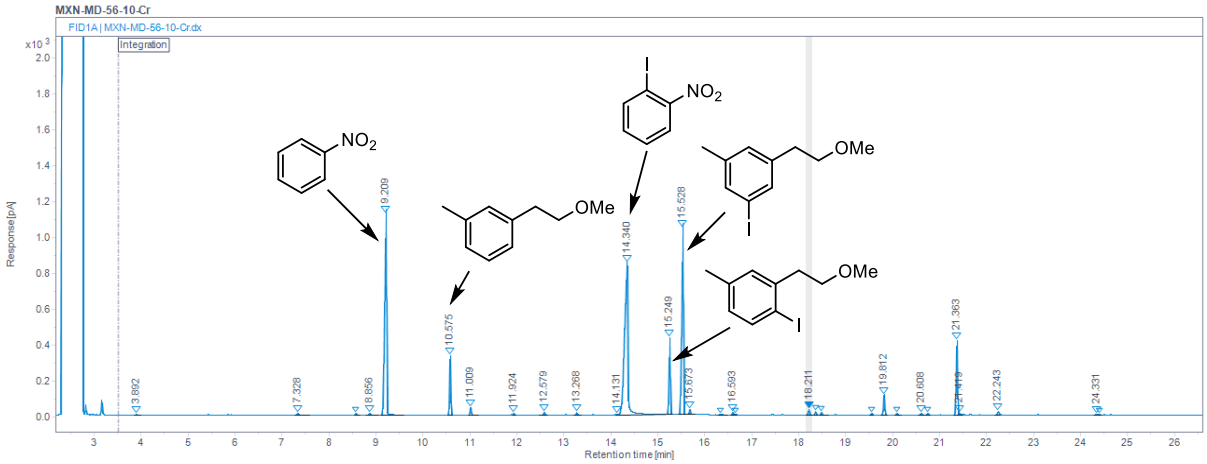
1-bromo-3-iodo-5-methylbenzene (3o): GC-FID trace of crude reaction mixture



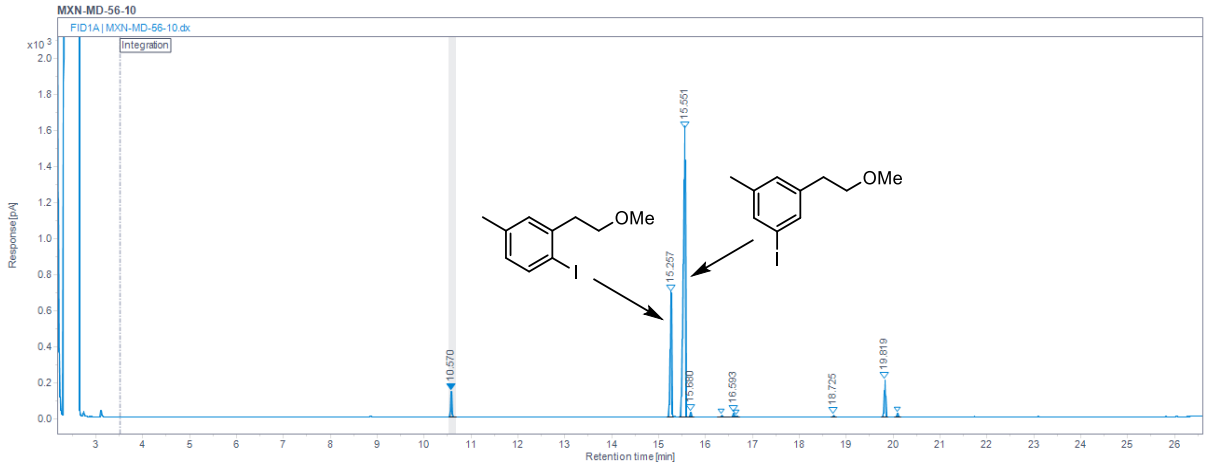
1-bromo-3-iodo-5-methylbenzene (3o): GC-FID trace of isolated compound



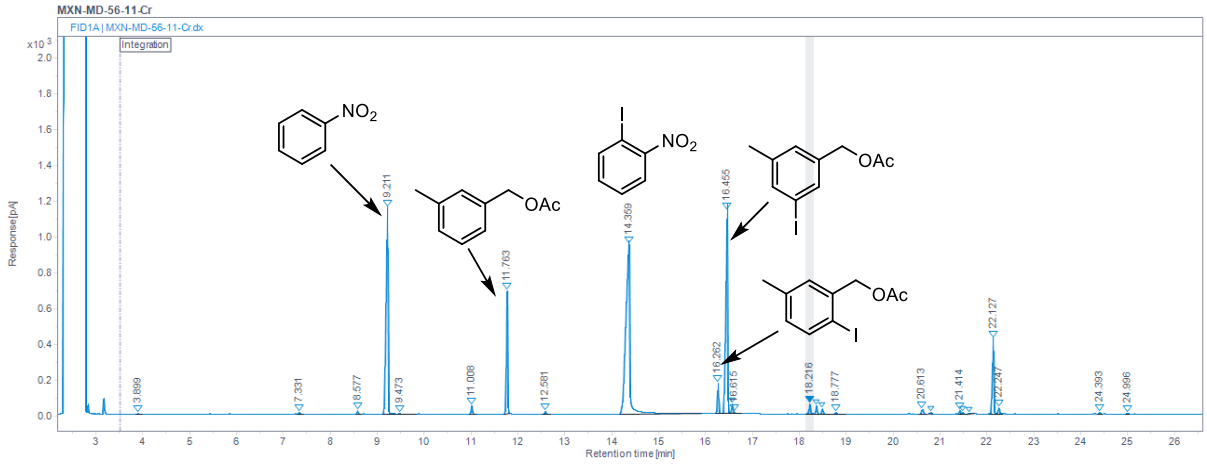
1-iodo-2-(2-methoxyethyl)-4-methylbenzene (3r-α) and 1-iodo-3-(2-methoxyethyl)-5-methylbenzene (3r-β): GC-FID trace of crude reaction mixture



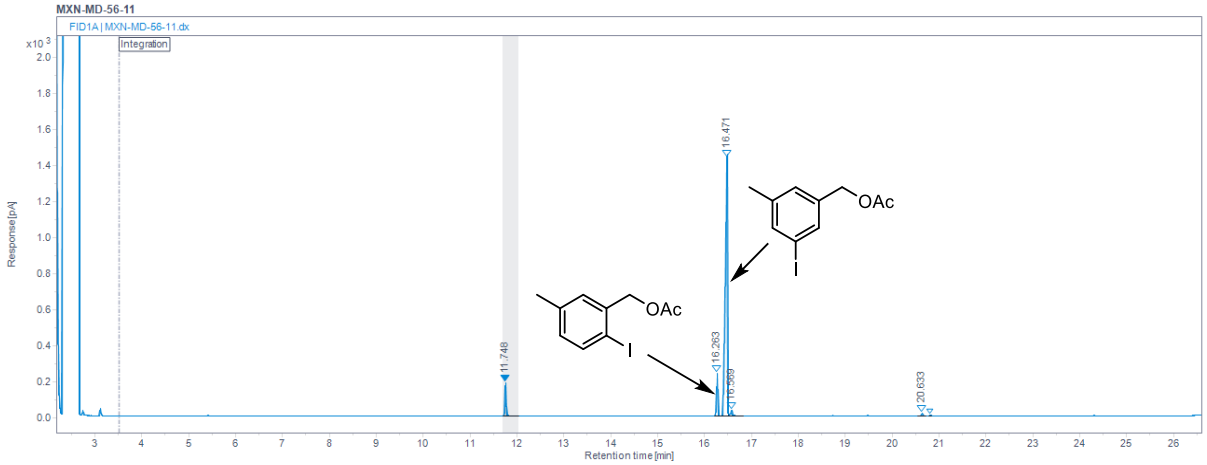
1-iodo-2-(2-methoxyethyl)-4-methylbenzene (3r-α) and 1-iodo-3-(2-methoxyethyl)-5-methylbenzene (3r-β): GC-FID trace of isolated compound



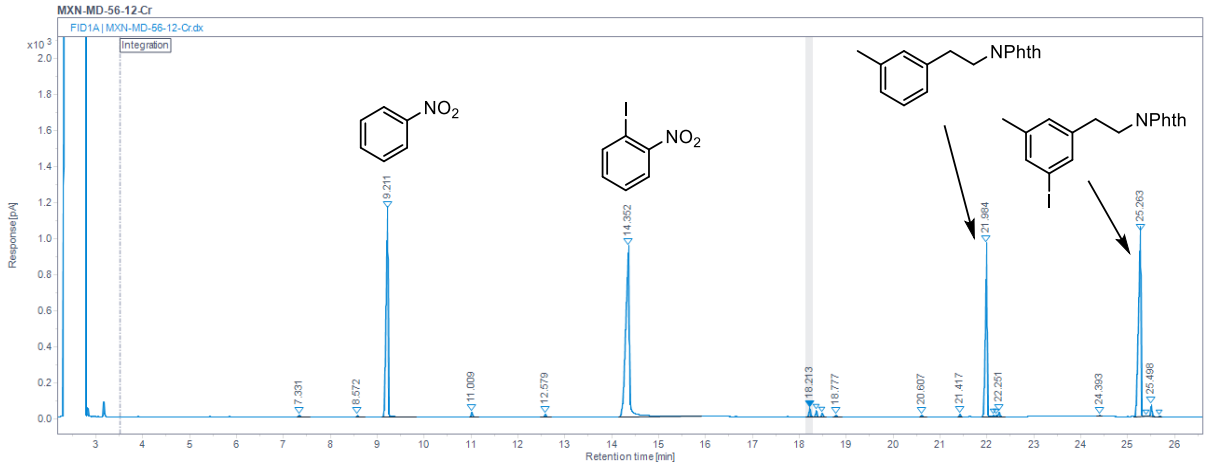
2-iodo-5-methylbenzyl acetate (3s-α) and 3-iodo-5-methylbenzyl acetate (3s-β): GC-FID trace of crude reaction mixture



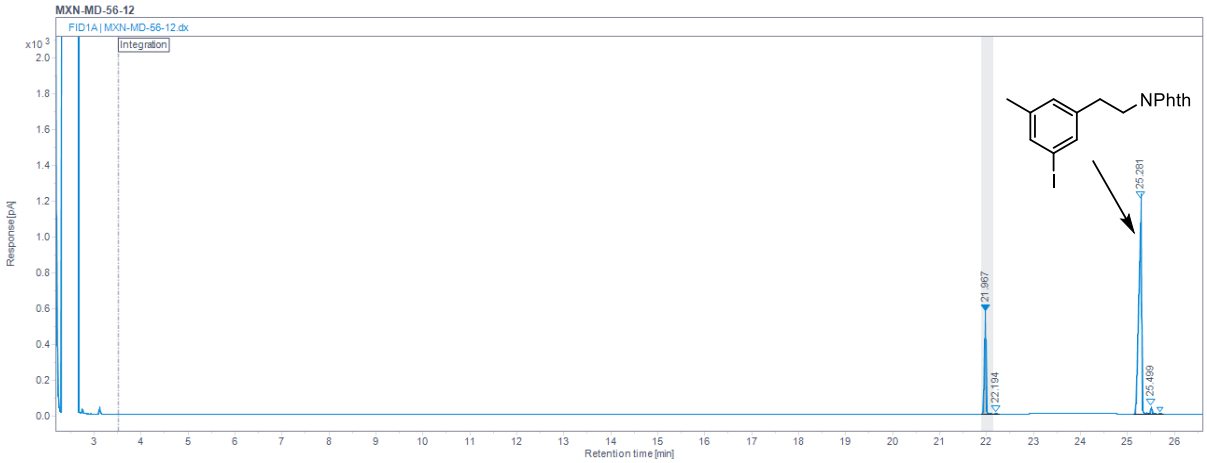
2-iodo-5-methylbenzyl acetate (3s-α) and 3-iodo-5-methylbenzyl acetate (3s-β): GC-FID trace of isolated compound



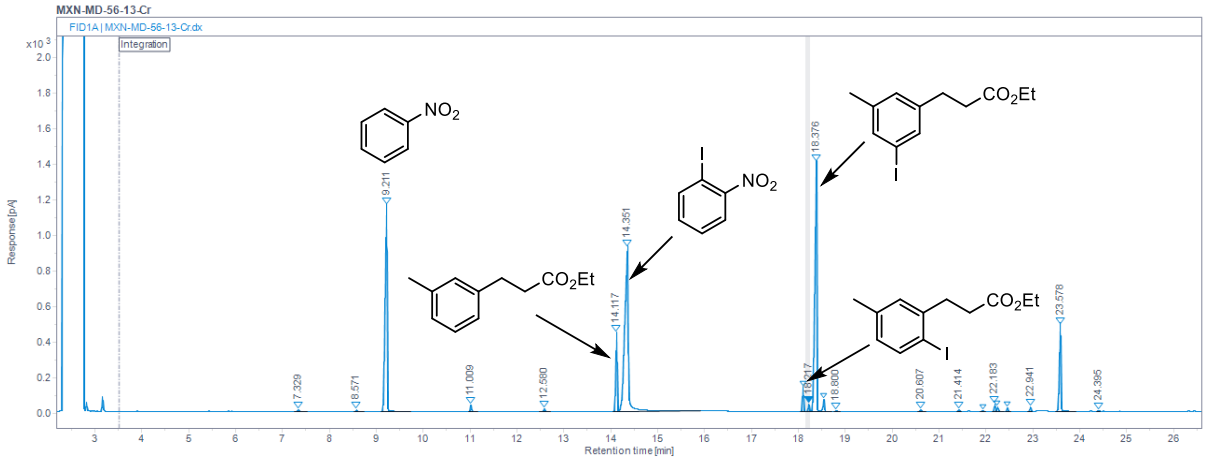
2-(3-iodo-5-methylphenethyl)isoindoline-1,3-dione (3t): GC-FID trace of crude reaction mixture



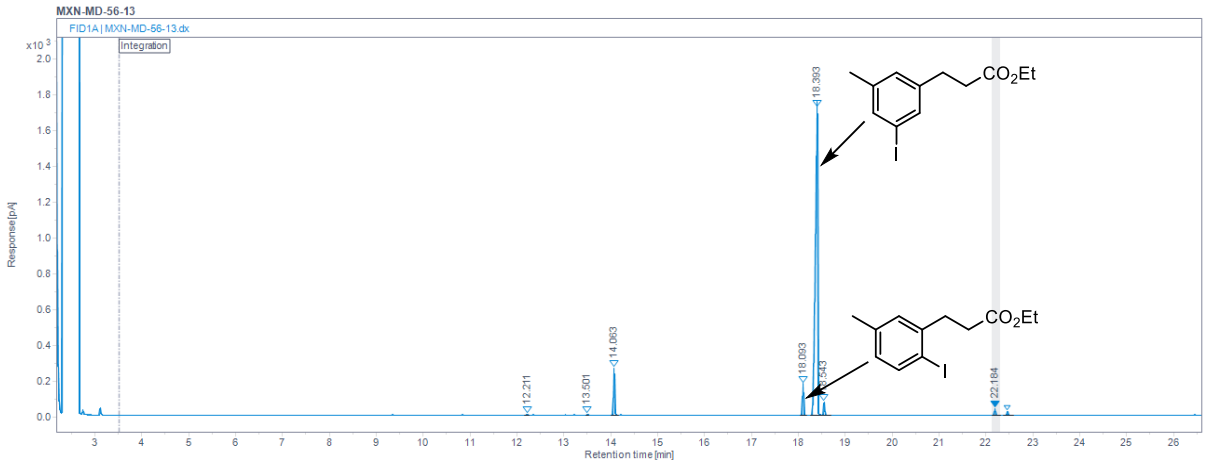
2-(3-iodo-5-methylphenethyl)isoindoline-1,3-dione (3t): GC-FID trace of isolated compound



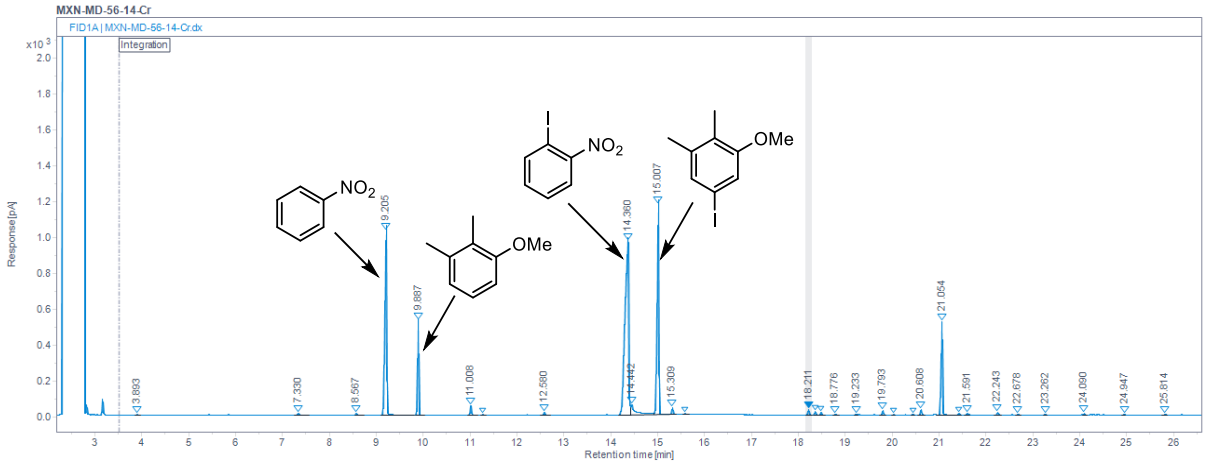
ethyl 3-(2-iodo-5-methylphenyl)propanoate (3v-α) and ethyl 3-(3-iodo-5-methylphenyl)propanoate (3v-β): GC-FID trace of crude reaction mixture



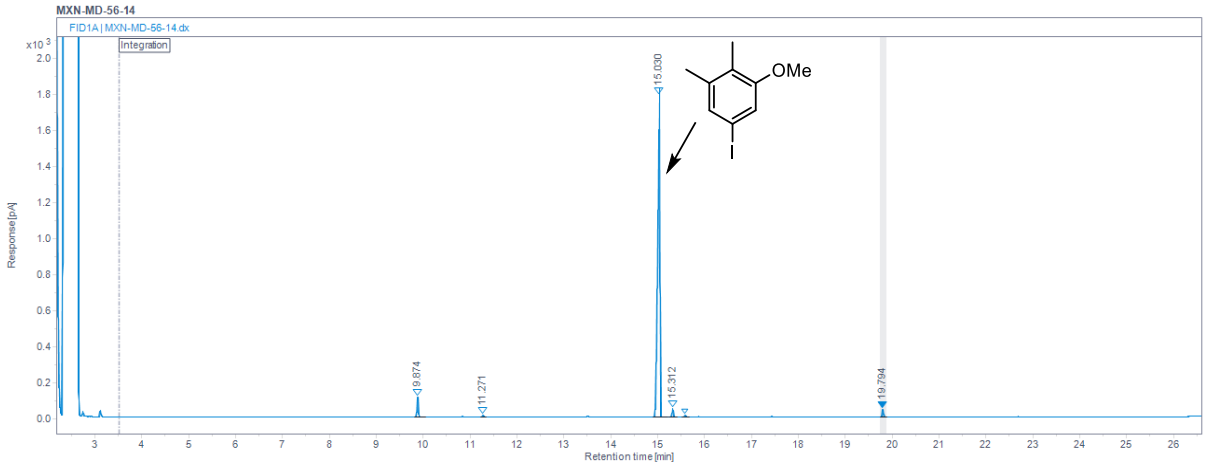
ethyl 3-(2-iodo-5-methylphenyl)propanoate (3v-α) and ethyl 3-(3-iodo-5-methylphenyl)propanoate (3v-β): GC-FID trace of isolated compound



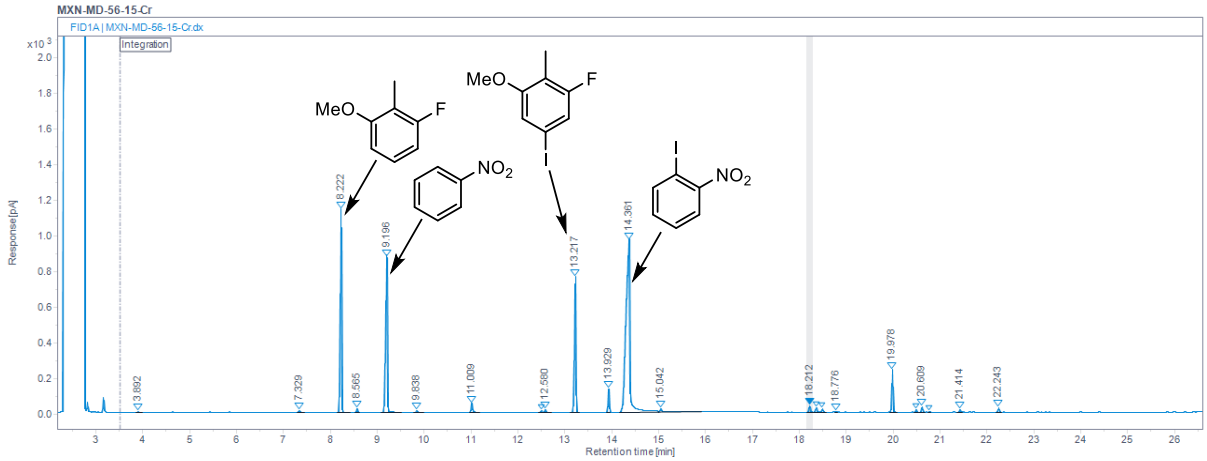
5-iodo-1-methoxy-2,3-dimethylbenzene (3w): GC-FID trace of crude reaction mixture



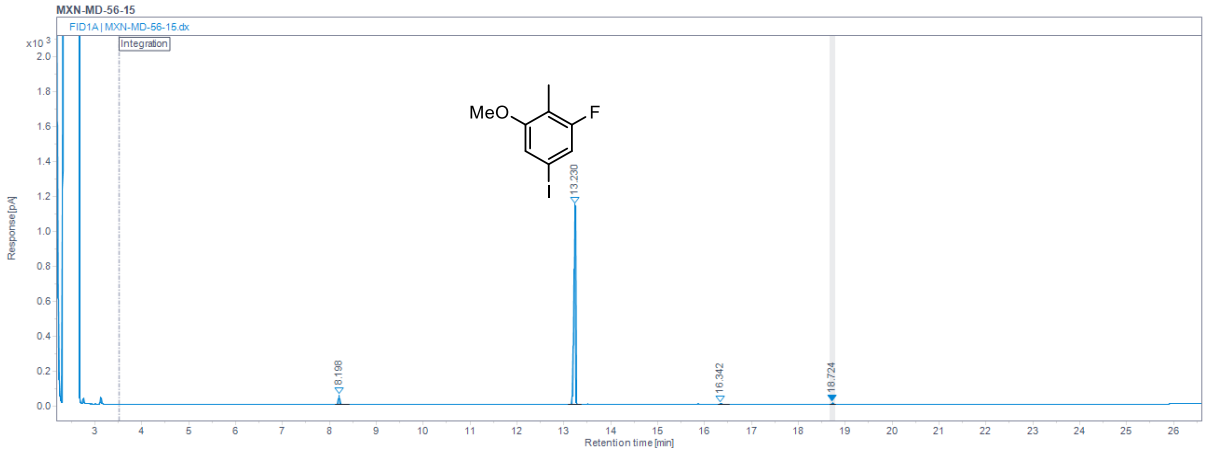
5-iodo-1-methoxy-2,3-dimethylbenzene (3w): GC-FID trace of isolated compound



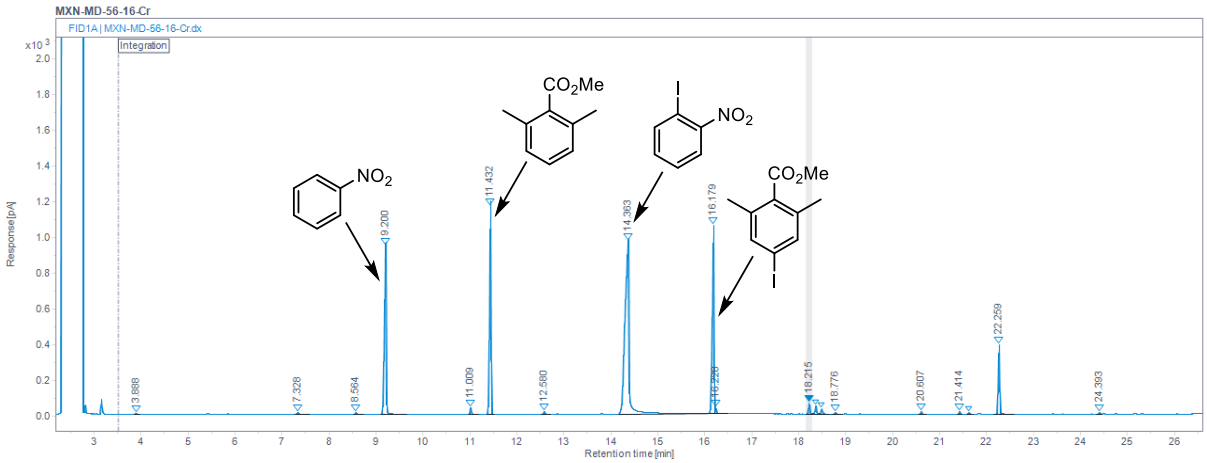
1-fluoro-5-iodo-3-methoxy-2-methylbenzene (3x): GC-FID trace of crude reaction mixture



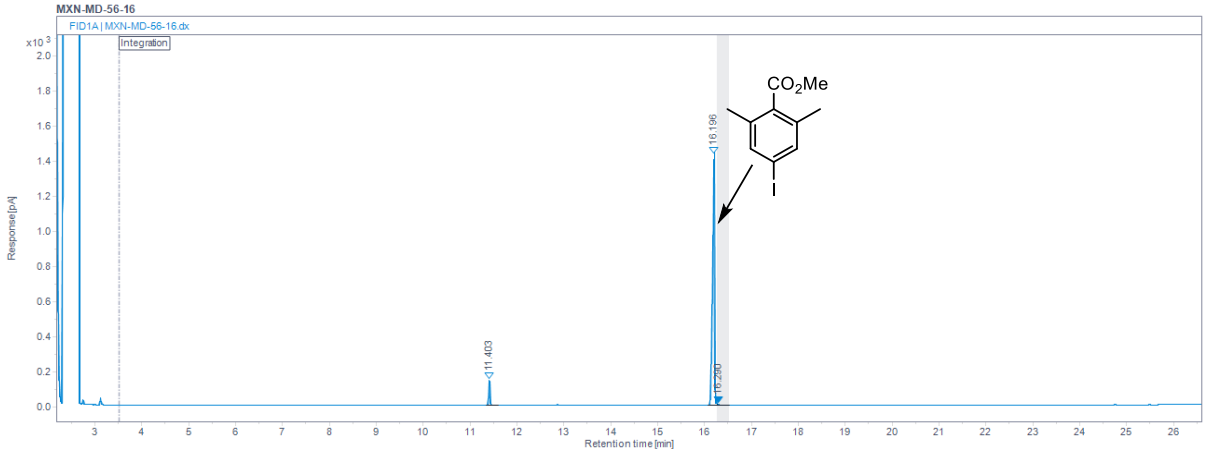
1-fluoro-5-iodo-3-methoxy-2-methylbenzene (3x): GC-FID trace of isolated compound



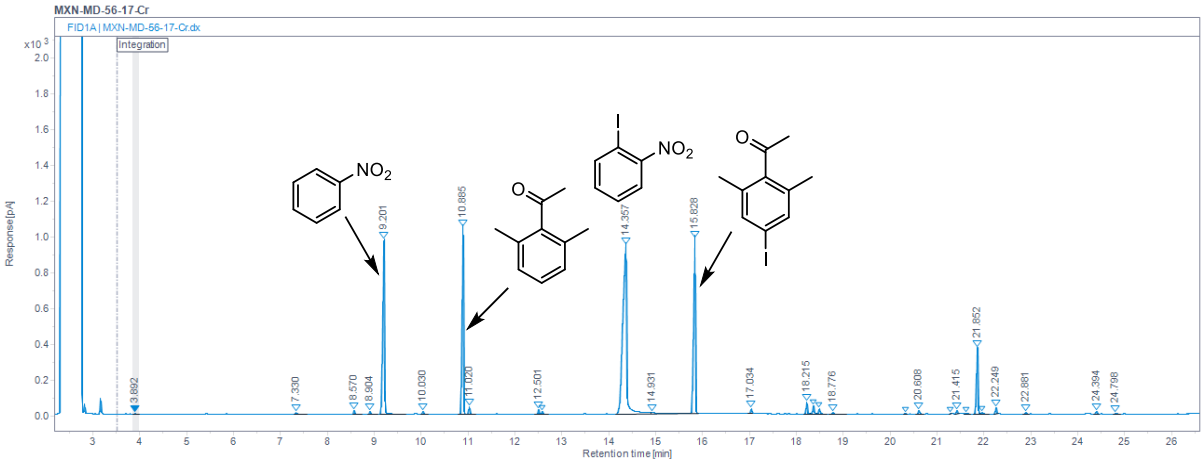
methyl 4-iodo-2,6-dimethylbenzoate (3y): GC-FID trace of crude reaction mixture



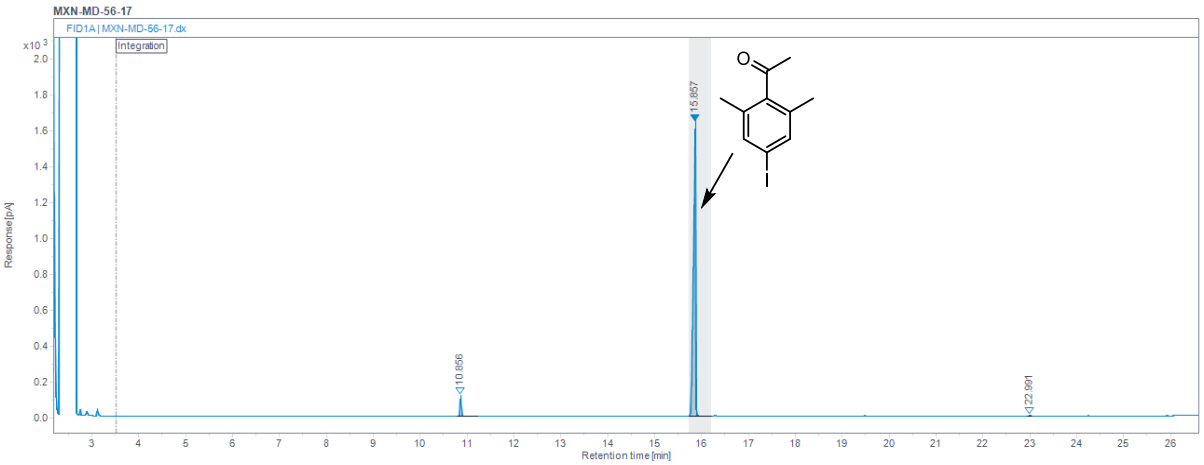
methyl 4-iodo-2,6-dimethylbenzoate (3y): GC-FID trace of isolated compound



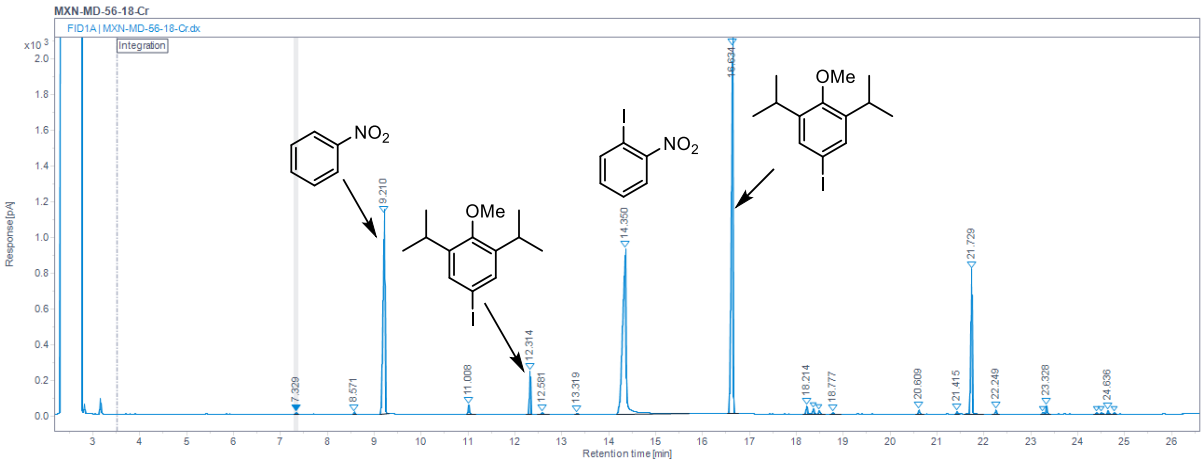
1-(4-iodo-2,6-dimethylphenyl)ethan-1-one (3ab): GC-FID trace of crude reaction mixture



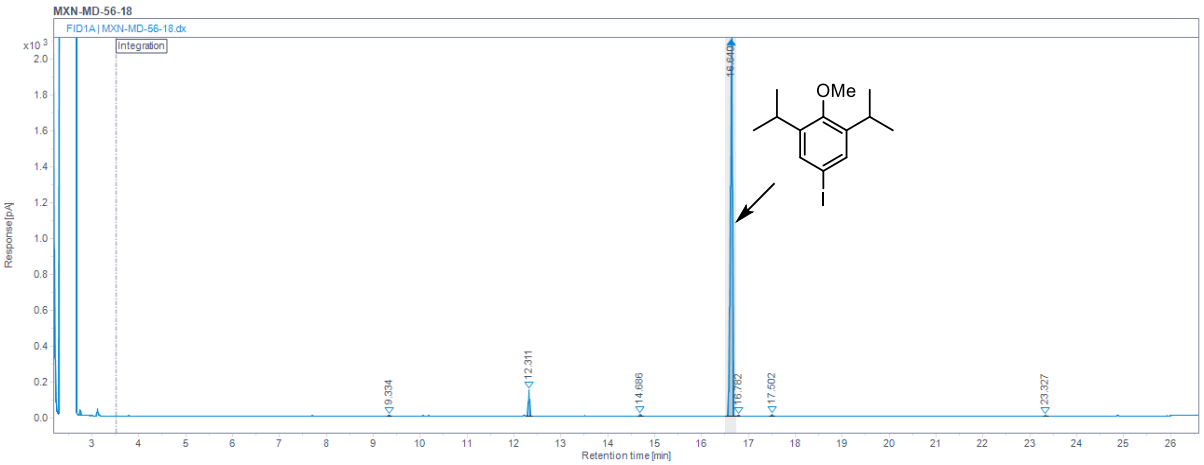
1-(4-iodo-2,6-dimethylphenyl)ethan-1-one (3ab): GC-FID trace of isolated compound



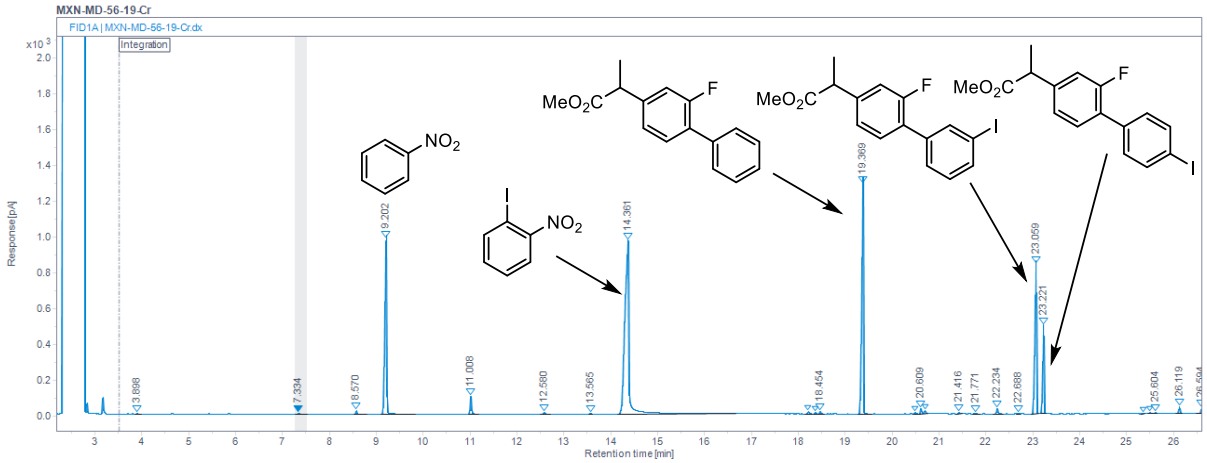
5-iodo-1,3-diisopropyl-2-methoxybenzene (3ac): GC-FID trace of crude reaction mixture



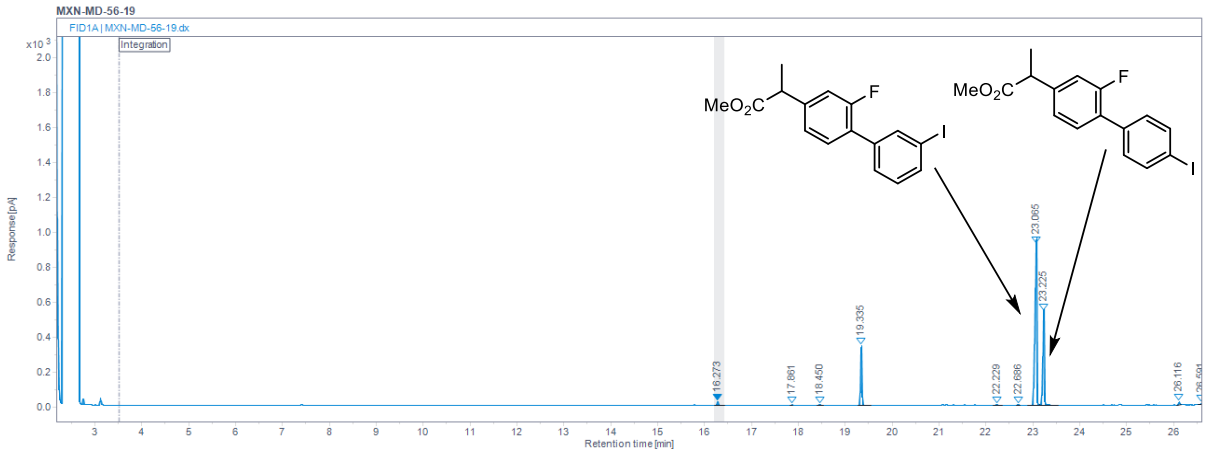
5-iodo-1,3-diisopropyl-2-methoxybenzene (3ac): GC-FID trace of isolated compound



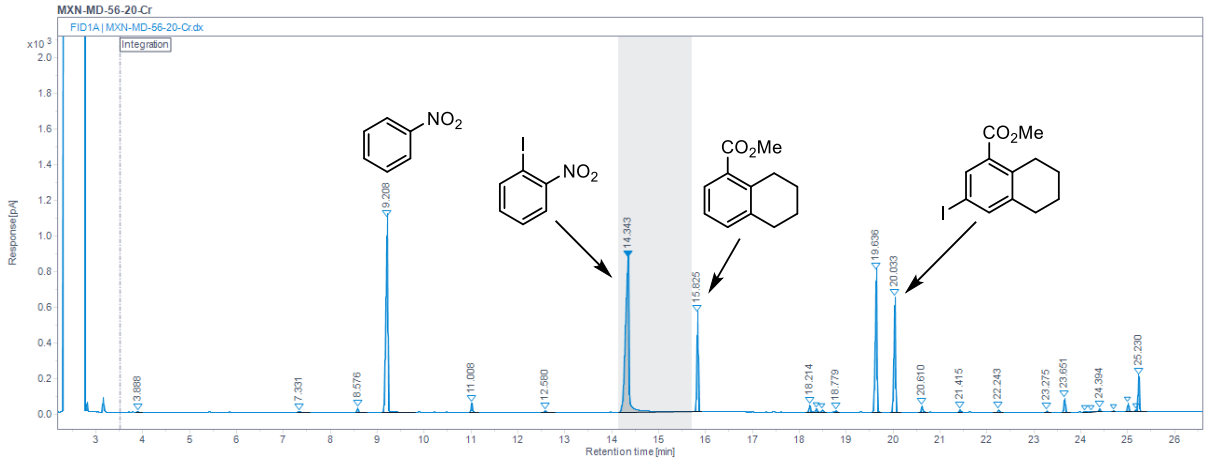
methyl 2-(2-fluoro-3'-iodo-[1,1'-biphenyl]-4-yl)propanoate (3ag-meta) and methyl 2-(2-fluoro-4'-iodo-[1,1'-biphenyl]-4-yl)propanoate (3ag-para): GC-FID trace of crude reaction mixture



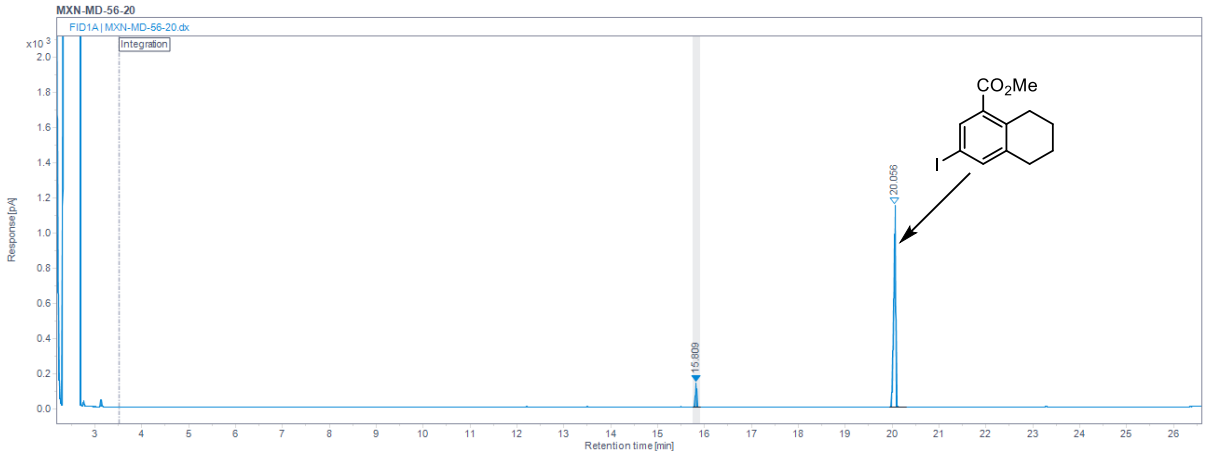
methyl 2-(2-fluoro-3'-iodo-[1,1'-biphenyl]-4-yl)propanoate (3ag-meta) and methyl 2-(2-fluoro-4'-iodo-[1,1'-biphenyl]-4-yl)propanoate (3ag-para): GC-FID trace of isolated compound



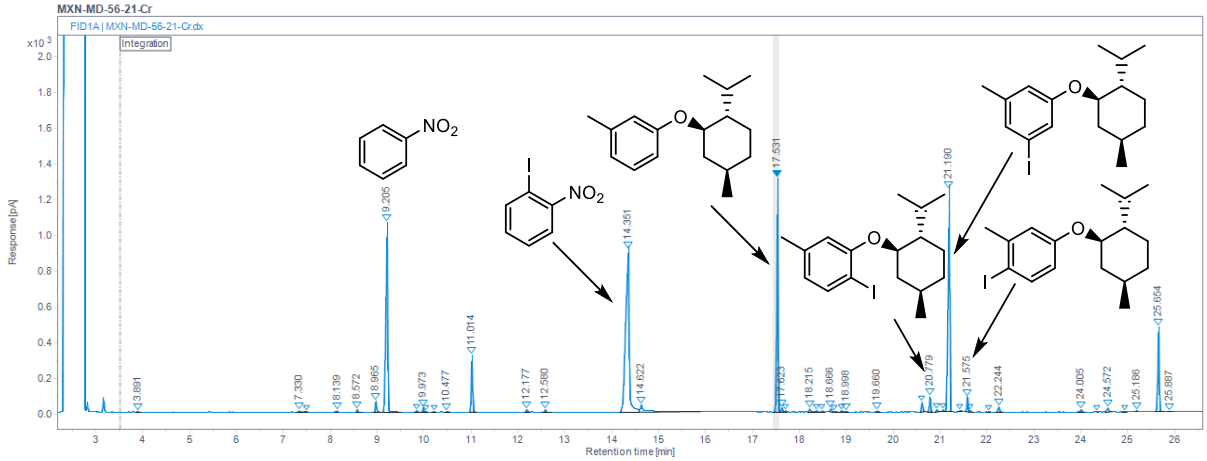
methyl 3-iodo-5,6,7,8-tetrahydronaphthalene-1-carboxylate (3ah): GC-FID trace of crude reaction mixture



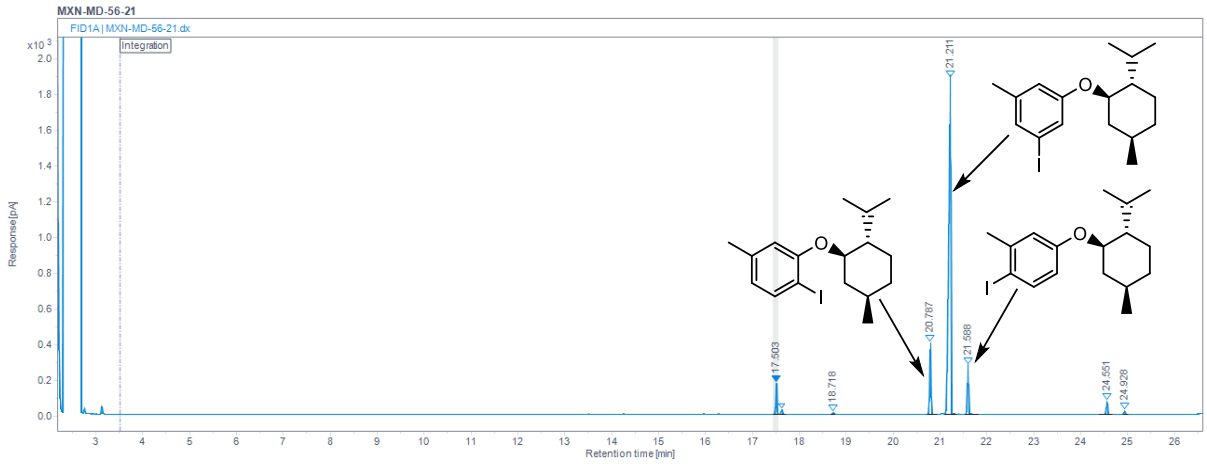
methyl 3-iodo-5,6,7,8-tetrahydronaphthalene-1-carboxylate (3ah): GC-FID trace of isolated compound



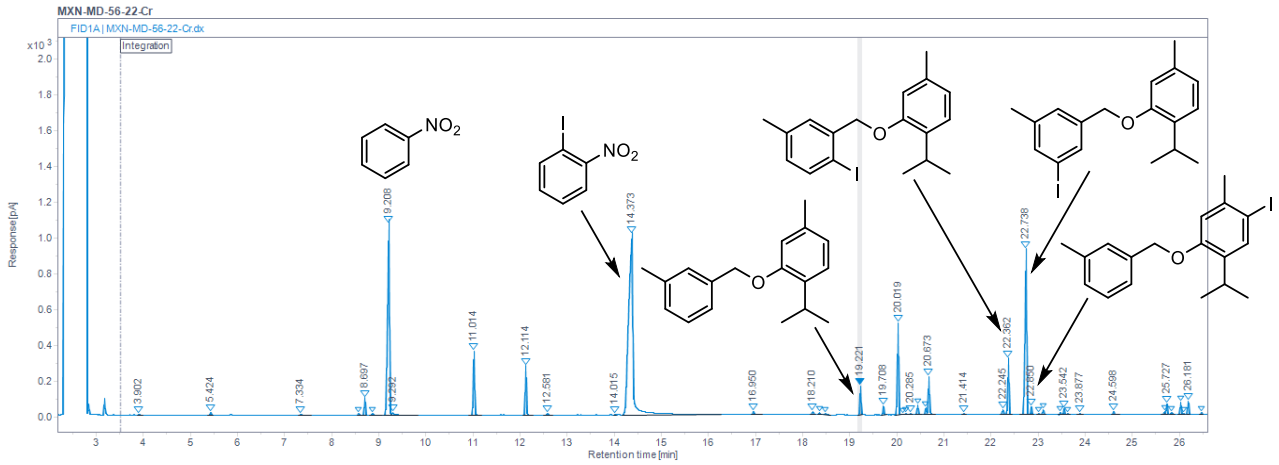
1-iodo-2-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)-4-methylbenzene (3al-α), 1-iodo-3-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)-5-methylbenzene (3al-β) and 1-iodo-4-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)-2-methylbenzene (3al-γ): GC-FID trace of crude reaction mixture



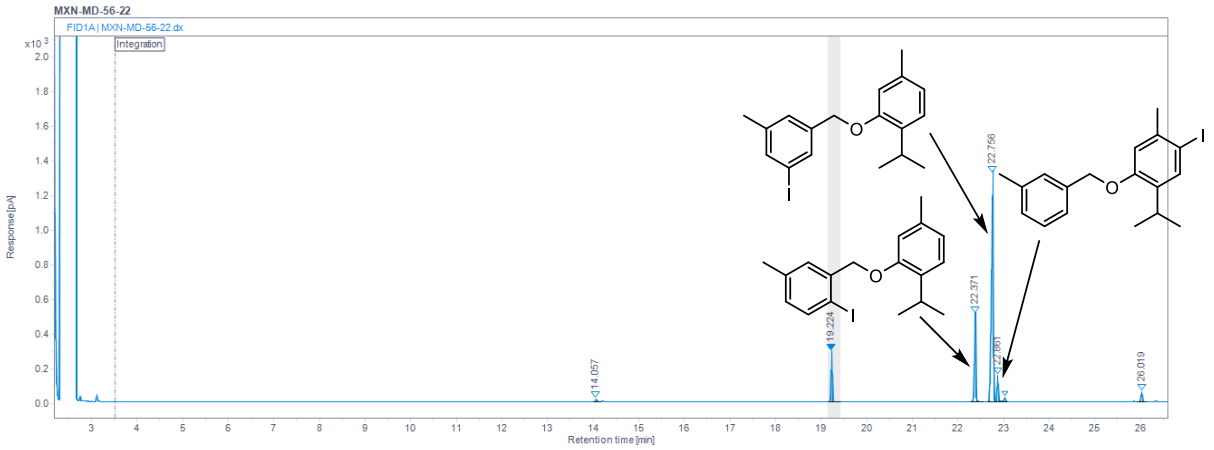
1-iodo-2-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)-4-methylbenzene (3al-α), 1-iodo-3-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)-5-methylbenzene (3al-β) and 1-iodo-4-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)-2-methylbenzene (3al-γ): GC-FID trace of isolated compound



1-iodo-2-((2-isopropyl-5-methylphenoxy)methyl)-4-methylbenzene (3am-α), 2-((3-iodo-5-methylbenzyl)oxy)-1-isopropyl-4-methylbenzene (3am-β) and 1-iodo-5-isopropyl-2-methyl-4-((3-methylbenzyl)oxy)benzene (3am-α´): GC-FID trace of crude reaction mixture



1-iodo-2-((2-isopropyl-5-methylphenoxy)methyl)-4-methylbenzene (3am-α), 2-((3-iodo-5-methylbenzyl)oxy)-1-isopropyl-4-methylbenzene (3am-β) and 1-iodo-5-isopropyl-2-methyl-4-((3-methylbenzyl)oxy)benzene (3am-α´): GC-FID trace of isolated compound



6 Preliminary Mechanistic Studies

General procedure C: Kinetic Analysis by Initial Rates

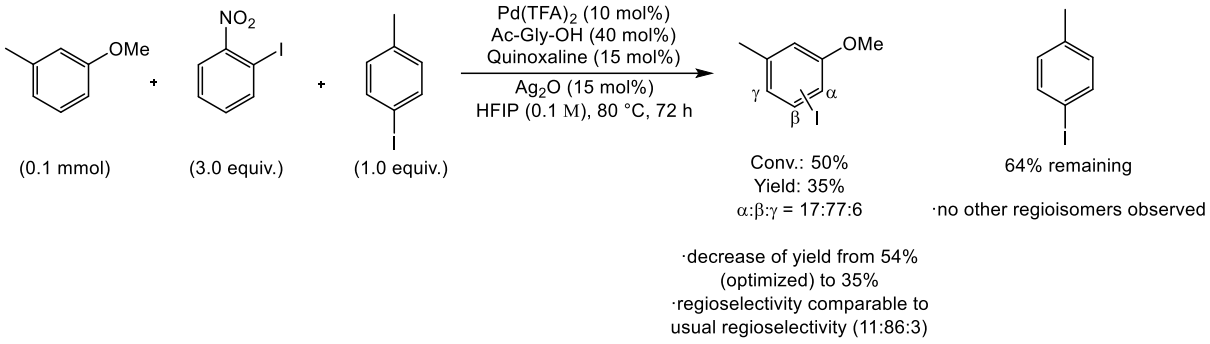
Reactions for determining initial rates were conducted in an oven-dried 10 mL Schlenk tube to which a Teflon-coated magnetic stirring bar was added. The Schlenk tube was evacuated and backfilled with argon. A stock solution was prepared with the solvent and the ligands. An aliquot (1.0 mL) was used to dispense Ac-Gly-OH (4.68 mg, 0.040 mmol, 0.4 equiv), quinoxaline (1.95 mg, 0.015 mmol, 0.15 equiv) and HFIP (1.0 mL) to each vial. The reaction vial was charged with Ag_2O (3.48 mg, 0.015 mmol, 0.15 equiv) or $AgNO_3$ (10.2 mg, 0.030 mmol, 0.3 equiv.), ortho-xylene (**1i**) (10.6 mg, 0.100 mmol), 1-iodo-2-nitrobenzene (**2**) (50.0 mg, 0.200 mmol, 2.0 equiv.), and the catalyst stock solution (1.0 mL). The reaction vessel was tightly sealed with a screw cap and placed into a preheated aluminum metal block with a tightly fitting recess on a magnetic stirrer with 1000 rotations per minute. After the reaction time, which was precisely measured by a timer, the reaction mixture was quickly cooled to −78 °C in an acetone/dry ice bath for approximately 2 minutes until frozen solid.

After letting the reaction mixture warm up to room temperature, 1,3,5-trimethylbenzene (6.9 mg, 0.058 mmol) was added to the vial and the reaction mixture was diluted with ethyl acetate (2 mL). After thorough mixing, an aliquot (500 µL) of the resulting solution was filtered over a short silica column using ethyl acetate as the eluent and the filtrate collected in a 2 mL vial. All yields given for the determination of initial rates result from GC-FID analysis of the crude reaction mixture using 1,3,5-trimethylbenzene as internal standard. The yields were used to obtain the initial rates and standard errors using the linear fit tool of the OriginPro 2022 program.[12] For each initial rate 5 individual experiments were conducted with a reaction time of 20, 40, 60, 80 and 100 minutes for ortho-xylene (**1i**). The initial rates were then plotted against the varied reagent.

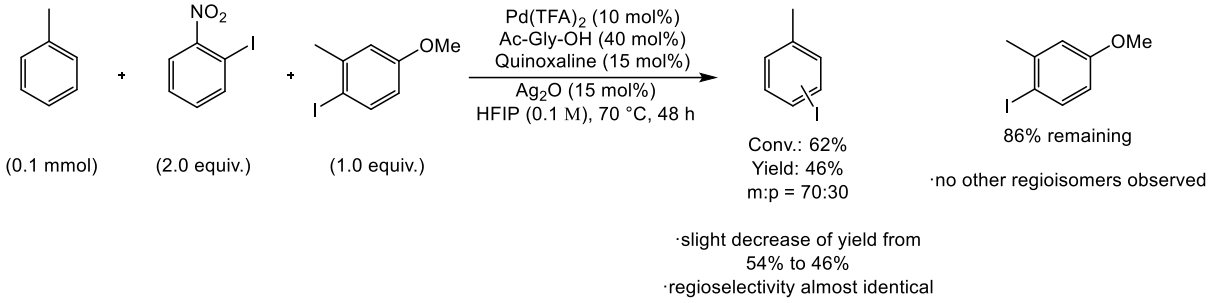
Scrambling Experiments

In order to elucidate the nature of the reaction being either a process where the product formation is kinetically or thermodynamically controlled, scrambling experiments have been performed.

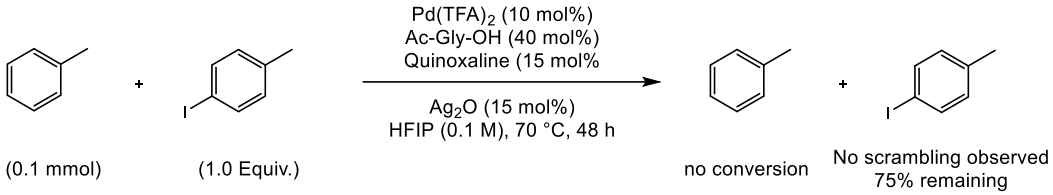
Scheme S44: Iodination of m-cresol methyl ether (**1a**) with addition of p-iodotoluene (**3c**)

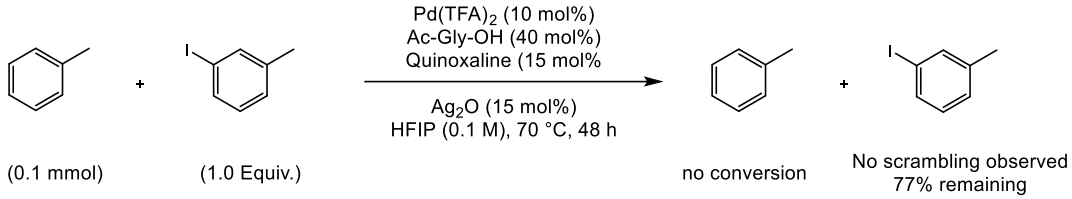


Scheme S45: Iodination of toluene (**1c**) with addition of iodinated m-cresole methyl ether **3a-α**.

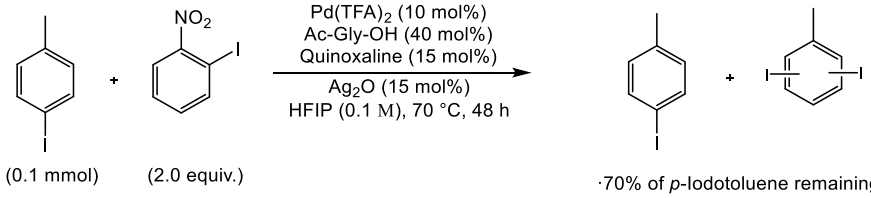


Scheme S46: Reaction subjecting toluene (**1c**) and meta- or para-iodotoluene (**3c**) to reaction conditions without I-Reagent **2**.





Scheme S47: Reaction subjecting p-iodotoluene (**3c**) to reaction conditions.

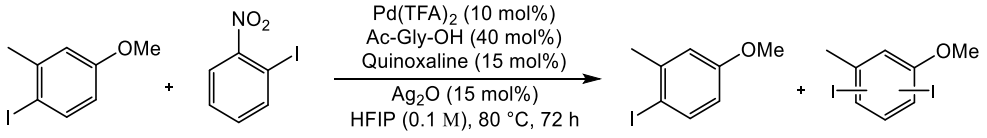


·70% of *p*-Iodotoluene remaining

·no other regioisomers observed (no scrambling)

· GC-MS analysis shows formation of significant amount di-iodinated product

Scheme S48: Reaction subjecting iodinated m-cresole methyl ether **3a-α** to reaction conditions.



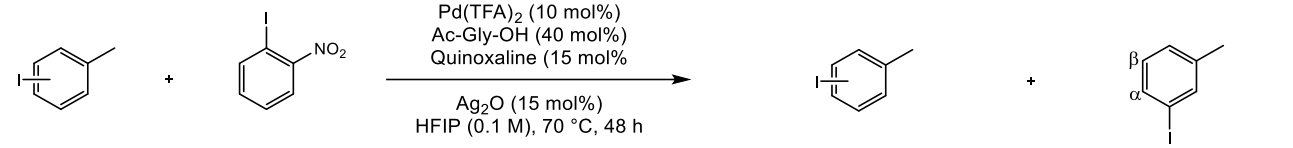
(0.1 mmol) (3.0 equiv.)

·49% of iodinated *m*-cresol methyl ether remaining

·no other regioisomers observed (no scrambling)

· GC-MS analysis shows formation of significant amount di-iodinated product

Scheme S49: Reaction subjecting mixture of iodinated product **3c** to reaction conditions.



0.1 mmol
m:p = 68:32

2.0 equiv.

58% remaining
m:p = 58:42
no ortho iodinated toluene observed

34% di-iodinated toluene
α:β = 37:63

Kinetic Isotope Experiments

Before performing the KIE studies, we began by monitoring the reaction of o-xylene (**1i**)over the course of the first 160 minutes, in order to determine the range in which initial rate data could be obtained.

Scheme S50: Reaction conditions for investigation of reaction course.

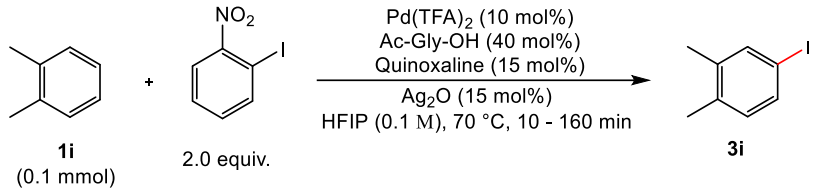


Table 1. Reaction analysis in the first 160 minutes using o-xylene.

Entry	**arene**	**reaction time (min)**	**conversion (%)**	**yield (%)**	**product (mmol)**
1	*ortho*-xylene (**1i**)	10	1.1	0.4	0.00035
2	*ortho*-xylene (**1i**)	20	1.8	1.4	0.00143
3	*ortho*-xylene (**1i**)	40	4.1	3.4	0.00346
4	*ortho*-xylene (**1i**)	80	8.6	6.3	0.00635
5	*ortho*-xylene (**1i**)	160	11.1	8.5	0.00843

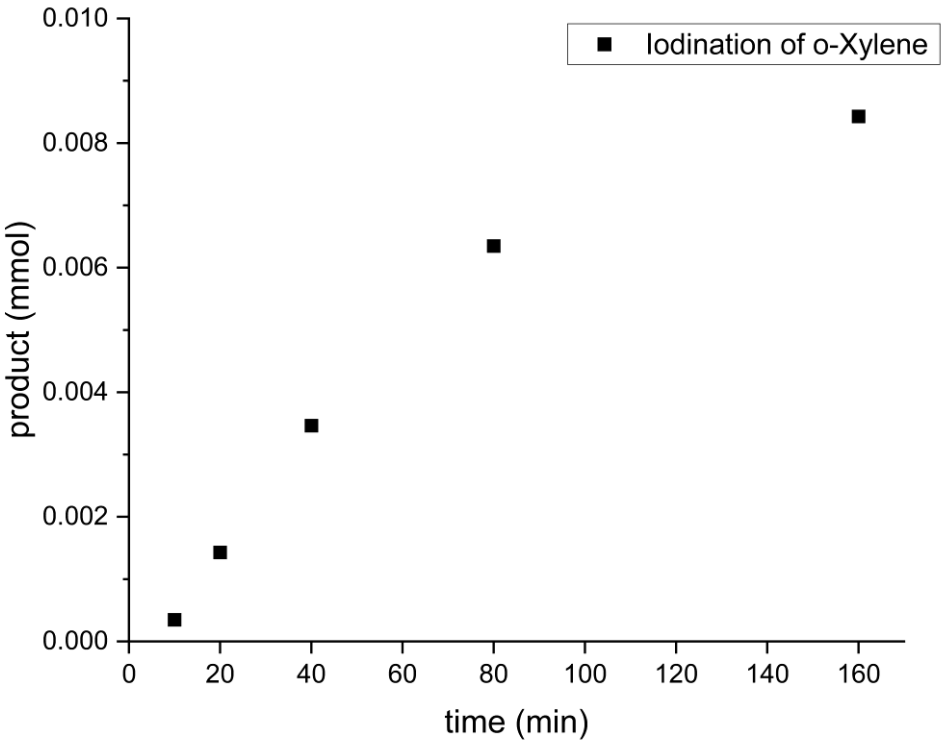
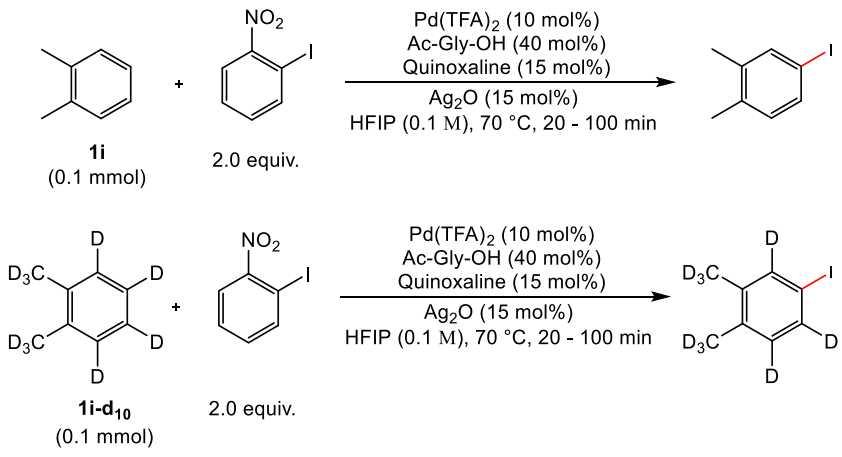


Figure 1: Reaction profile over the first 160 min with substrate **1i** to determine the linear range and establish the suitability of initial rate measurements for KIE studies. All reactions conducted with substrate (0.1 mmol), iodine reagent (2.0 equiv.), Ag_2O (15 mol%) in HFIP (1.0 mL) at 70 °C.

The data in Figure **1** shows that for o-xylene (**1i**) parallel KIE studies can be performed using initial rate kinetic measurements with linear approximation, since no substantial induction period is observed, and the reaction shows a near linear kinetic behavior in the first 100 minutes of the reaction.

Scheme S51: Reaction conditions for parallel kinetic isotope experiments.



The initial rates for the parallel experiments were determined following the general procedure C. Deuterium kinetic isotope effects (KIEs) were determined by dividing the initial rate of **1i** (k_H) by the initial rate of **1i-d$_{10}$** (k_D).

Table 2. Parallel kinetic isotope experiments.

Entry	**arene**	**reaction time (min)**	**conversion (%)**	**yield (%)**	**product (mmol)**
1	*ortho*-xylene (**1i**)	20	2.1	1.0	0.0010
2	*ortho*-xylene (**1i**)	40	3.4	3.0	0.0030
3	*ortho*-xylene (**1i**)	60	6.3	5.5	0.0054
4	*ortho*-xylene (**1i**)	80	7.8	6.1	0.0060
5	*ortho*-xylene (**1i**)	100	9.8	7.9	0.0079
6	*ortho*-xylene-d$_{10}$ (**1i-d$_{10}$**)	20	0.9	0.3	0.0003
7	*ortho*-xylene-d$_{10}$ (**1i-d$_{10}$**)	40	1.9	1.3	0.0013
8	*ortho*-xylene-d$_{10}$ (**1i-d$_{10}$**)	60	2.8	2.0	0.0020
9	*ortho*-xylene-d$_{10}$ (**1i-d$_{10}$**)	80	4.1	2.8	0.0028
10	*ortho*-xylene-d$_{10}$ (**1i-d$_{10}$**)	100	6.1	4.1	0.0041

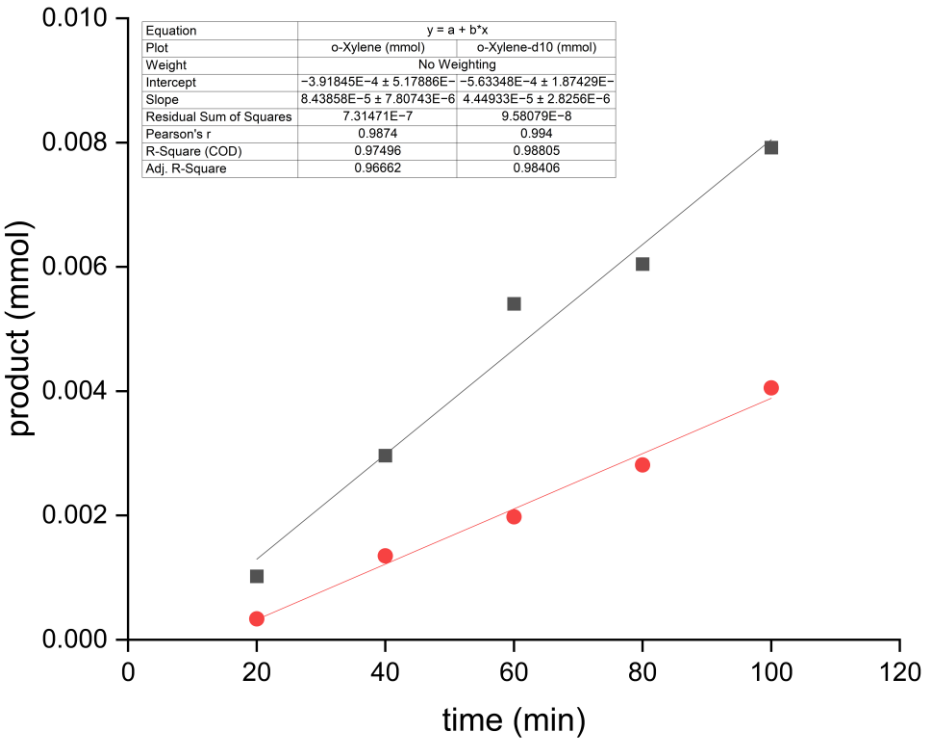
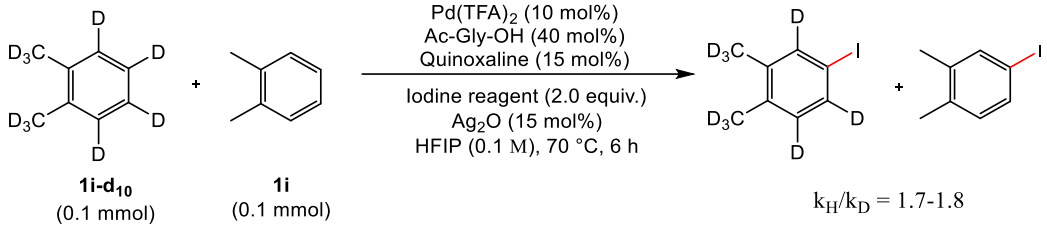


Figure 2: Plot of iodinated product (mmol) versus time (min) for *ortho*-xylene (**1i**) (black squares) and *ortho*-xylene-d$_{10}$ (**1i-d$_{10}$**) (red circles).

Equation: $KIE = \frac{k_H}{k_D} = \frac{8.44*10^{-5} \pm 7.81*10^{-6}}{4.45*10^{-5} \pm 2.83*10^{-6}} = 1.90 \pm 0.28$

Scheme S52: Reaction conditions for competition kinetic isotope experiments.



The initial rates for the competition experiments were determined following the general procedure C using *ortho*-xylene (**1i**) (10.6 mg, 0.100 mmol, 1.0 equiv.) and *ortho*-xylene-d_{10} (**1i-d_{10}**) (11.6 mg, 0.100 mmol, 1.0 equiv.) as the arene. The product ratio was determined by GC-FID analysis.

Table 3. Competition kinetic isotope experiments.

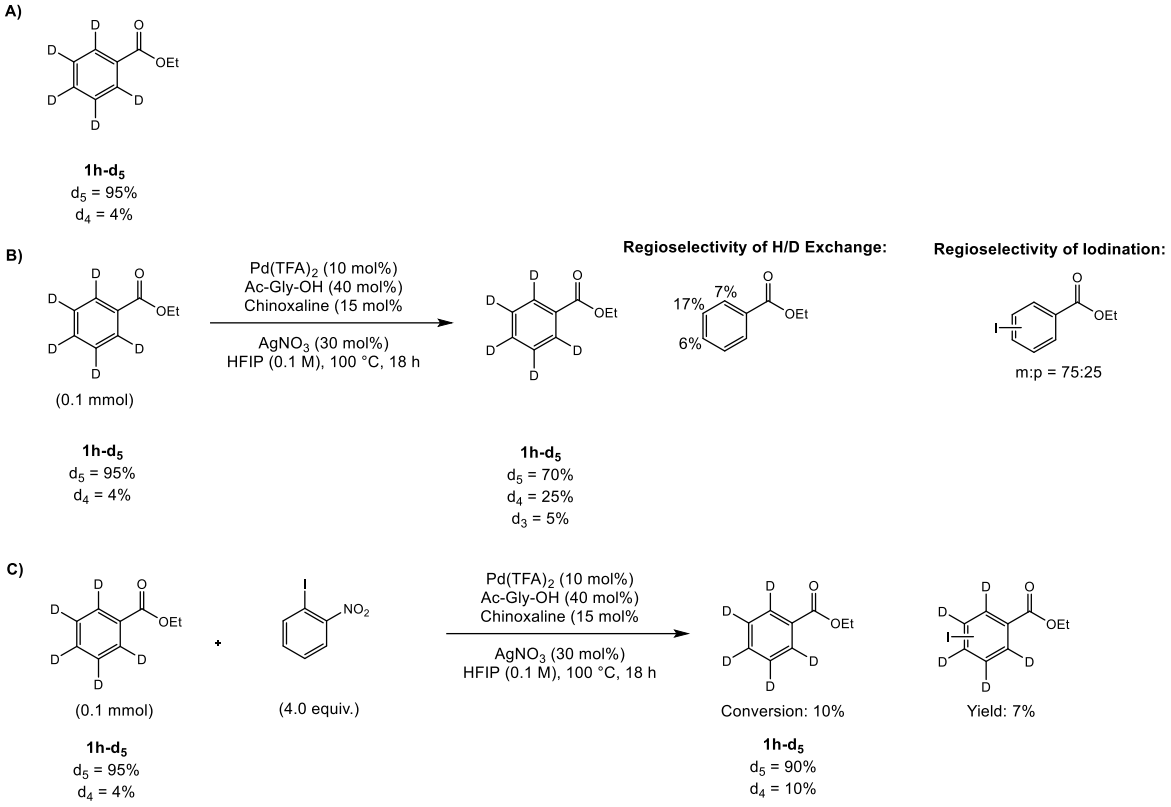
Entry	**arene**	**reaction time (min)**	**conversion (%)**	**yield (%)**	**product (mmol)**
1	*ortho*-xylene (**1i**)	6 h	16.0	12.1	0.0119
2	*ortho*-xylene-d_{10} (**1i-d_{10}**)	6 h	7.2	6.8	0.0069

The kinetic isotope effects observed indicate that the C–H activation step is at least in part rate-limiting.

Following the general procedure A, using Ethyl benzoate **1h-d$_5$** (15.5 mg, 0.100 mmol) as the arene, the reaction was stirred at 100 °C for the indicated time, cooled down in liquid nitrogen, and then allowed to warm to room temperature. The deuterium percentages for the starting material were calculated by mass spectrometric analysis using GC-MS and Universal Mass Calculator.[1]

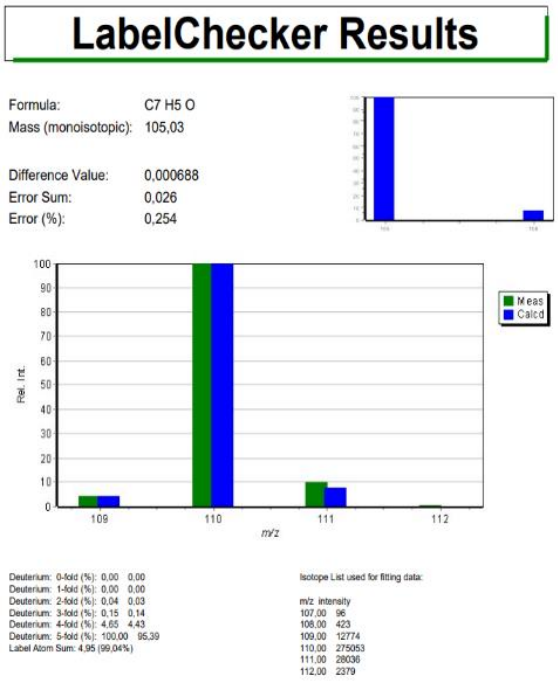
Our H/D-exchange experiments demonstrate that the C–H activation is a reversible process, causing a substantial H/D exchange in the absence of the iodinating reagent (B). The degree of H/D exchange in remaining starting material is significantly reduced in the presence of the iodinating reagent (C). This indicates that the reversion of the C–H activation step, while in principle possible, is outcompeted by product formation under the reaction conditions.

Scheme S53: Reversibility experiments using deuterated Ethyl benzoate (**1h-d$_5$**).

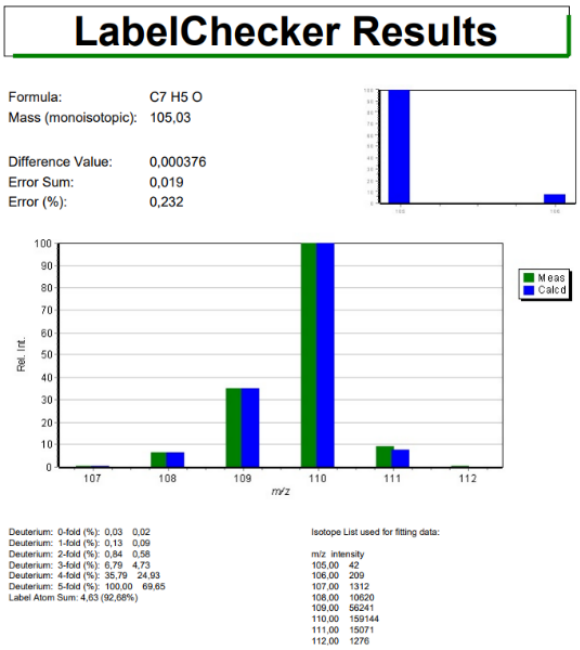


[1] The Universal Mass Calculator software package (V. 3.8.0.4) was developed by Dr. Matthias Letzel (WWU). The isotope pattern fitting was conducted with the module LabelChecker, which accounts for the natural abundance of all relevant isotopes.

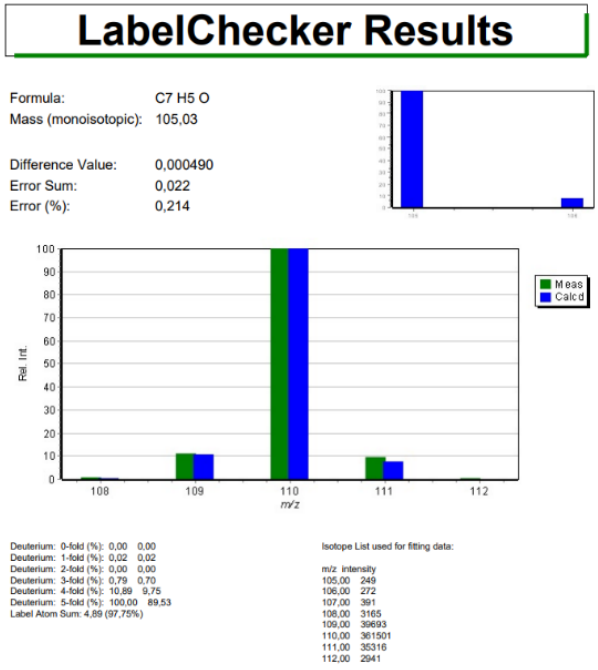
A)


LabelChecker Results
Formula: C7 H5 O
Mass (monoisotopic): 105,03
Difference Value: 0,000688
Error Sum: 0,026
Error (%): 0,254
Meas
Calcd
Rel. Int.
m/z
Deuterium: 0-fold (%): 0,00 0,00
Deuterium: 1-fold (%): 0,00 0,00
Deuterium: 2-fold (%): 0,04 0,03
Deuterium: 3-fold (%): 0,15 0,14
Deuterium: 4-fold (%): 4,65 4,43
Deuterium: 5-fold (%): 100,00 95,39
Label Atom Sum: 4,95 (99,04%)
Isotope List used for fitting data:
m/z intensity
107,00 96
108,00 423
109,00 12774
110,00 275053
111,00 28036
112,00 2379

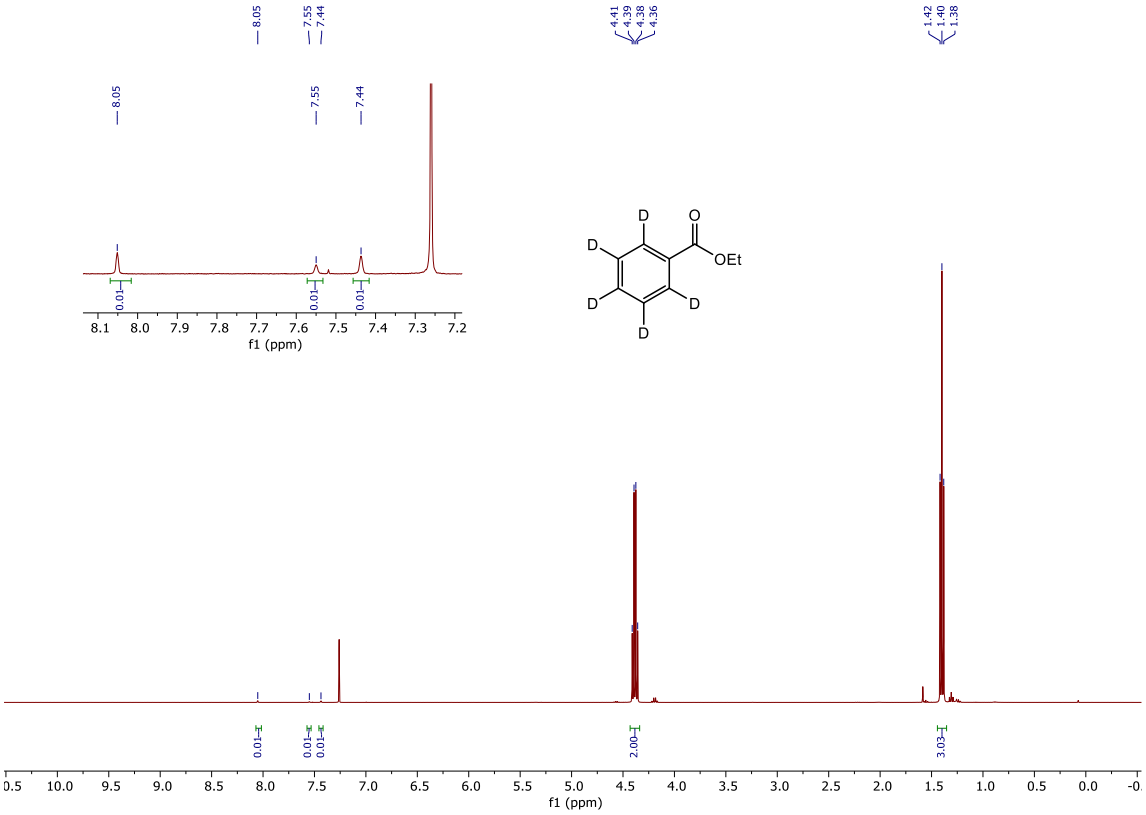
B)


LabelChecker Results
Formula: C7 H5 O
Mass (monoisotopic): 105,03
Difference Value: 0,000376
Error Sum: 0,019
Error (%): 0,232
Meas
Calcd
Rel. Int.
m/z
Deuterium: 0-fold (%): 0,03 0,02
Deuterium: 1-fold (%): 0,13 0,09
Deuterium: 2-fold (%): 0,84 0,58
Deuterium: 3-fold (%): 6,79 4,73
Deuterium: 4-fold (%): 35,79 24,93
Deuterium: 5-fold (%): 100,00 69,65
Label Atom Sum: 4,63 (92,68%)
Isotope List used for fitting data:
m/z intensity
105,00 42
106,00 209
107,00 1312
108,00 10620
109,00 56241
110,00 159144
111,00 15071
112,00 1276

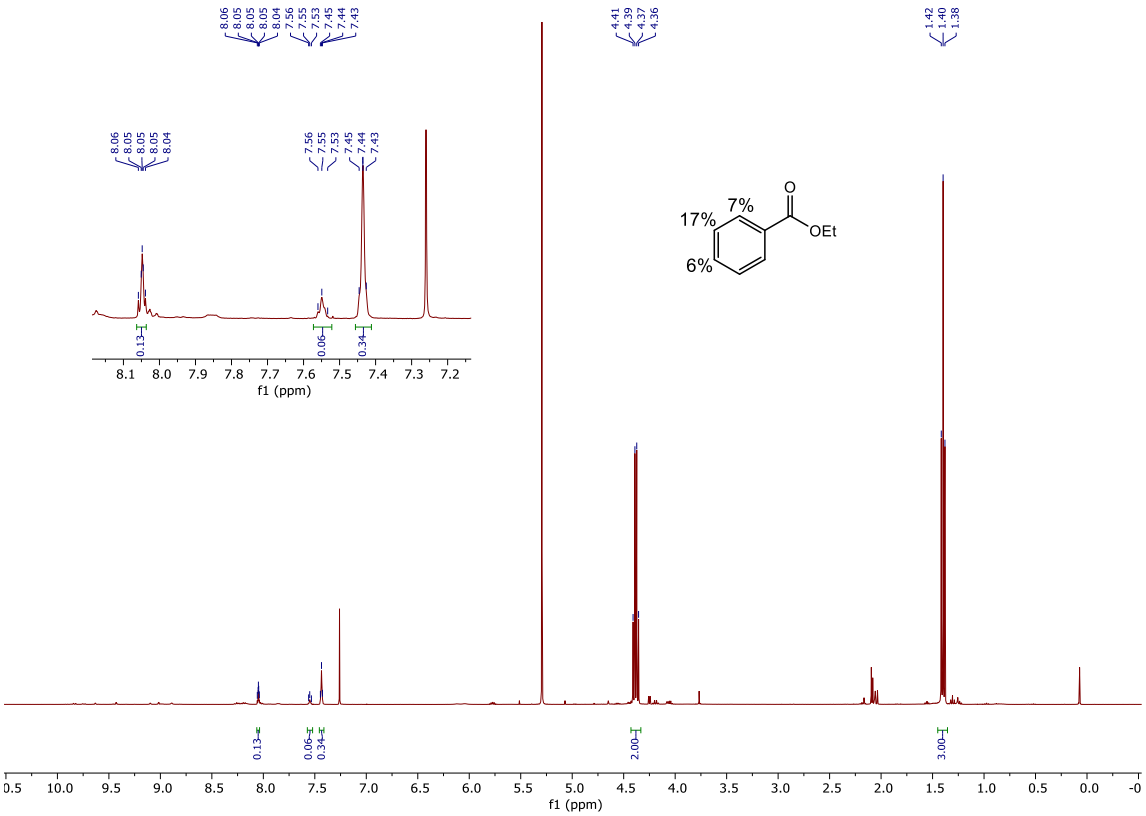
C)


LabelChecker Results
Formula: C7 H5 O
Mass (monoisotopic): 105,03
Difference Value: 0,000490
Error Sum: 0,022
Error (%): 0,214
Meas
Calcd
Rel. Int.
m/z
Deuterium: 0-fold (%): 0,00 0,00
Deuterium: 1-fold (%): 0,02 0,02
Deuterium: 2-fold (%): 0,00 0,00
Deuterium: 3-fold (%): 0,79 0,70
Deuterium: 4-fold (%): 10,89 9,75
Deuterium: 5-fold (%): 100,00 89,53
Label Atom Sum: 4,89 (97,75%)
Isotope List used for fitting data:
m/z intensity
105,00 249
106,00 272
107,00 391
108,00 3165
109,00 39693
110,00 361501
111,00 35316
112,00 2941

^{1}H of D5-Ethylbenzoate (1h-d5)

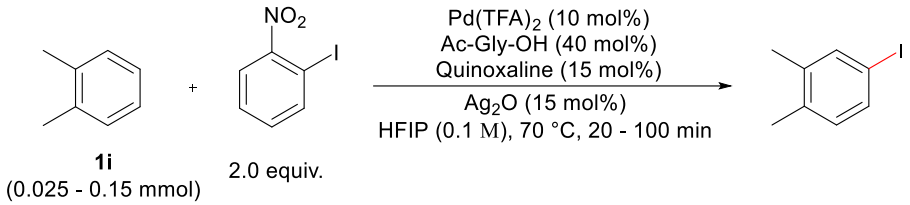


^{1}H of D5-Ethylbenzoate (1h-d5) after Reaction without I-Reagent



Order in Arene

Scheme S54: Initial rate method to determine the order in *ortho*-xylene (**1i**).

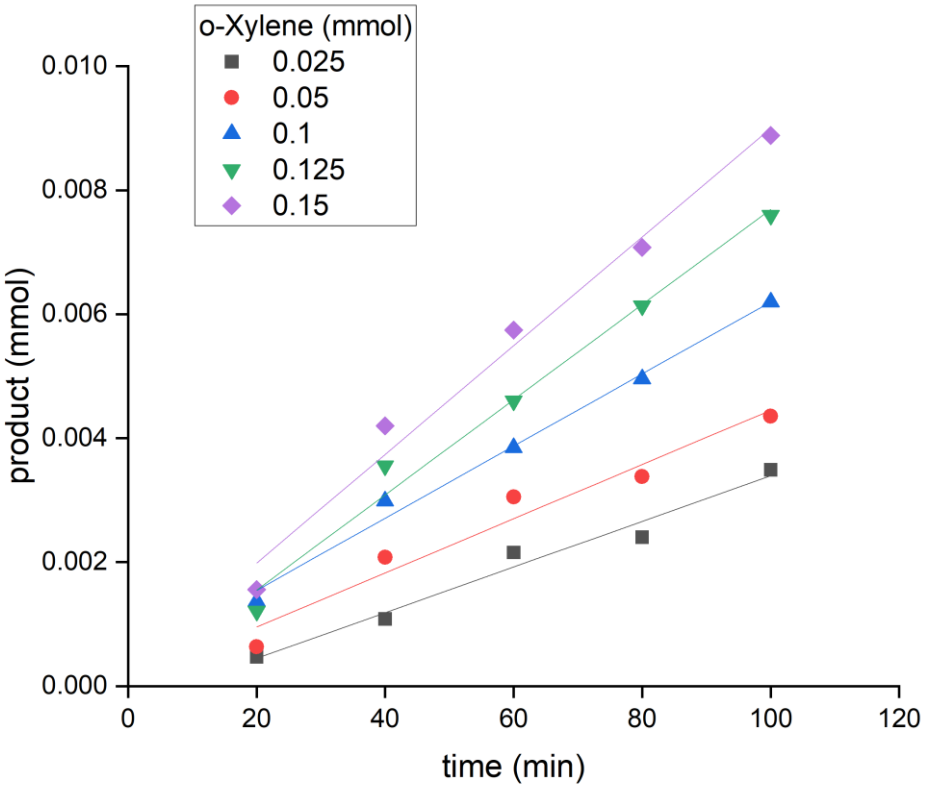


General reaction procedure C was used with the following modifications: The amount of *ortho*-xylene (**1i**) (3.25 - 18.4 µL, 0.025 - 0.150 mmol, 0.25 - 1.50 equiv) was varied. The initial rates and the corresponding standard error were plotted as a function of concentration of the varied reagent. A non-linear least squares fit ($y = A*x^B$) was applied with y = initial rate, x = concentration of the varied reagent, A = rate constant and B = reaction order in varied reagent (**Figure 4**).[13]

Table 4. Initial rate method to determine the order in *ortho*-xylene (**1i**).

Entry	Amount of *ortho*-xylene (1i) (mmol)	reaction time (min)	yield (%)[a]	product (mmol)
1	0.025 mmol	20	0.5%	0.00047
2	0.025 mmol	40	1.1%	0.00108
3	0.025 mmol	60	2.2%	0.00216
4	0.025 mmol	80	2.4%	0.00240
5	0.025 mmol	100	3.5%	0.00349
6	0.05 mmol	20	0.6%	0.00064
7	0.05 mmol	40	2.1%	0.00208
8	0.05 mmol	60	3.1%	0.00305
9	0.05 mmol	80	3.4%	0.00338
10	0.05 mmol	100	4.4%	0.00436
11	0.1 mmol	20	1.4%	0.00137
12	0.1 mmol	40	3.0%	0.00299
13	0.1 mmol	60	3.9%	0.00385
14	0.1 mmol	80	5.0%	0.00496
15	0.1 mmol	100	6.2%	0.00620
16	0.125 mmol	20	1.2%	0.00121
17	0.125 mmol	40	3.6%	0.00355
18	0.125 mmol	60	4.6%	0.00460
19	0.125 mmol	80	6.1%	0.00614
20	0.125 mmol	100	7.6%	0.00759
21	0.15 mmol	20	1.6%	0.00156
22	0.15 mmol	40	4.2%	0.00420
23	0.15 mmol	60	5.7%	0.00574
24	0.15 mmol	80	7.1%	0.00708
25	0.15 mmol	100	8.9%	0.00888

[a] The yield has been normalized for an *ortho*-xylene (**1i**) amount of 0.1 mmol.



Equation	y = a + b*x				
Plot	0.025 mmol arene	0.05 mmol arene	0.1 mmol arene	0.125 mmol arene	0.15 mmol arene
Weight	No Weighting				
Intercept	−2,8571E−4 ± 2,26665E−4	7,81654E−5 ± 3,47405E−4	3,82404E−4 ± 2,05307E−4	1,4678E−5 ± 3,53507E−4	2,32756E−4 ± 4,27625E−4
Slope	3,67843E−5 ± 3,4171E−6	4,37171E−5 ± 5,23732E−6	5,81708E−5 ± 3,09512E−6	7,67488E−5 ± 5,32932E−6	8,76537E−5 ± 6,44669E−6
Residual Sum of Squares	1,40119E−7	3,29155E−7	1,14957E−7	3,40819E−7	4,98718E−7
Pearson's r	0,9873	0,97914	0,99578	0,99284	0,99198
R-Square (COD)	0,97476	0,95872	0,99158	0,98574	0,98403
Adj. R-Square	0,96635	0,94496	0,98877	0,98099	0,97871

Figure 3: Plot of product (mmol) versus time (min) following general reaction procedure C with linear fits for arene = 0.025 mmol (black), 0.05 mmol (red), 0.1 mmol (blue), 0.125 mmol (green), and 0.15 mmol (pink).

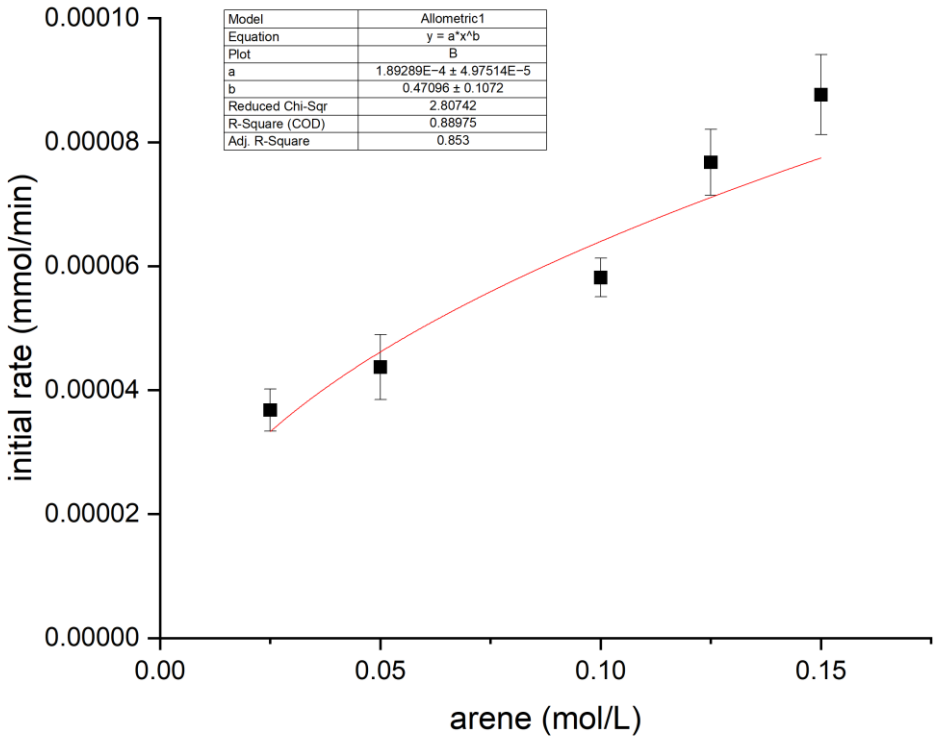
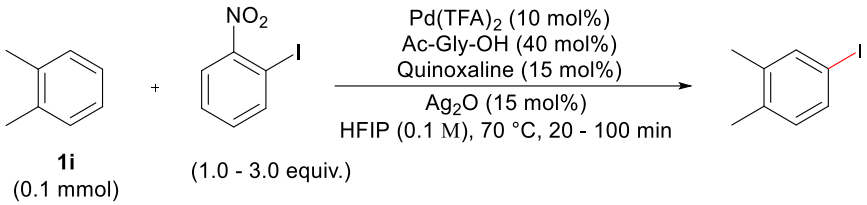


Figure 4: Plot of initial rate (mmol/min) versus arene (mmol) with exponential fit to $y = a*x^b$ where b = reaction order.

Order in I-Reagent

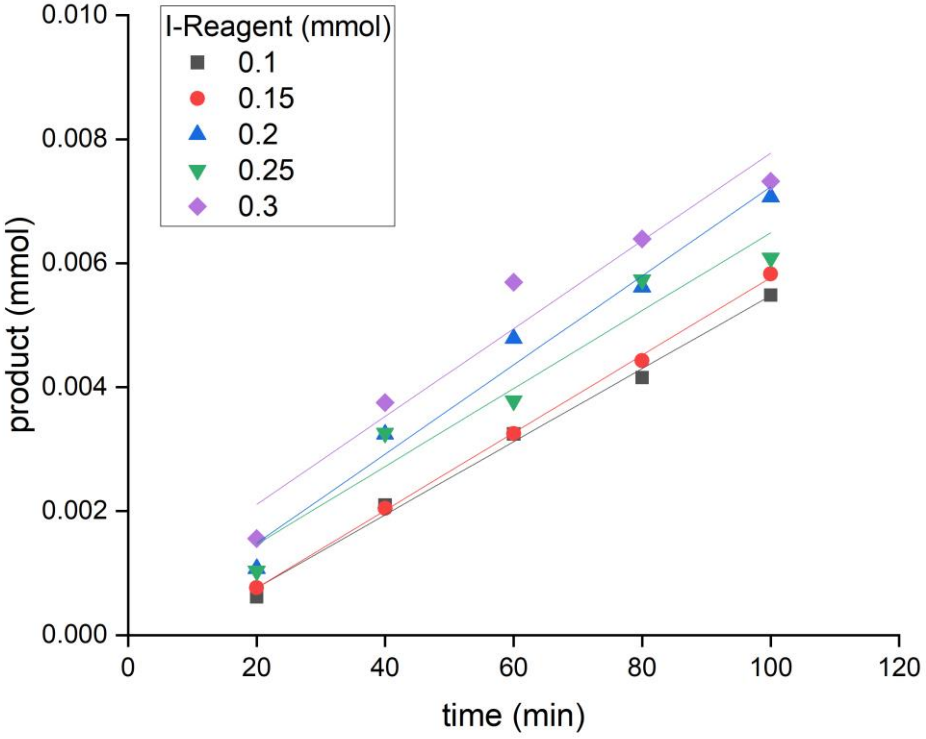
Scheme S55: Initial rate method to determine the order in iodinating reagent.



General reaction procedure C was used with the following modifications: The amount of I-Reagent (24.9 – 74.7 mg, 0.1 - 0.3 mmol, 1.00 – 3.00 equiv) was varied.

Table 5. Initial rate method to determine the order in iodinating reagent.

Entry	Amount of I-Reagent (mmol)	reaction time (min)	yield (%)[a]	product (mmol)
1	0.1 mmol	20	0.6%	0,00062
2	0.1 mmol	40	2.1%	0,00210
3	0.1 mmol	60	3.3%	0,00325
4	0.1 mmol	80	4.2%	0,00415
5	0.1 mmol	100	5.5%	0,00549
6	0.15 mmol	20	0.8%	0,00077
7	0.15 mmol	40	2.0%	0,00204
8	0.15 mmol	60	3.3%	0,00325
9	0.15 mmol	80	4.4%	0,00443
10	0.15 mmol	100	5.8%	0,00583
11	0.2 mmol	20	1.1%	0,00108
12	0.2 mmol	40	3.2%	0,00324
13	0.2 mmol	60	4.8%	0,00479
14	0.2 mmol	80	5.6%	0,00562
15	0.2 mmol	100	7.1%	0,00707
16	0.25 mmol	20	1.0%	0,00104
17	0.25 mmol	40	3.3%	0,00326
18	0.25 mmol	60	3.8%	0,00378
19	0.25 mmol	80	5.7%	0,00573
20	0.25 mmol	100	6.1%	0,00608
21	0.3 mmol	20	1.6%	0,00156
22	0.3 mmol	40	3.8%	0,00375
23	0.3 mmol	60	5.7%	0,00569
24	0.3 mmol	80	6.4%	0,00639
25	0.3 mmol	100	7.3%	0,00732



Equation	y = a + b*x				
Plot	1.0 equiv. I-Reagent	1.5 equiv. I-Reagent	2.0 equiv. I-Reagent	2.5 equiv. I-Reagent	3.0 equiv. I-Reagent
Weight	No Weighting				
Intercept	−4,1711E−4 ± 1,74378E−4	−4,89455E−4 ± 6,63917E−5	4,89267E−5 ± 4,335E−4	2,09273E−4 ± 5,82792E−4	6,94894E−4 ± 6,42144E−4
Slope	5,89567E−5 ± 2,62885E−6	6,25645E−5 ± 1,00089E−6	7,18296E−5 ± 6,53526E−6	6,28169E−5 ± 8,78592E−6	7,08304E−5 ± 9,68069E−6
Residual Sum of Squares	8,29302E−8	1,20214E−8	5,12515E−7	9,26309E−7	1,12459E−6
Pearson's r	0,99703	0,99962	0,98781	0,97189	0,97311
R-Square (COD)	0,99407	0,99923	0,97577	0,94457	0,94693
Adj. R-Square	0,99209	0,99898	0,96769	0,92609	0,92925

Figure 5: Plot of product (mmol) versus time (min) following general reaction procedure C with linear fits for I-Reagent = 0.10 mmol (black), 0.15 mmol (red), 0.20 mmol (blue), 0.25 mmol (green), and 0.30 mmol (pink).

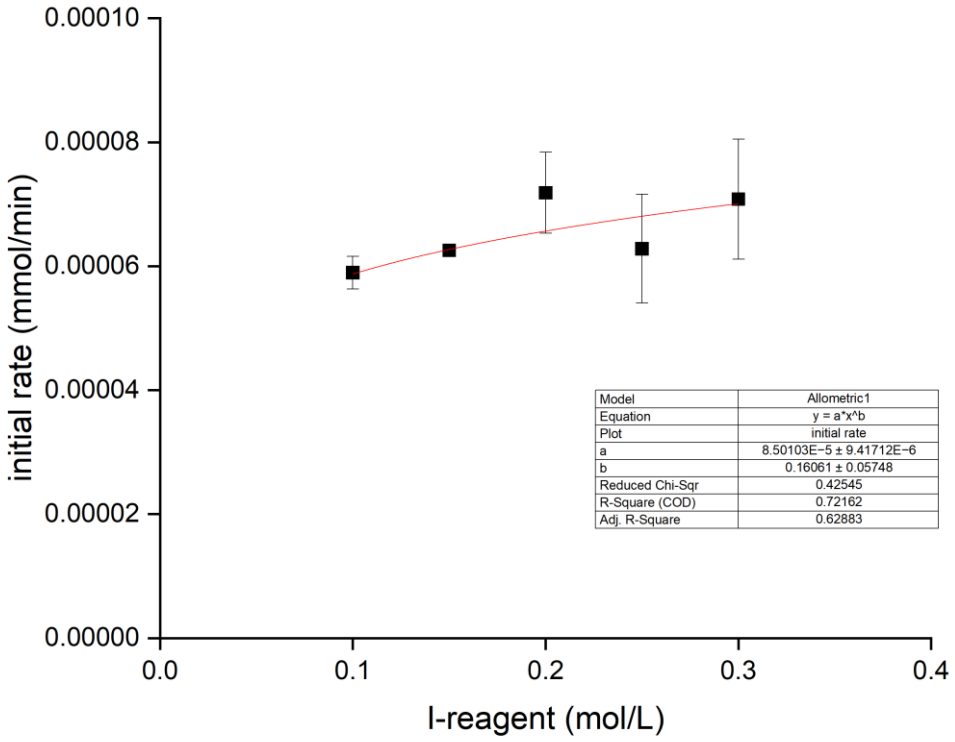
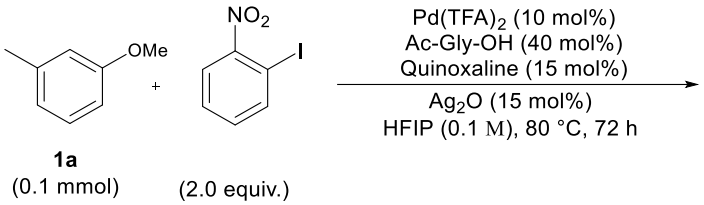


Figure 6: Plot of initial rate (mmol/min) versus I-reagent (mmol) with exponential fit to $y = a*x^b$ where b = reaction order.

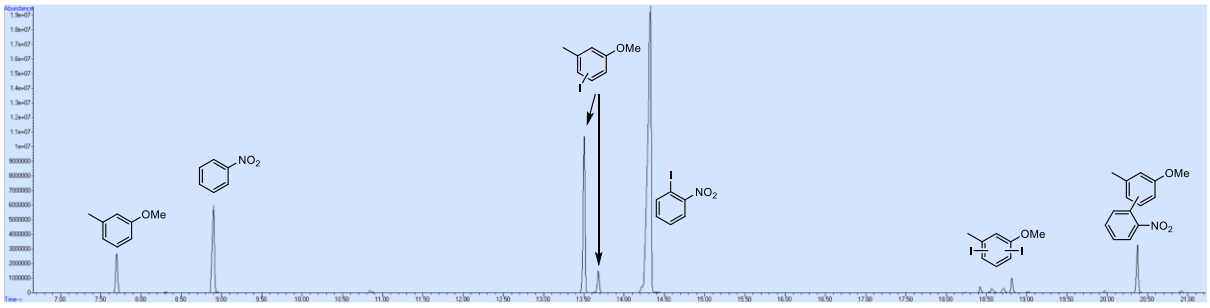
GC-MS traces: Iodination of 1-methoxy-3-methylbenzene (1a) and toluene (1c)

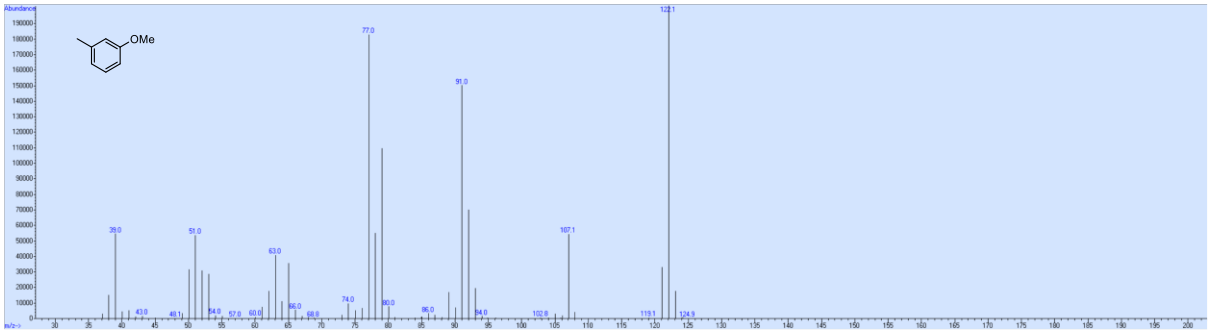


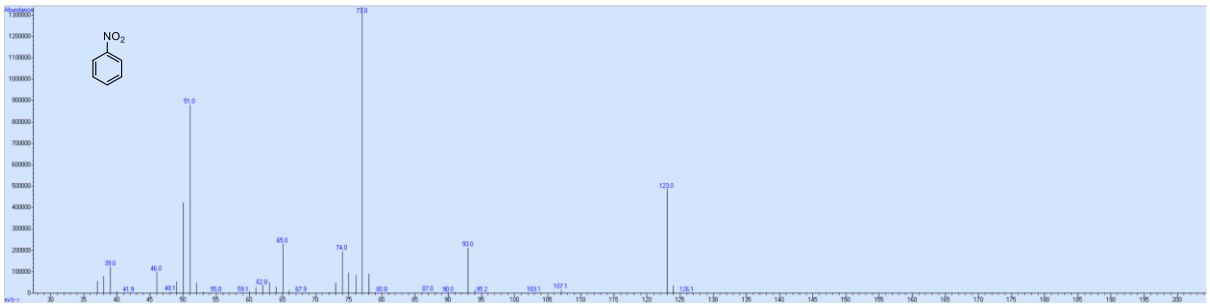
1a
(0.1 mmol)

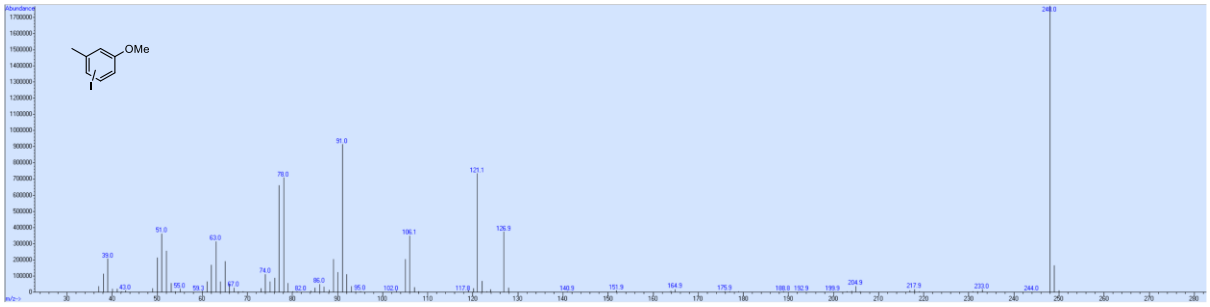
(2.0 equiv.)

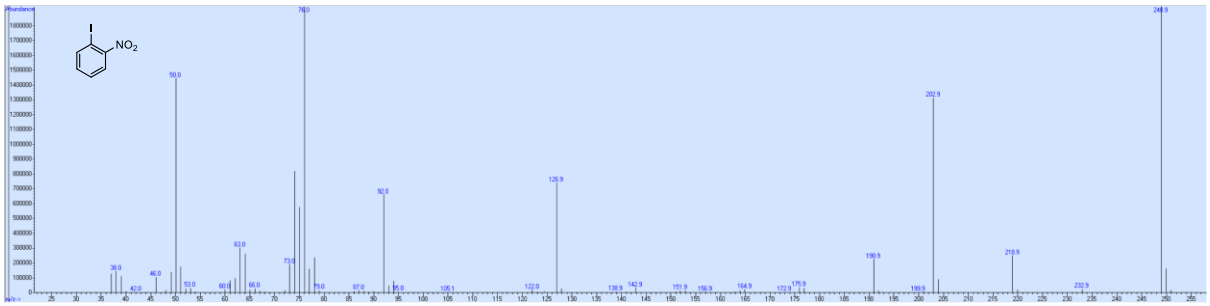
1-iodo-2-methoxy-4-methylbenzene (3a-α), 1-iodo-3-methoxy-5-methylbenzene (3a-β) and 1-iodo-4-methoxy-2-methylbenzene (3a-γ): GC-MS trace of crude reaction mixture

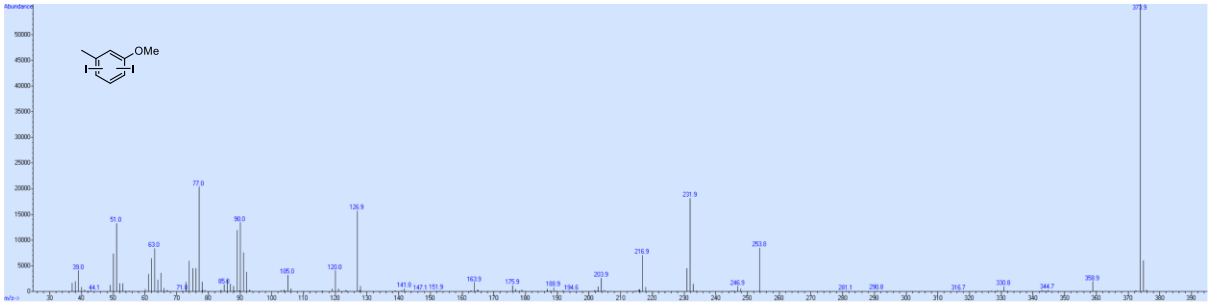


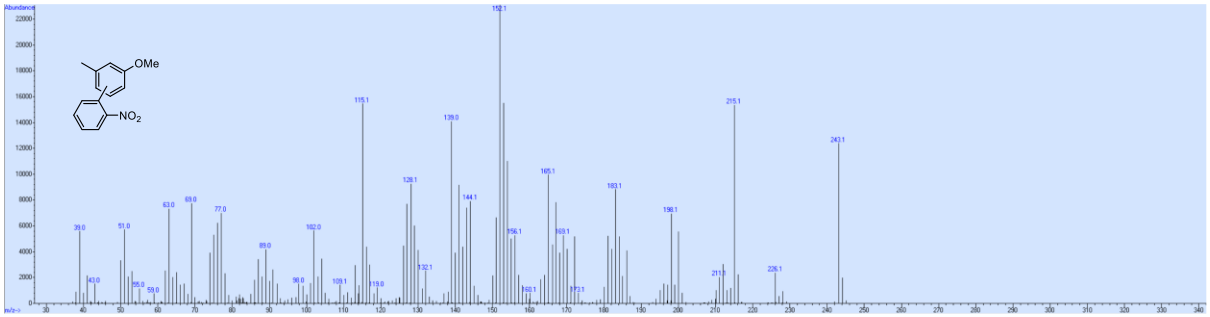


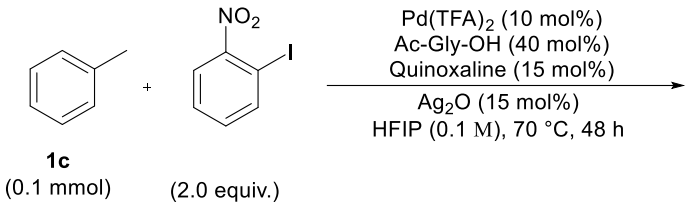




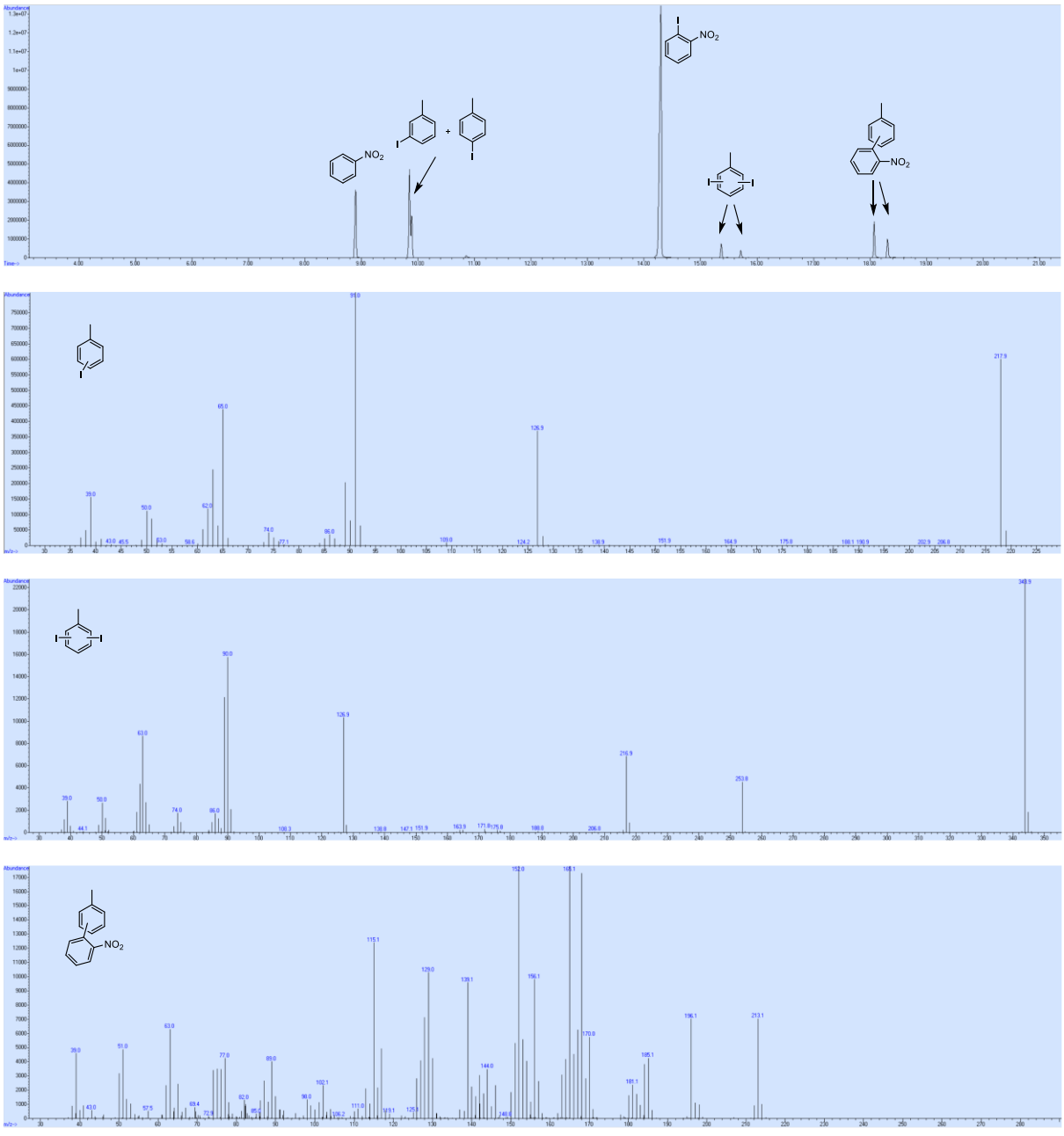

NO2
76.0
50.0
202.9
125.9
92.0
63.0
196.9
218.9
248.9


OMe
373.9
77.0
51.0
126.9
90.0
63.0
221.9
216.9
253.0
39.0


OMe
NO2
152.1
115.1
139.0
215.1
243.1
128.1
105.1
144.1
183.1
77.0
63.0
69.0
51.0
39.0
182.0
89.0
198.1
226.1



1-iodo-3-methylbenzene (3c-meta) and 1-iodo-4-methylbenzene (3c-para): GC-MS trace of crude reaction mixture



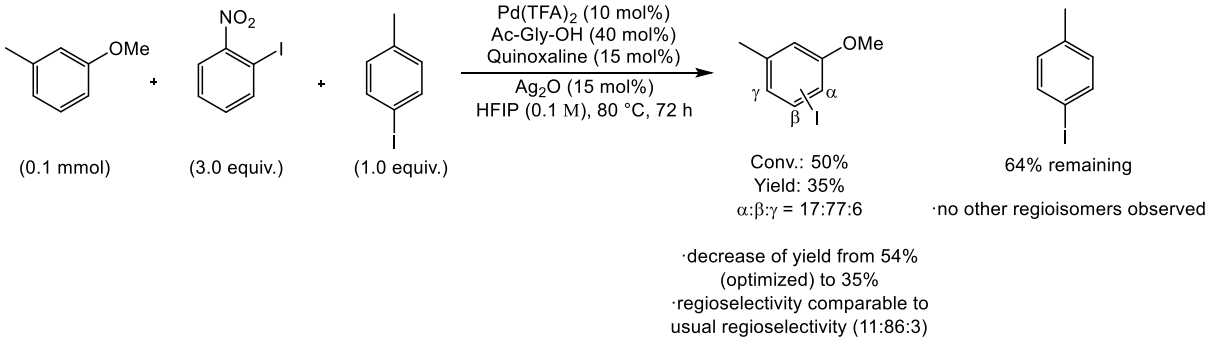
Expanded mechanistic discussion

In order to elucidate whether the product formation is kinetically or thermodynamically controlled, scrambling experiments were performed. Note: The schemes from the scrambling experiments above have been included for clarity reasons.

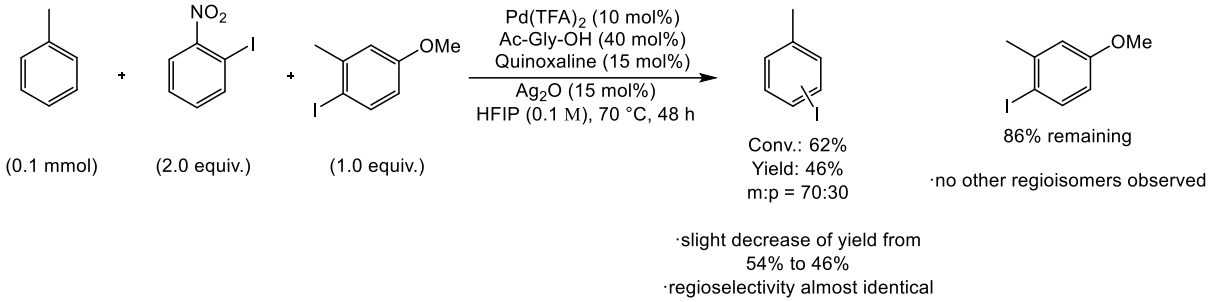
We started our investigation with the reaction of substrates **1a** and **1c** under the respective optimized reaction conditions using 1-iodo-2-nitrobenzene (**2**) (Schemes **S44** and **S45**).

In each case we added an isomerically pure iodinated arene (**p-3c** in Scheme **S44** and **γ-3a** in **S45**) derived from another substrate. Importantly, this experimental setup guarantees that the reaction is ongoing and that thus the catalytically active species are proven to be formed. This is evidenced by the formation of the expected product with comparable yields and selectivities as without the added aryl iodide. Note: A thermodynamically controlled reaction would imply that the regioselectivities obtained in our scope studies are the result of an equilibrium in which all product regioisomers can be converted into the other regioisomers by intermediately being converted back to the starting material. Consequently, the added isomerically pure aryl iodides should likewise be converted into regioisomeric mixtures with the same ratios observed during the scope studies. Specifically, in **S44** meta-iodotoluene is expected to form in large quantities. Likewise, the addition of **γ-3a** in **S45** should result in the formation of the other more stable isomers **α-3a** and **β-3a**.

Scheme S44: Iodination of m-cresol methyl ether (**1a**) with addition of p-iodotoluene (**3c**)



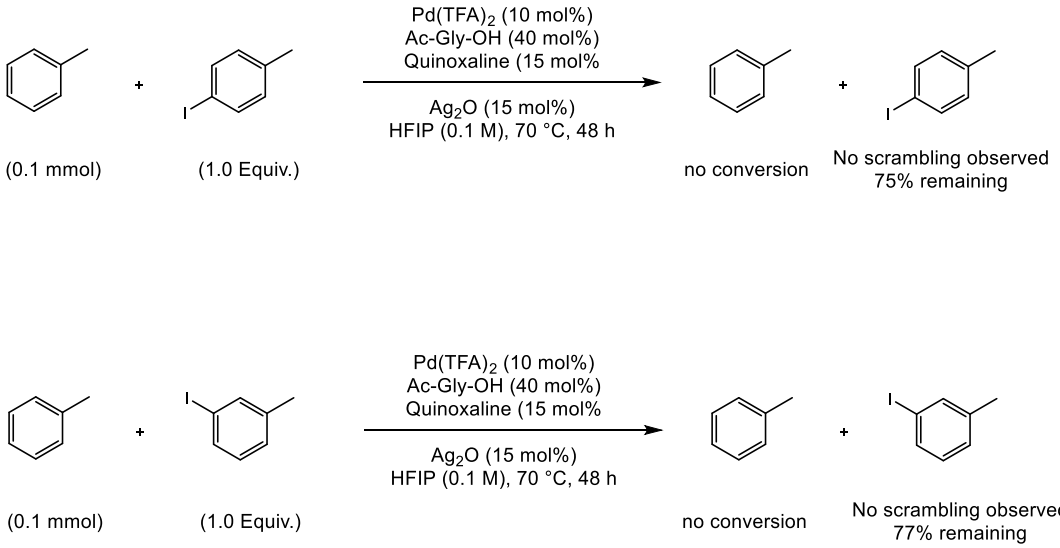
Scheme S45: Iodination of toluene (**1c**) with addition of iodinated m-cresol methyl ether **γ-3a**.



However, while the iodination of the arenes **1a** (**S43**) and **1c** (**S44**) delivered the respective iodinated arenes with almost identical results to the scope studies, the GC-FID analysis of these reactions showed no isomerization of the added iodoarenes. This observation allows to exclude an equilibrium between products and starting materials under our reaction conditions, thereby also ruling out a thermodynamically controlled process.

To further corroborate to this conclusion, we performed reactions where we subjected toluene (**1c**) along with either *para*-iodotoluene (**p-3c**) or *meta*-iodotoluene (**m-3c**) to the reaction conditions (Scheme **S46**). This reaction design would demonstrate if the catalyst system is capable of inducing a reversible reaction in the absence of iodine reagent **2** leading to a regioisomeric mixture of meta-and para-iodotoluene.

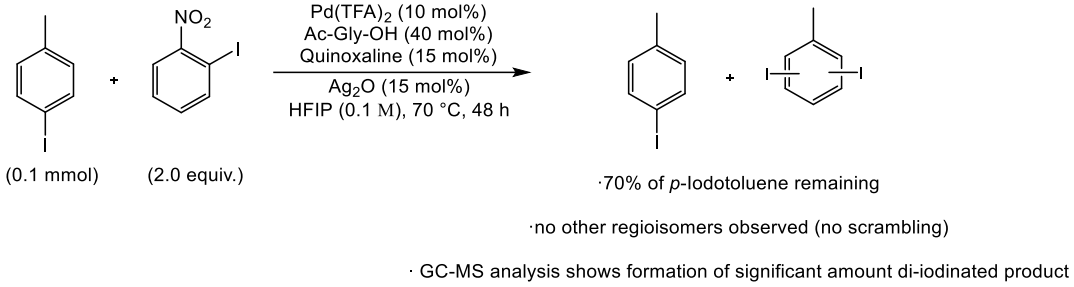
Scheme S46: Reaction subjecting toluene (**1c**) and meta- or para-iodotoluene (**3c**) to reaction conditions without I-Reagent **2**.



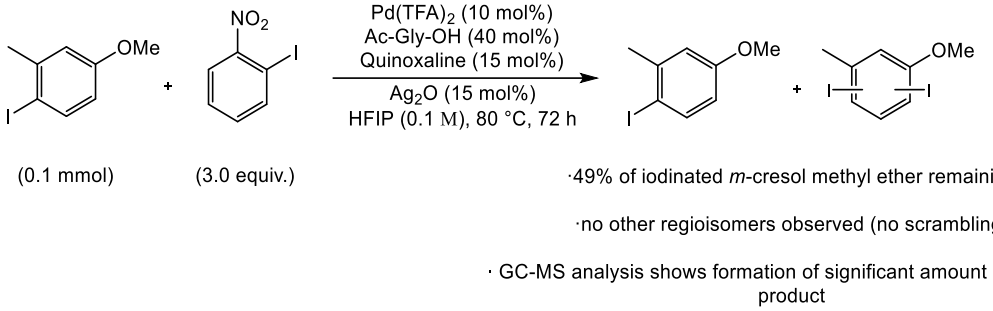
An analysis of the crude reaction mixture did not show any signs of scrambling of the iodine atom to other positions in the arene. Most of the aryl iodide remained unconverted.

To further investigate the reaction with regards to the presence of a possible equilibrium of isomers, isomerically pure molecules **p-3c** and **γ-3a** were subjected to the reaction conditions with iodine reagent **2** to identify whether these reaction conditions would induce an equilibration between the aryl iodide isomers (Schemes **S47** and **S48**).

Scheme S47: Reaction subjecting p-iodotoluene (**3c**) to reaction conditions.

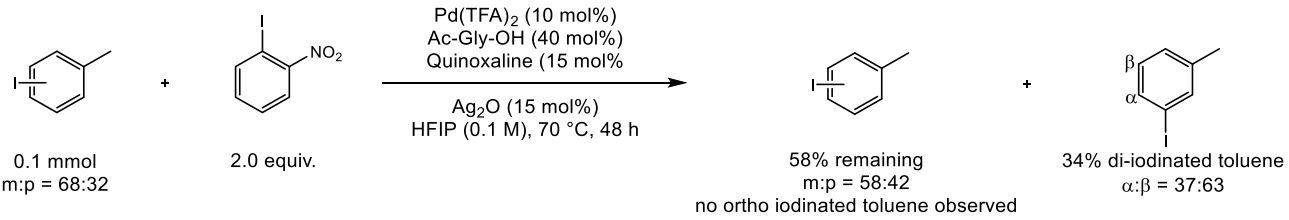


Scheme S48: Reaction subjecting iodinated m-cresol methyl ether **γ-3a** to reaction conditions.



Other regioisomers of the respective iodoarenes were not observed. However, we could observe that di-iodination can occur and consume some of the starting aryl iodide. In addition to these experiments a product mixture of m:p = 68:32 resulting from the iodination of toluene (**1c**) was subjected to the reaction conditions (Scheme **S49**). The formation of ortho-iodinated toluene as well as a variation of the isomeric distribution would suggest the presence of an equilibrium with the formation of ortho iodinated product being kinetically slower.

Scheme S49: Reaction subjecting mixture of iodinated product **3c** to reaction conditions.



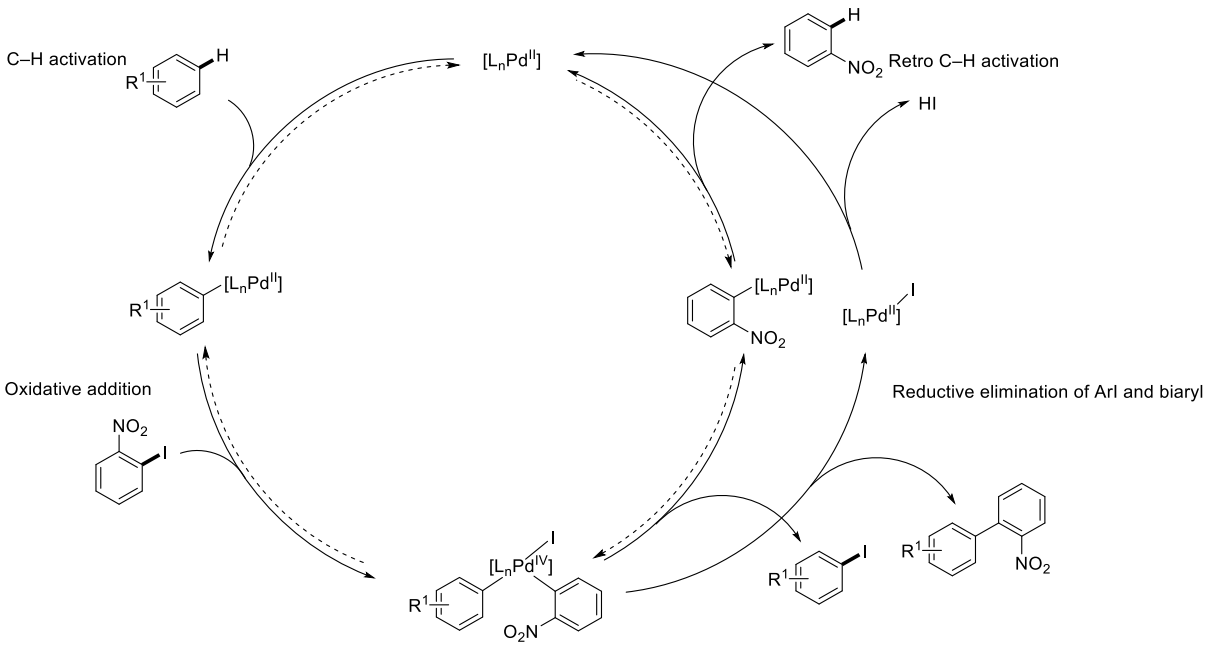
A thorough analysis of the reaction outcome showed that a significant amount of the product mixture **3c** was further iodinated to diiodinated toluene either forming 3,5- or 3,4-diiodinated toluene. This caused the variation of isomeric distribution of mixture **3c**. No ortho iodinated toluene was formed.

In summary, the lack of equilibria as well as the preservation of added isomerically pure iodoarenes unambiguously excludes a thermodynamically controlled process, conversely demonstrating that the process is kinetically controlled.

Having stated the nature of this reaction being kinetically controlled, at least one of the mechanistic steps must be irreversible (Scheme **S56**).

We therefore started to investigate the reversibility of the reaction steps as well as their analysis as to whether they are selectivity and/or rate determining.

Scheme S56: Possible mechanism of the isodesmic C–H iodination.



By inspecting the above scrambling experiments, it can be seen that under the reaction conditions and related conditions, the C–H activation of simple arenes is possible. Likewise the

reductive elimination from an intermediate Pd(IV) species with two aryl substituents and an iodide ligand must be feasible as evidenced by the product formation. Consequently, the absence of scrambling in all of the above cases can only be explained by the conclusion that our catalyst system does not engage in an oxidative addition with simple aryl iodides under the reaction conditions while the oxidative addition can occur with reagent **2**, in which this step is particularly favored, thus rendering the overall process unidirectional (Note: Iodoarenes with an electron-withdrawing substituent in ortho position like the iodine reagent **2** used in this transformation are known for their ease of OA on a Pd(II) complex leading to a Pd(IV) species[14]).

This leads to the identification of the reductive elimination as an irreversible step of our catalytic cycle. Additionally, the subsequent retro-C–H activation to give nitrobenzene is expected to be irreversible, since our previous studies have shown that our catalysts do not engage in the C–H activation of such very electron-poor substrates.

The investigation of the turnover-limiting step(s) and the selectivity determining step(s) will be discussed separately:

1) Turnover-limiting step(s)

KIE (kinetic isotope effect) experiments were performed using o-xylene (**1i**) and deuterated o-xylene (**1i-d_{10}**) indicating that the C–H activation step is at least in part turnover-limiting (parallel KIE = 1.9±0.3, competition KIE = 1.7-1.8). Reversibility experiments using deuterated ethylbenzoate (**1h-d_5**) confirm that the C–H activation step is in principle reversible, but that substantially less retro-C–H activation occurs in the presence of reagent, when product formation is feasible. To gain further insight regarding the turnover-limiting step(s), kinetic orders with respect to arene **1i** (0.5) and iodine reagent **2** (0.2) were determined suggesting that the C–H activation step is the main but not the only turnover-limiting step.

Fractional orders indicate that several steps are close to one another in energy barrier and thus contribute to the overall rate. The order in arene confirms that the C–H activation is one of the steps with the highest activation barrier, but that further steps with competitively high barriers exist in the overall cycle. The order of 0.2 in reagent **2** indicates that either the oxidative addition (OA) of the iodine reagent or the reductive elimination (RE) leading to the iodinated product also contribute to the overall rate. These two steps constitute analogous reactions and, when seen from the perspective of the Pd(IV)-intermediate, are two analogous REs. Considering that reagent **2** is particularly prone to undergo OA, the reverse will conversely be disfavored. In contrast, our experiments show that the OA of simple aryl iodides does not occur, rendering the

reverse RE a highly favorable step. Considering the Bell-Evans-Polanyi principle, the more favorable of two analogous reactions is expected to have the lower barrier. Thus, the RE step of our process is expected to be lower in activation energy than the retro-OA. For this reason, once the Pd(IV)-intermediate has formed, it is expected to proceed to product formation rather than reverting back to the C–H-activated substrate. This leads to the conclusion that the OA step of our catalytic cycle occurs irreversibly, since the subsequent steps are lower in activation barrier. Overall, based on our experimental data and concepts from basic physical organic chemistry, we can conclude that the C–H activation and oxidative addition steps are the turnover-limiting steps of our catalytic cycle.

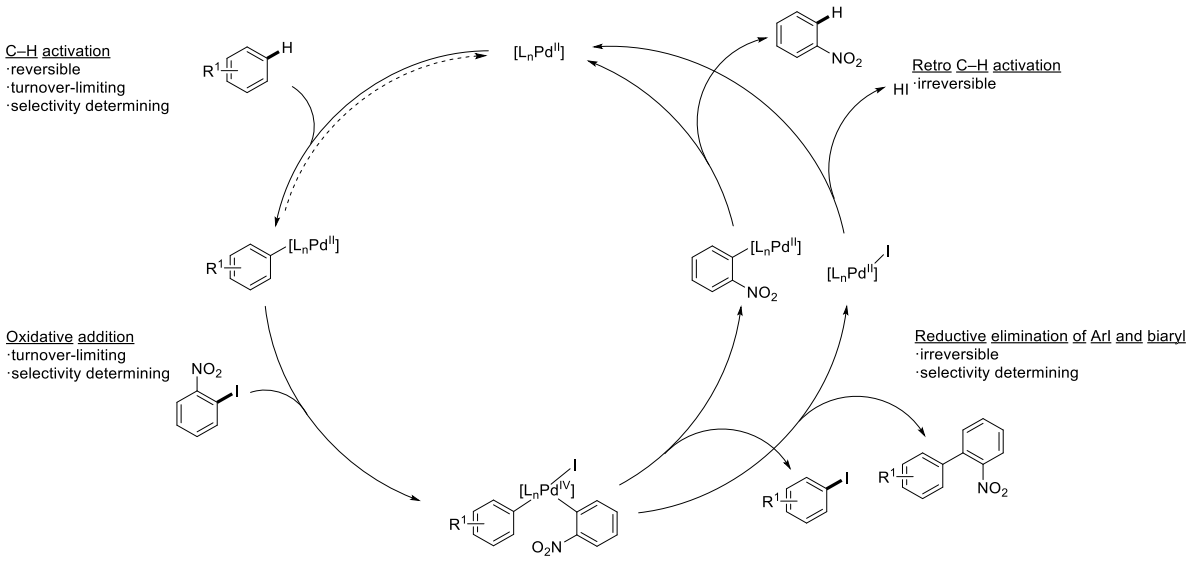
2) Selectivity determining step(s)

Reversibility experiments were performed using deuterated substrate **1h-d$_5$** and subjecting it to the reaction conditions with and without iodine reagent **2**. Significant H/D exchange occurred omitting reagent **2** which indicates the reversibility of the C–H activation step. The regioselectivity of the de-deuteration proves deuterium loss also in the ortho position of **1h-d$_5$** which demonstrates that the ortho position can undergo C–H activation using our catalyst system. This observation suggests that ortho iodination is most likely suppressed in the following steps.

The meta- and para C–H activated species presumably undergo OA with iodine reagent **2** faster than the ortho C–H activated species, allowing the latter to equilibrate back to the starting material and undergo C–H activation in another position. Another important factor regarding the regioselectivity of the iodination process is, that biaryls form as by-products (see SI pp. 181-183). Once the key Pd(IV) intermediate has formed, its regioisomeric forms could vary in their preference for aryl iodide formation vs. biaryl formation. In this sense, the reductive elimination step inherently contributes to the observed overall selectivity. For ortho-C–H activated intermediates it can furthermore be conceived that the barrier for the RE could become similar to the one of the retro-OA, thus allowing some ortho-C–H activated compound to return to the substrate and undergo C–H activation in another position. It should be noted that the comparison of regioselectivities between the deuterium-labelling experiments and the iodination of ethyl benzoate show the same m:p ratio, such that the above effects likely contribute to suppressing the formation of sterically hindered isomers, but do not seem to exert an influence on the ratio between varied sterically accessible positions, in which the C–H activation seems to be the dominant source of selectivity. Finally it should be noted that the observed selectivities closely resemble the regioselectivities observed with our catalyst system

in related transformations strongly suggest the C–H activation via a dual ligand based Pd(II) species rather than via a Pd(IV) species as major contributor to the overall selectivities.

Scheme S57: Properties of the reaction steps.



Regarding the rate- and selectivity-determining steps of the catalytic cycle, it is worth considering the effect of the Ag-additive. As shown in Schemes S32 and S33, the yield substantially drops and the regioselectivity changes favoring the electron-rich positions when no Ag is present. Two rationalizations are in principle possible: a) the observation could be indicative of Ag playing a role in the main rate- and selectivity-determining step, i.e. the C–H activation, or b) the Ag could be involved in another part of the catalytic cycle, which is not rate-/selectivity-determining in the presence of silver (or only contributes to a minor degree), but becomes the rate-/selectivity-determining step in the absence of Ag.[15] Several considerations lead us to favor the latter rationalization: Firstly, we have previously conducted extensive mechanistic studies on a related catalyst system, in which the Ag was demonstrated not to be part of the catalytic mode of action.[16] The related selectivities observed for the C–H activation step in the two studies and the similarity between the catalyst systems implies analogous catalytically active species and thus a C–H activation without the involvement of silver. From the discussion above regarding the rate- and selectivity-determining steps it can be concluded that the second step contributing to rate and selectivity is the oxidative addition step. An influence of the Ag-additive on the efficiency of this step would be in line with all observations within this study, as well as our own mechanistic data and the known influence of silver additives on this step.[17] This also agrees with the observation from Scheme S20 that using aryl iodide reagents with a lower tendency to undergo oxidative addition leads to analogous losses in yield and shifts in regioselectivity. We thus interpret the role of silver to affect the

oxidative addition part of the reaction mechanism in such way that the C–H activation remains the main selectivity-determining step while in its absence the oxidative addition contributes stronger and the overall process becomes less efficient, leading to the observed changes in yield and selectivity. Finally, besides these “active” roles of the Ag-additive, it must be considered that such an additive together with the reaction solvent HFIP forms a buffer with substantially altered solvent properties and proton activities, such that the positive effect observed on any stages of the catalytic cycle could well be explained by an indirect influence rather than a direct involvement of silver ions.

7 References

(1) G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw, K. I. Goldberg, *Organometallics* **2010**, *29*, 2176.

(2) R. K. Harris, E. D. Becker, S. M. Cabral de Menezes, R. Goodfellow, P. Granger, *Solid State Nucl. Magn. Reson.* **2002**, *22*, 458.

(3) B. M. Partridge, J. F. Hartwig, *Org. Lett.* **2013**, *15*, 140; G. J. P. Perry, J. M. Quibell, A. Panigrahi, I. Larrosa, *J. Am. Chem. Soc.* **2017**, *139*, 11527.

(4) H. Yang, Y. Li, M. Jiang, J. Wang, H. Fu, *Chem. Eur. J.* **2011**, *17*, 5652.

(5) P. Klein, V. D. Lechner, T. Schimmel, L. Hintermann, *Chem. Eur. J.* **2020**, *26*, 176.

(6) S. Mukhopadyay, S. Batra, *Chem. Eur. J.* **2018**, *24*, 14622.

(7) M. Jiang, H. Yang, Y. Jin, L. Ou, H. Fu, *Synlett* **2018**, *29*, 1572.

(8) A. A. Cant, R. Bhalla, S. L. Pimlott, A. Sutherland, *Chem. Commun.* **2012**, *48*, 3993.

(9) M. Bergström, G. Suresh, V. R. Naidu, C. R. Unelius, *Eur. J. Org. Chem.* **2017**, 3234.

(10) H. O. Sintim, E.T. Kool, *Angew. Chem. Int. Ed.* **2006**, *45*, 1974.

(11) J. Al-Ka´bi, J. A. Farooqi, P. H. Gore, A. M. G. Nassar, E. F. Saad, E. L. Short, D. N. Waters, *J. Chem. Soc. Perkin Trans. II* **1988**, 943-950.

(12) *OriginPro*, OriginLab Corporation, Northampton, MA, USA.

(13) A. K. Cook, M. S. Sanford, *J. Am. Chem. Soc.* **2015**, *137*, 3109.

(14) E. Motti, N. Della Ca´, S. Deledda, E. Fava, F. Panciroli, M. Catellani, *Chem. Commun.* **2010**, *46*, 4291; X.-C. Wang, W. Gong, L.-Z. Fang, R. Y. Zhu, S. Li, K. M. Engle, J.-Q. Yu, *Nature* **2015**, *519*, 334; Z. Dong, J. Wang, G. Dong, *J. Am. Chem. Soc.* **2015**, *137*, 5887; S. Li, H. Wang, Y. Weng, G. Li, *Angew. Chem. Int. Ed.* **2019**, *58*, 18502.

(15) R. Evans, J. Sampson, L. Wang, L. Lückemeier, B. P. Carrow, *Chem. Commun.* **2021**, *57*, 9076-9079.

(16) P. Wedi, M. Farizyan, K. Bergander, C. Mück-Lichtenfeld, M. van Gemmeren, *Angew. Chem. Int. Ed.* **2021**, *60*, 15641-15649.

(17) N. Zhao, X. Jin, Y. Dang, *Chin. Chem. Lett.* **2021**, *32*, 3980-3983.