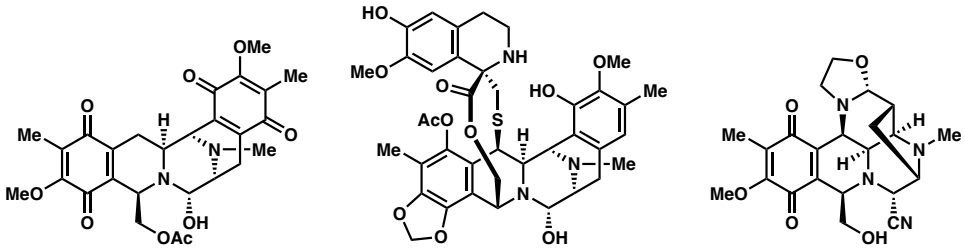
APPENDIX 7

Revised Route Toward the bis-THIQ Natural Products and Synthesis of Non-Natural Analogs[†]

A7.1 INTRODUCTION

Tetrahydroisoquinoline (THIQ) natural products, including the saframycin, ecteinascidin and naphthyridinomycin families, demonstrate remarkable and diverse biological activities, most notably as antitumor antibiotics (Figure A7.1).[1,2]

Figure A7.1 *THIQ natural products.*



(–)-Jorumycin (254) ***Ecteinascidin 743 (Et-743) (255)*** ***(+)-Cyanocycline A (256)***

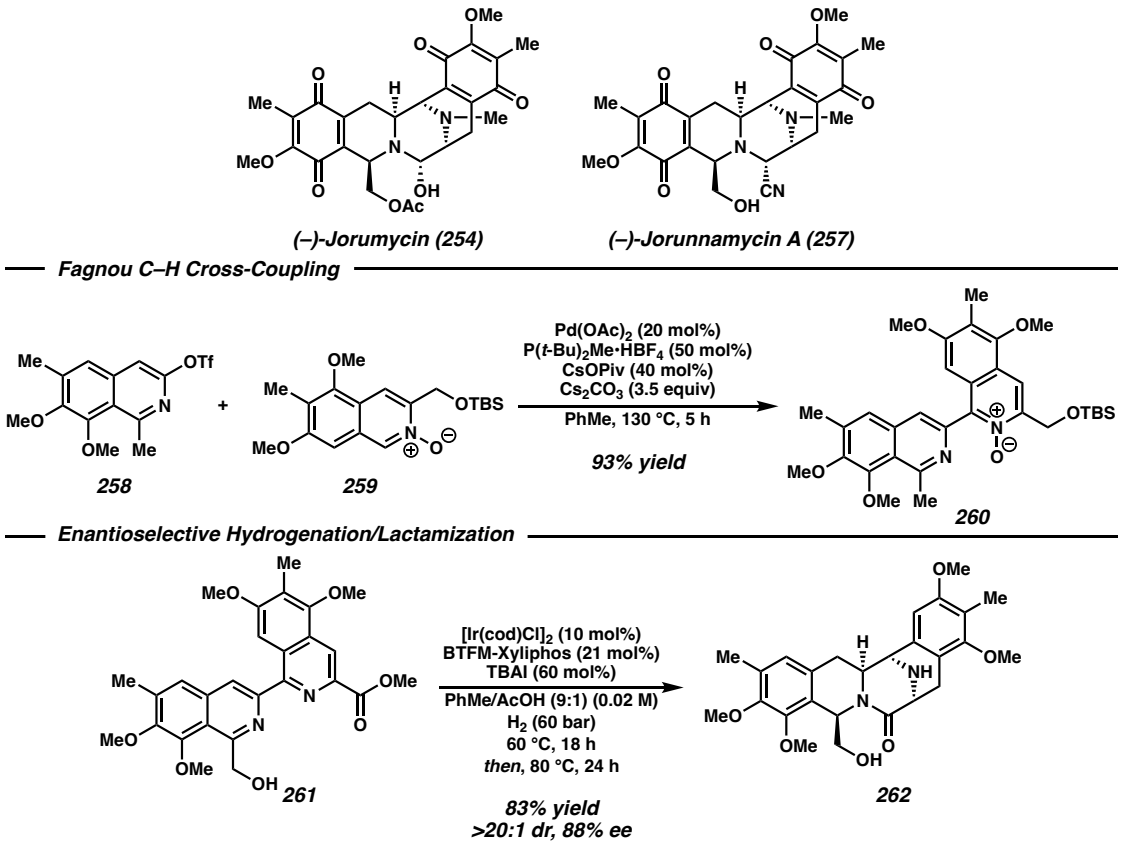
Essential to the biological activities of these natural products is a latent iminium ion—either a hemiaminal, as in (–)-jorumycin or ecteinascidin 743 (Et-743), or an amino nitrile

[†] This research was performed as an extension of the chemistry developed by Dr. Eric Welin, Dr. Gerit Pototschnig, and Dr. Aurapat Ngamnithiporn in collaboration with Rakel Ang and has not been published.

moiety as in (+)-cyanocycline A—which functions as a potent alkylating agent *in vivo*, covalently modifying DNA which ultimately leads to cell death.[3] The promise of these natural products as antitumor agents has already been demonstrated in the case of Et-743, a tris-THIQ natural product used in the treatment of advanced soft-tissue sarcoma (SCS) and ovarian cancer.[3,4]

In 2019, our group completed the convergent total syntheses of (–)-jorumycin and (–)-jorunnamycin A.[5] Key to the synthetic strategy of these complex natural products is a highly enabling C–H cross coupling of the two isoquinoline fragments. Following a series of redox manipulations, we utilized a novel Ir-catalyzed asymmetric hydrogenation to forge all requisite stereochemistry and cyclize the central ring (Figure A7.2).[6]

Figure A7.2 *Key synthetic steps toward (–)-jorumycin and (–)-jorunnamycin A.*

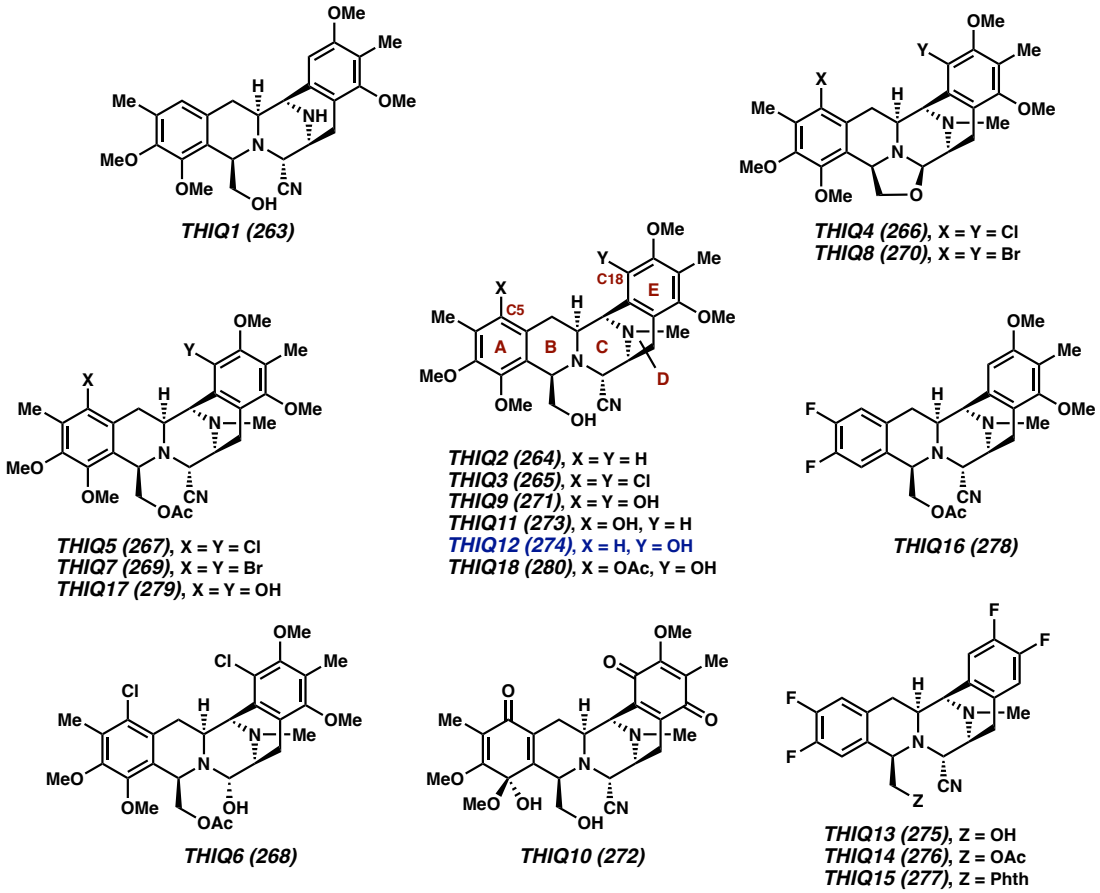


Importantly, this non-biomimetic strategy enables access to derivatives with substantial structural and electronic variation. Although structurally simplified bis-THIQ analogs have been developed by other groups, synthetic efforts have largely focused on alteration of groups appendant to the hydroxymethyl group due to the synthetic constraints of synthesizing electronically differentiated THIQ rings, and electron-deficient analogs have yet to be explored.[7]

A7.2 NON-NATURAL ANALOGS

A7.2.1 SAR of Non-Natural Analogs

Figure A7.3 *Non-natural analogs of (–)-jorumycin and (–)-jorunnamycin A.*



In addition to the completed synthesis of (–)-jorumycin and (–)-jorunnamycin A, our group synthesized a set of 18 non-natural analogs, varying both the substitution and oxidation of the outer aromatic rings as well as exploring alteration to the hydroxymethyl appended to the B ring (Figure A7.3).

Table A7.1 *Assay data for selected analogs of* ***THIQ1*** *(**263**) through* ***THIQ18*** *(**280**).*

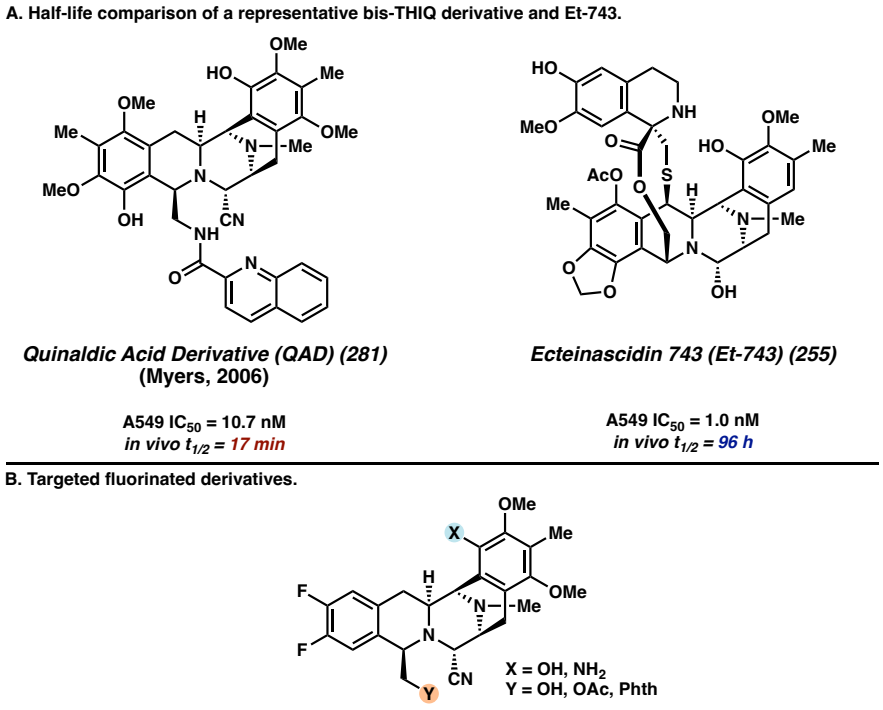
	EC_{50} (uM)		
analog	A427	H810	H1437
THIQ1	38	34	>42
THIQ2	21	11	24
THIQ3	15	18	26
THIQ5	34	>42	>42
THIQ6	42	>42	>42
THIQ7	37	>42	>42
THIQ9	0.71	0.68	3.0
THIQ11	6.3	9.6	21
THIQ12	0.60	0.59	1.5
THIQ13	19	18	15
THIQ14	8.3	5.0	19
THIQ15	6.8	6.3	33
THIQ16	21	16	37
THIQ17	0.07	0.063	0.2
THIQ18	0.32	0.28	1.3

In subsequent biological studies against three cancer cell lines, **THIQ12** (**274**)—an amino nitrile derivative with oxidation deleted at C5 of the A ring—was found to be one of the most potent analogs developed by our group, displaying broad-spectrum activity exceeding **THIQ9** (**271**) bearing both C5 and C18 oxidation (Table A7.1).[5] Moreover, both **THIQ17** (**279**) and **THIQ18** (**280**) possess remarkable potency, with **THIQ17** (**279**) demonstrating sub-micromolar potency against all cell lines tested.

Other groups, most notably Corey and Myers, have also prepared non-natural bis-THIQ derivatives, and our observations are in alignment with the structure-activity relationships (SAR) that their studies established.[7a,b] Their studies suggest that the presence of a hydrogen-bond donor at C18 on the E ring improves biological potency, and

modification of the hydroxymethyl has also been correlated with improved potency.[7a,b] Computational studies examining the pre-covalent interactions of Et-743 suggest that the hydroxyl at C18 participates in critical H-bonding interactions within the DNA minor groove, enhancing their binding affinity prior to covalent alkylation.[8]

Figure A7.4 *Comparison of metabolic stability and targeted fluorinated analogs.*



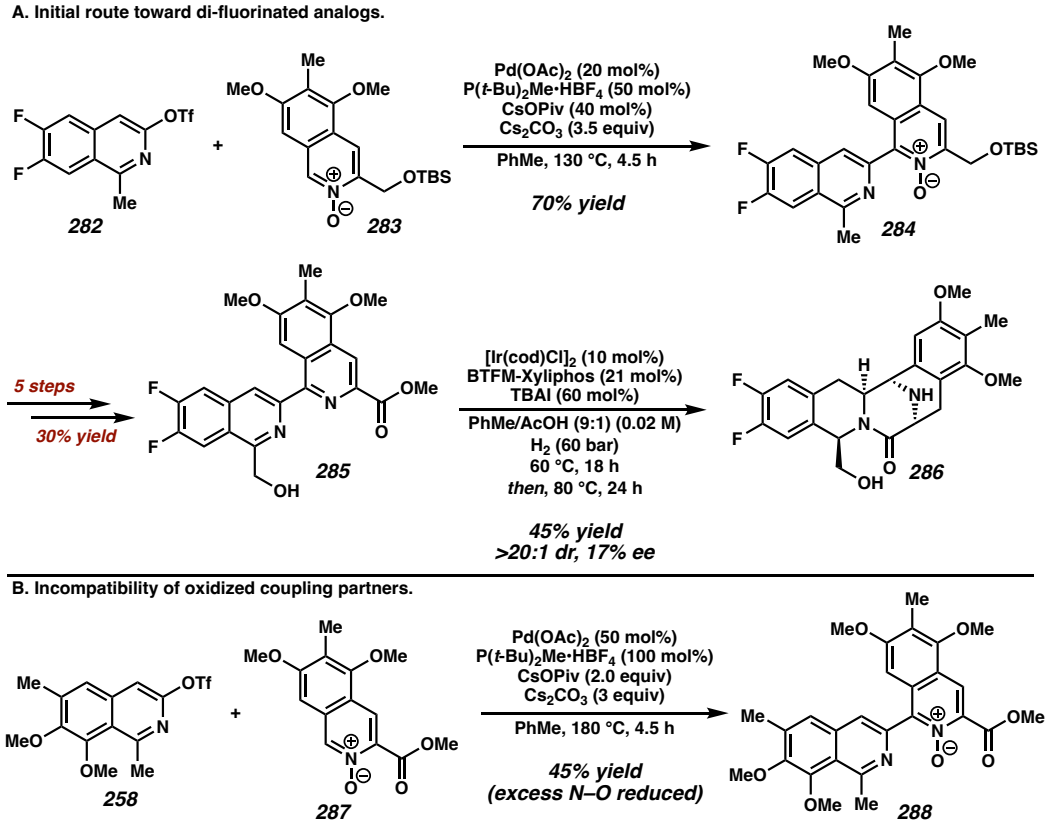
Although typically displaying similar potency, bis-THIQ natural products tend to have shorter half-lives than the larger tris-THIQs, like Et-743 (Figure A7.4a). Because the installation of electron-withdrawing groups is a commonly employed strategy to improve a drug molecule's metabolic stability, we postulate the exploration of simpler, electron-deficient analogs may reveal a promising direction for future antitumor drug development. With these precedents in mind, we are now targeting fluorinated compounds bearing a hydrogen-bond donor at C18 with the aim of exploring whether these derivatives might have improved metabolic stability while maintaining or improving their overall potency (Figure A7.4b). Although the biological activity of fluorinated derivatives **THIQ13** (**275**)–

THIQ16 (**278**) is quite modest, we are optimistic that further oxidation of the E ring may restore potency.

A7.2.1 Development of a Revised Synthetic Route

As we set out to synthesize these fluorinated derivatives, we began our studies following roughly the same route as had been utilized for the synthesis of (–)-jorumycin and (–)-jorunnamycin A, adapting as needed (Scheme A7.1a).[9]

Scheme A7.1 *Initial attempts toward fluorinated analogs.*

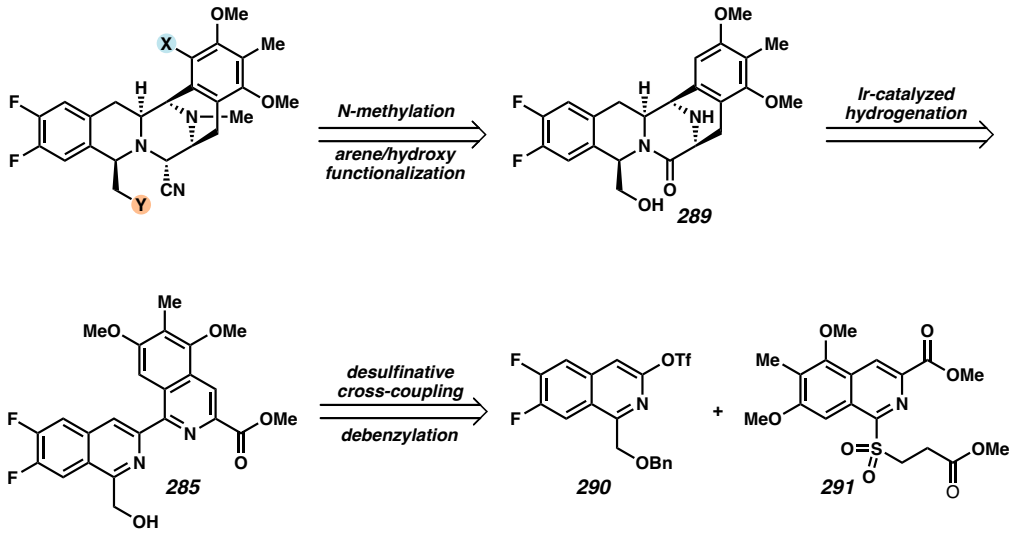


Although the key C-H cross-coupling could be performed in satisfactory yield, the enantioselectivity of the Ir-catalyzed hydrogenation was much poorer, yielding **286** in 45% yield and 17% ee, albeit maintaining an excellent >20:1 dr. We hypothesize that the lower enantioselectivity is due to the poorer chelation of the electron-deficient western isoquinoline, and future studies aim to identify ligands that may be able to better effect this

hydrogenation with improved enantioselectivity. Critically, as adapted for these compounds, the series of redox manipulations utilized to transform **284** to **285** had to be carried out over five steps, losing roughly 70% of the material in the middle of the synthetic sequence.

The initial decision to couple two isoquinoline fragments in the incorrect oxidation state was not an oversight. During the development of the original synthetic route toward these natural products, the isoquinoline oxide **287** was found to be incompatible with the C-H cross-coupling (Scheme A7.1b).[10] To overcome this limitation, we searched the literature for an alternative coupling strategy that might be amenable to more heavily decorated coupling partners, and we were drawn to reports of the desulfinative cross-couplings developed by the Willis group (Scheme A7.2).[11] We envisioned that we may be able to utilize this type of coupling to design a more efficient sequence. To explore this strategy, we first needed to devise new synthetic routes toward the oxidized coupling partners **290** and **291**.

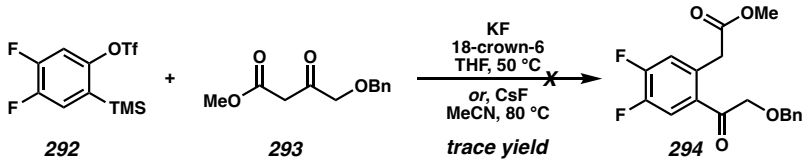
Scheme A7.2 *Retrosynthetic analysis.*



A7.2.1 Synthesis of di-Fluorinated Isoquinoline Triflate

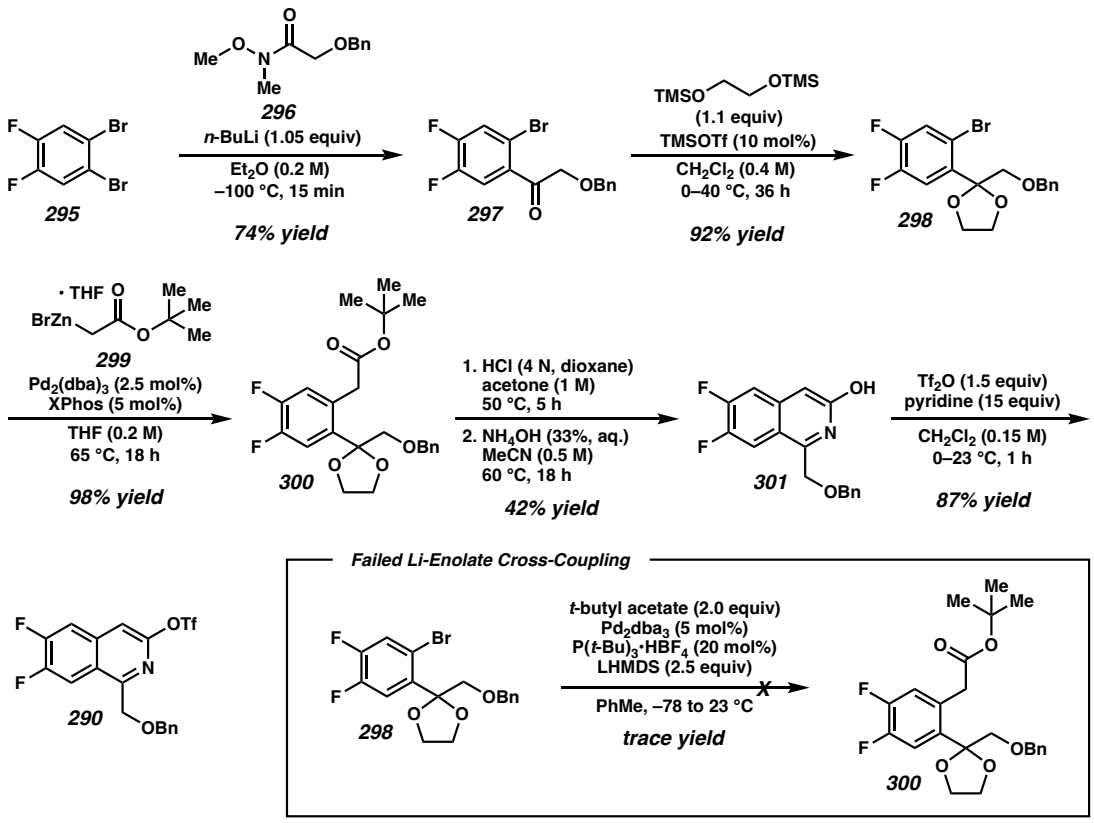
To synthesize the isoquinoline triflate **290**, we first attempted to utilize the aryne annulation strategy developed by our group (Scheme A7.3).[5,12,13]

Scheme A7.3 *Failed aryne annulation.*



Unfortunately, under a variety of conditions, we only observed trace product formation, instead obtaining an intractable mixture of constitutional isomers and oligomers. Owing to the symmetry of our targeted arene, we instead decided to pursue a desymmetrizing strategy (Scheme A7.4).

Scheme A7.4 *Desymmetrizing strategy toward isoquinoline* ***290****.*



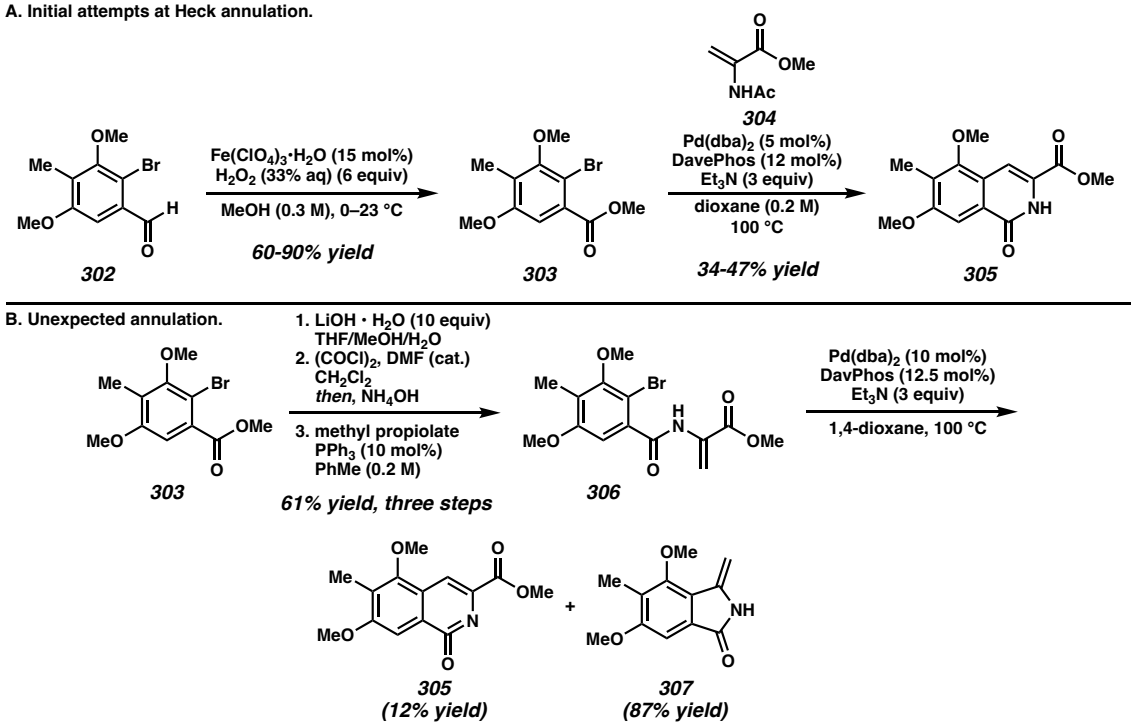
Treatment of dibrominated arene **295** with *n*-BuLi in Et_2O at –100 °C enabled lithium halogen exchange while minimizing formation of an undesired aryne;[14] nucleophilic addition with Weinreb amide **296** delivered ketone **297** in good yield.[15] Noyori ketalization at slightly elevated temperatures proceeded smoothly; all other attempts to generate the desired ketal failed to deliver meaningful yields of **298**, possibly due to the stability of the hemiketal. While a Pd-catalyzed cross-coupling with a lithium enolate only afforded complex mixtures of byproducts, a Negishi reaction with Zn-enolate **299** delivered **300** in near quantitative yield.[16] Exhaustive acid-mediated cleavage of the *t*-butyl ester and ketal and subsequent cyclization with ammonium hydroxide delivered 3-hydroxy isoquinoline **301** in good yield.[5] Triflation completes the synthesis of coupling partner **290**.

A7.2.2 Synthesis of Isoquinoline Sulfone

To synthesize the nucleophilic coupling partner, we first envisioned utilizing a Heck annulation with ester **303** and enamide **304** to generate isoquinolinone **305** that could later be elaborated to the sulfone (Scheme A7.5a).[17] Oxidation of aldehyde **302** with $Fe(ClO_4)_3 \bullet H_2O$ and hydrogen peroxide in the presence of methanol yielded ester **303** in variable, but generally good, yields.[5,18] After surveying a wide array of conditions to effect the desired annulation, we identified DavePhos as the optimal ligand; however, the reaction failed to deliver product exceeding 50% yield, and significant Pd black was formed throughout the reaction, indicating catalyst instability. In addition to the desired isoquinolinone **305**, we noticed an uncyclized Heck byproduct as the main mass balance. To address this issue, we developed an alternative strategy starting from enamide **306**, which we then subjected to our previously developed Heck conditions (Scheme A7.5b).

Surprisingly, this transformation delivered high yields of isoindolinone **307**, presumambly via a decarboxylative annulation. To the best of our knowledge, this specific transformation has not been explicitly studied, and this undesired reaction may serve as inspiration for a future methods project.

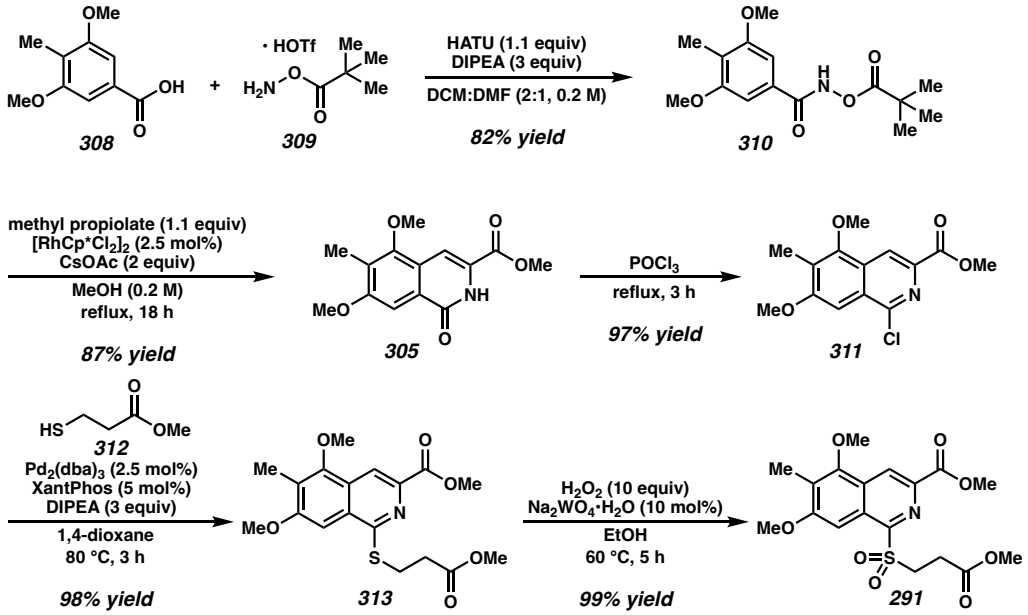
Scheme A7.5 *Heck annulation strategy to access isoquinolinone **305**.*



Due to the difficult oxidative addition of the electron-rich aryl bromide, we devised an alternative strategy utilizing C-H insertion chemistry (Scheme A7.6). Starting from known carboxylic acid **308**, amide coupling with hydroxylamine derivative **309** delivers hydroxamate **310**, which can undergo a subsequent Rh-catalyzed annulation with methyl propiolate to deliver isoquinolinone **305** in good yield.[19] Dehydrative chlorination with $POCl_3$ proceeded smoothly, and the sulfone could be installed over two steps utilizing a sequential Buchwald cross-coupling followed by oxidation of the thioether to the sulfone.[11c] We settled with this two-step approach rather than direct installation of the

sulfone utilizing CuI and SMOPS from a related isoquinoline bromide, which delivered **291** in inferior yields.[11c]

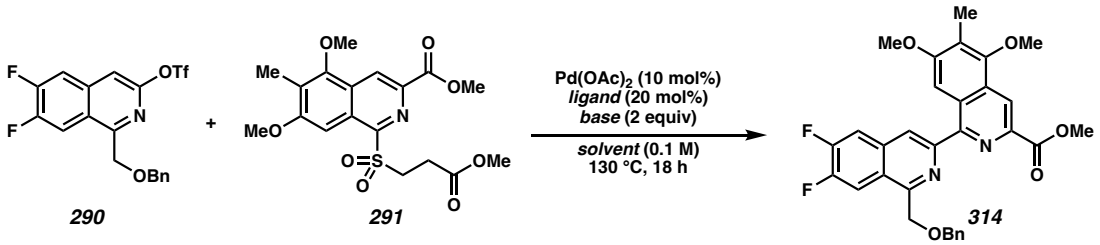
Scheme A7.6 *Optimized route toward sulfone* ***291***.



A7.3 SYNTHESIS OF FLUORINATED ANALOGS

A7.3.1 Optimization of Desulfinative Cross-Coupling

Table A7.2 *Optimization of desulfinative cross-coupling.*



entry	ligand	base	solvent	NMR Yield (%)
1	cataCXium A	K_2CO_3	*m*-xylene	40
2	cataCXium A	Cs_2CO_3	*m*-xylene	0
3	cataCXium A	K_2CO_3	DMF	38
4	P(*t*-Bu)$_3$·HBF$_4$	K_2CO_3	*m*-xylene	5
5	PCy$_3$·HBF$_4$	K_2CO_3	*m*-xylene	10
6	P(*t*-Bu)$_2$Me·HBF$_4$	K_2CO_3	*m*-xylene	81
7[a]	P(*t*-Bu)$_2$Me·HBF$_4$	K_2CO_3	*m*-xylene	92 (88[b])

With both coupling partners in hand, we began optimizing the desulfinative cross-coupling (Table A7.2). Excitingly, using the exact conditions from Willis, we were able to obtain a 40% yield of our desired product.[11c] We found that the use of K_2CO_3 was essential, as a reaction with Cs_2CO_3 failed to product any product. After surveying an array of electron-rich phosphine ligands, we were pleased to find that the use of P(*t*-Bu)$_2$Me•HBF$_4$ delivered our desired product in an excellent 81% yield. Increasing the temperature of the reaction to 140 °C improved the yield to an optimized 88% isolated yield. Gratifyingly, this yield was found to be generally reproducible in up to 2 mmol scale.

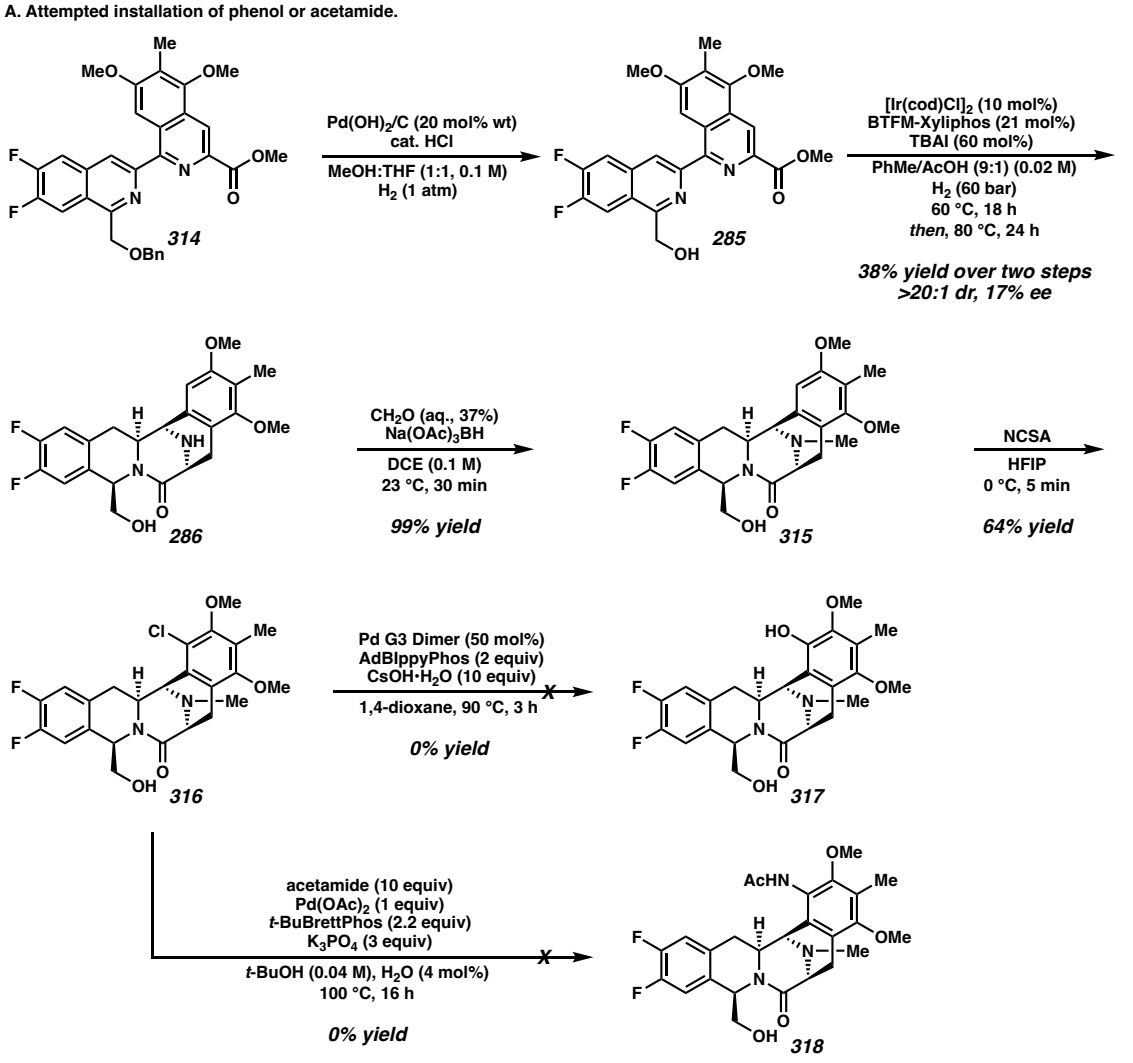
A7.3.2 Endgame Synthesis of Fluorinated Derivatives

Having validated our new strategy, we carried forward with the synthesis of the fluorinated derivatives (Scheme A7.7). The benzyl ether could be efficiently cleaved with Pearlman's catalyst under an atmosphere of H_2, and intermediate **285** was directly subjected to the Ir-catalyzed enantioselective hydrogenation, delivering intermediate **286** in 38% yield over two steps. Methylation via reductive amination proceeded smoothly, and similar to the endgame utilized in our synthesis of (–)-jorumycin and (–)-jorunnamycin A, we could chlorinate the E ring using *N*-chlorosaccharin.[5] Unfortunately, we failed to advance this material to the phenolic aniline derivatives using Buchwald chemistry, although we were able to advance the chlorinated intermediates onward to THIQ19 (**319**) and THIQ20 (**320**).[5]

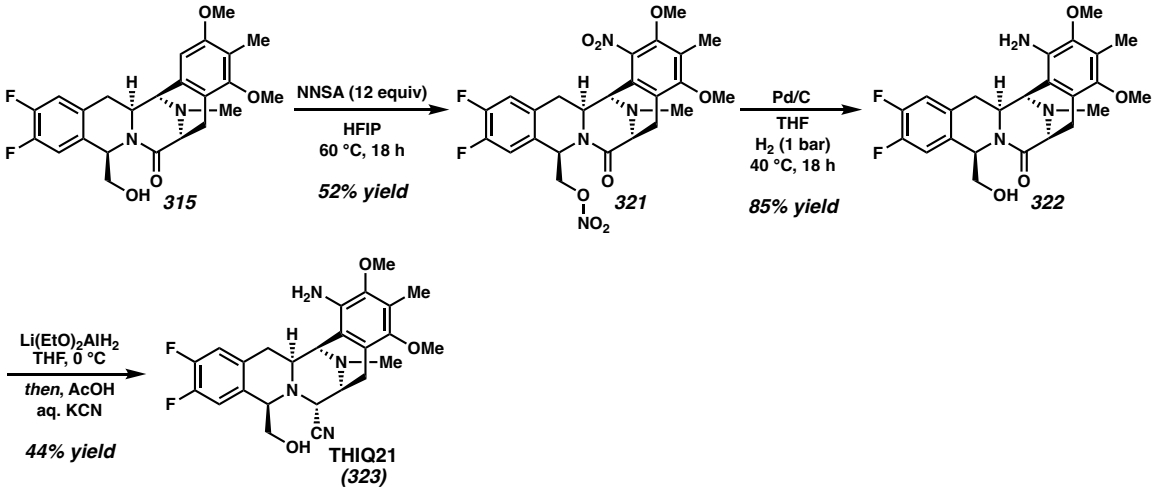
Owing to the efficiency of the chlorination reaction, we decided to utilize *N*-nitrosaccharin to nitrate the E ring, which occurred with concomitant formation of a nitrate ester (Scheme A7.8).[20] Hydrogenolysis with Pd/C reduced both the nitro group and cleaved

the nitrate ester, delivering aniline **322**. Finally, we were able to advance this material onward to derivative **323** following the same previously utilized protocol.

Scheme A7.7 *Endgame toward chlorinated difluorinated analogs* ***THIQ19*** *and* ***THIQ20****.*



Scheme A7.8 *Endgame toward aminated difluorinated analog* ***THIQ21***.



A7.5 BIOLOGICAL ACTIVITY OF FLUORINATED DERIVATIVES

Although we are still awaiting the assay results for **THIQ21**, we were able to assess the biological activity of fluorinated derivatives **THIQ19** and **THIQ20** against three cancer cell lines (Table A7.3).

Table A7.3 *Biological activity of fluorinated derivatives.*

	EC_{50} (uM)		
analog	A427	H810	H1437
THIQ13	19	18	15
THIQ14	8.3	5.0	19
THIQ15	6.8	6.3	33
THIQ16	21	16	37
THIQ19	9.7	7.4	17
THIQ20	5.4	4.6	10

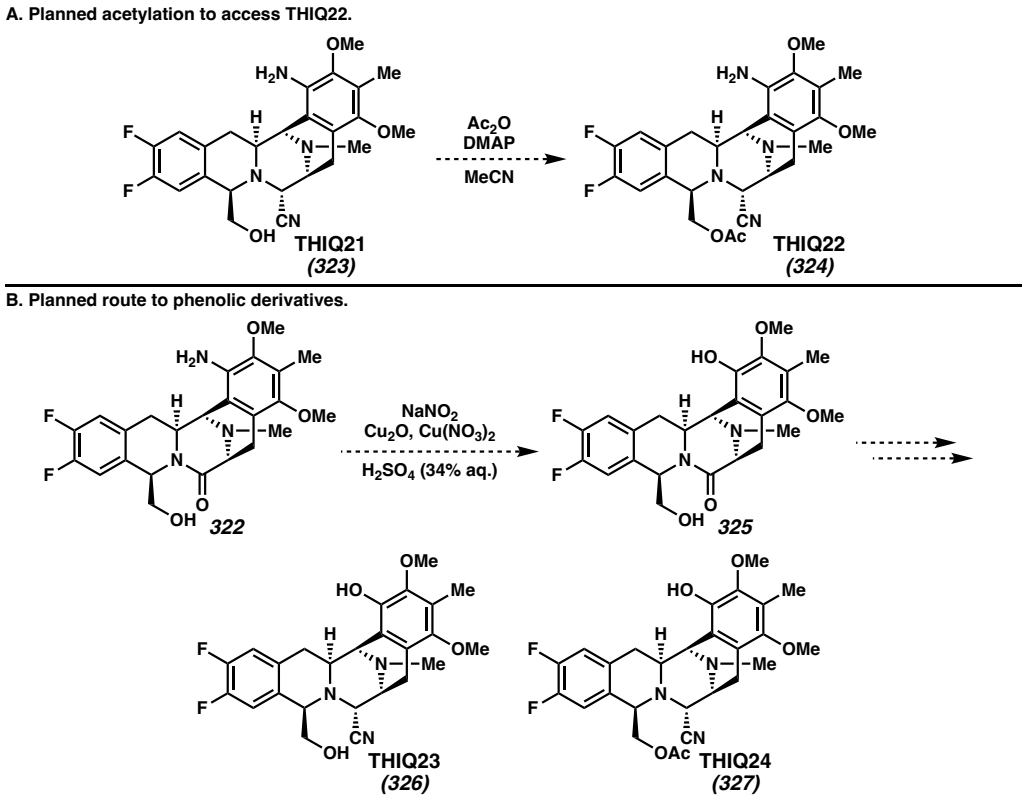
We had anticipated that the chlorinated derivatives would not be as potent as analogs **THIQ17** and **THIQ18** due to the lack of a hydrogen bond donor on the A and E ring. Excitingly, however, we do see an improvement in potency as compared to the other fluorinated derivatives. Comparing **THIQ20** against **THIQ16**, differing only in chlorination at C18, we observe about a three- to four-fold improvement in activity across

all evaluated cell lines, suggesting that regardless of the presence of a hydrogen bond-donor, substitution of C18 is beneficial for activity.

A7.5 CONCLUSIONS AND FUTURE DIRECTIONS

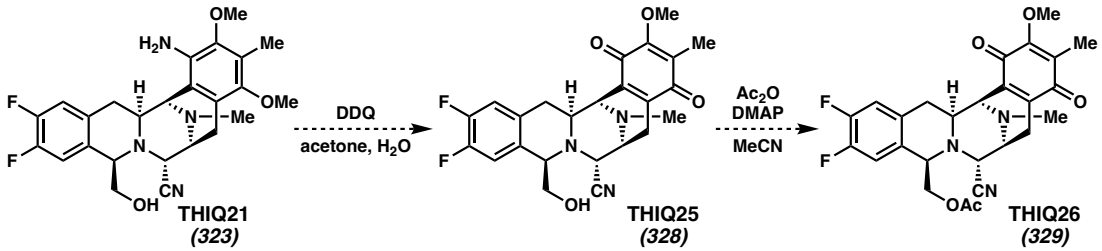
In conclusion, we have presented a modified route toward the bis-THIQ natural product scaffold. Maintaining the same core strategy as the route previously developed in our group, we have redesigned the route to utilize a Pd-catalyzed desulfinative coupling, minimizing redox manipulations and maximizing the convergency of the overall sequence. While we have successfully utilized this strategy to synthesize **THIQ19**, **THIQ20**, and **THIQ21**, in the immediate future, we intend to synthesize acetylated derivative **THIQ22** (Scheme A7.9).

Scheme A7.9 *Planned derivatization of* ***THIQ21***.



Additionally, we plan to explore whether the aniline of intermediate **322** can be converted to a phenol via the formation of a diazonium compound. Moreover, we envision treatment of **THIQ22** (**324**) with an oxidant, like DDQ, in the presence of water could deliver quinones **THIQ25** (**328**) and **THIQ26** (**329**) (Scheme A7.10).[5]

Scheme A7.9 *Planned synthesis of quinone derivatives.*



Ultimately, we intend to evaluate these compounds for both potency and metabolic stability to determine if fluorination is a viable strategy for improving the druglikeness of the smaller bis-THIQ compounds.

A7.6 EXPERIMENTAL SECTION

A7.6.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under a nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[35] Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, iodine, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 μm) was used for silica gel flash chromatography. Teledyne Isco RediSep Gold High Performance C18 columns were used for reverse phase flash chromatography. ^{1}H NMR spectra were recorded on Bruker 400

MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer (101 MHz) and are reported relative to residual $CHCl_3$ (δ 77.16 ppm).^{19}F NMR spectra were recorded on a Varian Mercury 300 MHz spectrometer (282 MHz) and referenced to an external standard (hexafluorobenzene; ^{19}F NMR (282 MHz, $CDCl_3$) δ -161.64.[36] Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet. Data for ^{13}C NMR and ^{19}F NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a ThermoScientific Nicolet iS50 FT-IR spectrometer, or a Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from the Caltech Center for Catalysis and Chemical Synthesis, using an Agilent 6230 Series TOF LC/MS with an Agilent Jet Stream source in electrospray mode (ESI), and the Caltech Mass Spectral Facility, using a JEOL JMS-T2000 AccuTOF GC-Alpha time-of-flight mass spectrometer using Field Desorption (FD) ionization (ions detected are $M^{+\bullet}$).

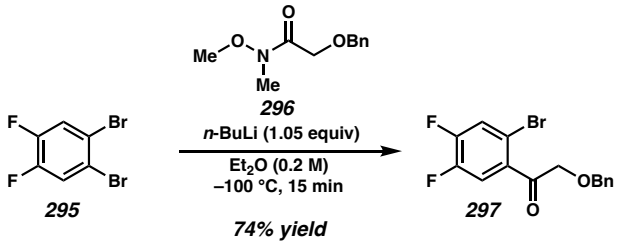
A7.6.1.1 Preparation of Known Compounds

Reagents were purchased from commercial sources and used as received unless otherwise stated. 6,7-difluoro-1-methylisoquinolin-3-yl trifluoromethanesulfonate (**282**),[9] 3-(((tert-butyldimethylsilyl)oxy)methyl)-5,7-dimethoxy-6-methylisoquinoline 2-oxide (**283**),[5] 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate.(**292**),[12b] methyl 4-(benzyloxy)-3-oxobutanoate (**293**),[13] 2-(benzyloxy)-N-methoxy-N-methylacetamide (**296**),[15] (2-(tert-butoxy)-2-oxoethyl)zinc(II) bromide THF adduct (**299**),[16b] and 2-bromo-

3,5-dimethoxy-4-methylbenzaldehyde (**302**)[5] were prepared according to literature procedures. Although known carboxylic acid **308** is commercially available, it was typically accessed via a Pinnick oxidation of the corresponding aldehyde, which can be prepared following a literature procedure.[5]

A7.6.2 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

A7.6.2.1 Synthesis of di-Fluorinated Isoquinoline Triflate (290)



2-(benzyloxy)-1-(2-bromo-4,5-difluorophenyl)ethan-1-one (297)

To a flame-dried 250 mL round bottom flask was added aryl bromide **295** (4.08 g, 15 mmol) and Et_2O (140 mL). The flask was purged with N_2 for 3 minutes and cooled to –100 °C. Then, *n*-BuLi (2.5 M in hexanes, 6 mL, 1 equiv) was added dropwise. After 1 minute, Weinreb amide **296** (3.14 g, 15 mmol, 1 equiv) in Et_2O (7 mL) was added in a thin stream, washing with Et_2O (3 mL). After 30 minutes, the reaction was quenched with HCl (50 mL, 1 N) after removal of the cold bath, stirred for 10 minutes, and then transferred to a separatory funnel. The organic layer was removed, and the aqueous layer was extracted twice with Et_2O. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude oil was purified with silica gel chromatography (0–10% EtOAc/hexanes) to yield ketone **297** (3.81 g, 11.2 mmol, 74% yield).

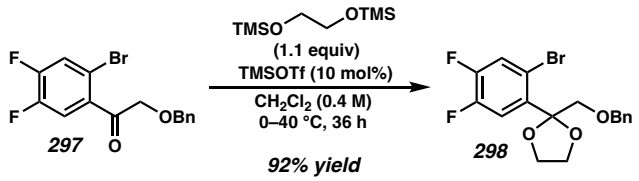
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (dd, *J* = 9.4, 6.9 Hz, 1H), 7.41 – 7.28 (m, 6H), 4.64 (s, 2H), 4.57 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.59, 151.77 (dd, *J* = 206.1, 13.0 Hz), 149.23 (dd, *J* = 200.0, 13.1 Hz), 136.85, 135.41 (t, *J* = 4.3 Hz), 128.68, 128.30, 128.19, 123.03 (d, *J* = 20.2 Hz), 118.70 (d, *J* = 19.6 Hz), 113.95 (dd, *J* = 7.5, 4.1 Hz), 74.28, 73.71.

^{19}F NMR (282 MHz, $CDCl_3$): δ -130.00, -136.85

IR (neat film, NaCl): 3059, 1717, 1598, 1531, 1493, 1384, 1293, 1167, 1125, 1030, 883, 777 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{15}H_{11}BrF_2O_2$ $[M]^{+\bullet}$: 339.9905, found 339.9904.



To an oven-dried microwave vial was added ketone **297** (500 mg, 1.47 mmol) in CH_2Cl_2 (4 mL, 0.4 M). The solution was purged with N_2 for 3 minutes, and then 1,2-bis(trimethylsiloxy)ethane (0.40 mL, 1.61 mmol, 1.1 equiv) was added. The reaction was cooled to 0 °C, and TMSOTf (0.03 mL, 0.147 mmol, 10 mol%) was added dropwise. The cooling bath was removed, and the reaction was heated to 40 °C for 18 h, or until starting material was consumed by TLC. The reaction was cooled, quenched with saturated aqueous $NaHCO_3$, transferred to a separatory funnel, and the organic layer was separated. The aqueous layer was extracted three times with CH_2Cl_2, and the combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude oil was purified with silica gel chromatography (0–10% EtOAc/hexanes) to yield ketal **298** (519.3 mg, 1.35 mmol, 92% yield).

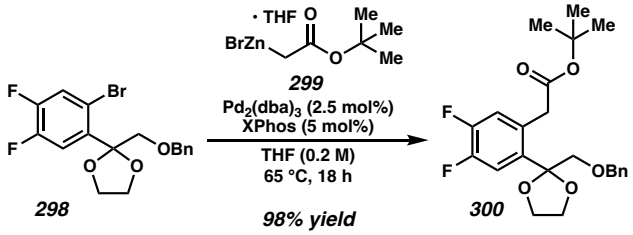
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (dd, *J* = 11.6, 8.5 Hz, 1H), 7.40 (dd, *J* = 9.6, 7.3 Hz, 1H), 7.34 – 7.20 (m, 5H), 4.60 (s, 2H), 4.20 – 4.08 (m, 2H), 3.91 (s, 2H), 3.90 – 3.86 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.78 (dd, *J* = 253.9, 13.5 Hz), 149.21 (dd, *J* = 249.2, 12.0 Hz), 138.04, 136.12 (dd, *J* = 4.0, 4.0 Hz), 128.44, 127.74, 127.71, 123.60 (d, *J* = 19.9 Hz), 118.55 (d, *J* = 19.9 Hz), 114.30 (dd, *J* = 7.1, 3.8 Hz), 108.58, 73.87, 71.66, 65.40.

^{19}F NMR (282 MHz, $CDCl_3$): δ -135.76 (d, *J* = 21.5 Hz), -138.53 (d, *J* = 21.5 Hz).

IR (neat film, NaCl): 3059, 2891, 1604, 1491, 1453, 1383, 1287, 1212, 1167, 1105, 1031, 951, 893, 796, 741 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{17}H_{15}BrF_2O_2$ $[M]^{+\bullet}$: 384.0167, found 384.0164.



To a flame-dried two-neck round bottom flask equipped with a reflux condenser was added $Pd_2(dba)_3$ (81 mg, 0.089 mmol, 2.5 mol%), XPhos (85 mg, 0.178 mmol, 5 mol%) and freshly prepared solid **299** (1.77 g, 5.32 mmol, 1.5 equiv).[16b] The flask was backfilled three times with N_2, and a solution of ketal **298** (1.37 g, 3.56 mmol) in THF (15 mL) was added, rinsing with THF (3 mL). The reaction was heated to 65 °C and continued overnight. Upon completion, the reaction was cooled, quenched with saturated aqueous NH_4Cl, and transferred to a separatory funnel. The aqueous layer was extracted three times with ethyl acetate, and the combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude oil was purified with silica gel

chromatography (0–20% EtOAc/hexanes) to yield ester **300** (1.46 g, 3.47 mmol, 98% yield).

Note: although enolate **299** was typically isolated as a solid for this reaction following a literature procedure, solutions of **299** have also been utilized for this transformation to satisfactory yield.

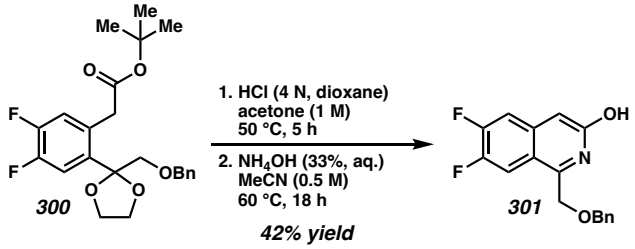
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (dd, *J* = 11.8, 8.4 Hz, 1H), 7.35 – 7.16 (m, 5H), 6.99 (dd, *J* = 11.1, 7.7 Hz, 1H), 4.58 (s, 2H), 4.12 – 4.00 (m, 2H), 3.88 – 3.76 (m, 2H), 3.70 (s, 2H), 3.64 (s, 2H), 1.45 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.94, 149.74 (dd, *J* = 248.8, 12.7 Hz), 148.95 (dd, *J* = 247.2, 12.4 Hz), 137.89, 135.59, 130.04 (dd, *J* = 6.0, 3.9 Hz), 128.35, 127.63, 127.51, 120.84 (d, *J* = 17.3 Hz), 116.93 (d, *J* = 18.8 Hz), 80.76, 73.80, 65.18, 39.81, 28.12.

^{19}F NMR (282 MHz, $CDCl_3$): δ -138.80 (d, *J* = 22.1 Hz), -140.23 (d, *J* = 22.1 Hz).

IR (neat film, NaCl): 2978, 1731, 1606, 1510, 1453, 1366, 1306, 1147 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{23}H_{26}F_2O_5$ $[M]^{+\bullet}$: 420.1743, found 420.1743.



To a round bottom flask equipped with a reflux condenser was added ester **300** (3.49 mg, 8.3 mmol), acetone (10 mL) and HCl (4N in dioxane, 21 mL, 83 mmol, 10 equiv). The mixture was heated to 50 °C for 5 h, or until an aliquot by ^{1}H NMR indicated full cleavage of both the *t*-butyl ester and ketal. The crude mixture was concentrated under reduced pressure and transferred to a Schlenk flask with MeCN (17 mL). NH_4OH (33 mL, 33% aq.) was added, and the flask was sealed and heated to 60 °C overnight, at which point

it was cooled, concentrated, partitioned between ethyl acetate and sat. aqueous NH_4Cl, and extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude oil was purified with silica gel chromatography (0–5% MeOH/CH_2Cl_2) to yield 3-hydroxy isoquinoline **301** (1.05 g, 3.5 mmol, 42% yield).

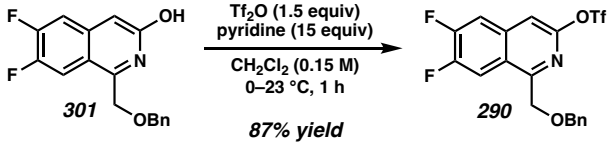
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (dd, *J* = 11.2, 8.0 Hz, 1H), 7.42 – 7.31 (m, 6H), 6.93 (s, 1H), 5.00 (s, 2H), 4.68 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.99 (d, *J* = 2.1 Hz), 154.03 (dd, *J* = 259.0, 16.9 Hz), 148.52 (dd, *J* = 251.0, 16.6 Hz), 139.75 (d, *J* = 9.2 Hz), 137.23, 128.68, 128.27, 118.21 (d, *J* = 6.9 Hz), 113.93 – 111.88 (m), 111.39 (d, *J* = 17.3 Hz), 104.12 – 103.50 (m), 73.41, 69.76, 65.36.

^{19}F NMR (282 MHz, $CDCl_3$): δ -128.00 (d, *J* = 19.5 Hz), -136.68 (d, *J* = 20.0 Hz).

IR (neat film, NaCl): 2863, 1573, 1515, 1331 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{17}H_{13}F_2NO_2$ $[M]^{+\bullet}$: 301.0909, found 301.0900.



To a flame-dried round bottom flask was added 3-hydroxy isoquinoline **301** (424 mg, 1.41 mmol), CH_2Cl_2 (10 mL) and pyridine (1.7 mL, 21 mmol, 15 equiv). The mixture was sparged with N_2 for three minutes and then cooled to 0 °C. Tf_2O (0.35 mL, 2.1 mmol, 2 equiv) was added dropwise, and the reaction was allowed to warm to room temperature and stirred for 1 h, or until starting material was consumed by TLC. The crude mixture was quenched with saturated aq. $NaHCO_3$ and extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and

concentrated. The crude oil was purified with silica gel chromatography (0–10% EtOAc/hexanes) to yield isoquinoline triflate **290** (531 mg, 1.23 mmol, 87% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (ddd, *J* = 10.8, 7.8, 0.9 Hz, 1H), 7.64 (dd, *J* = 9.9, 7.5 Hz, 1H), 7.48 (s, 1H), 7.41 – 7.29 (m, 5H), 5.02 (s, 2H), 4.61 (s, 2H).

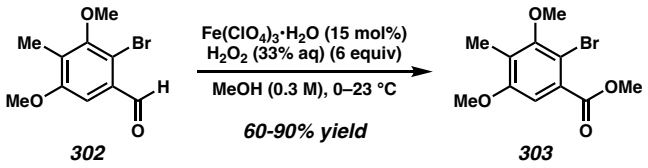
^{13}C NMR (101 MHz, $CDCl_3$): δ 157.85 (dd, *J* = 6.2, 1.6 Hz), 153.98 (dd, *J* = 260.7, 16.3 Hz), 151.37 (d, *J* = 3.2 Hz), 150.88 (dd, *J* = 256.1, 15.7 Hz), 137.18, 128.68, 128.33, 128.28, 124.65 (d, *J* = 6.2 Hz), 120.45, 117.27, 113.61 (d, *J* = 3.2 Hz), 113.52 – 113.38 (m), 110.56 (dd, *J* = 5.4, 2.1 Hz), 73.20, 72.14.

^{19}F NMR (282 MHz, $CDCl_3$): δ -72.81, -126.37 (dd, *J* = 20.3, 3.2 Hz), -130.00 (dd, *J* = 20.2, 2.7 Hz).

IR (neat film, NaCl): 3065, 2864, 1606, 1572, 1518, 1452, 1422, 1384, 1222, 1132, 1089, 964, 889, 831, 744 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{18}H_{12}F_5NSO_4$ $[M]^{+\bullet}$: 433.0367, found 433.0350.

A7.6.2.2 Synthesis of Isoquinoline Sulfone (291)



302 *303*

To a round bottom flask was added aldehyde **302** (300 mg, 1.16 mmol), $Fe(ClO_4)_3$•H_2O (62 mg, 0.174 mmol, 15 mol%) and methanol (4 mL). The mixture was cooled to 0 °C. H_2O_2 (0.91 mL, 11.6 mmol, 10 equiv) was added dropwise via syringe pump over 4 h. Upon the complete addition of H_2O_2, the reaction was allowed to warm to room temperature and stirred overnight. The crude mixture was concentrated behind a blast shield, then quenched with aq. $Na_2S_2O_3$ and extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and

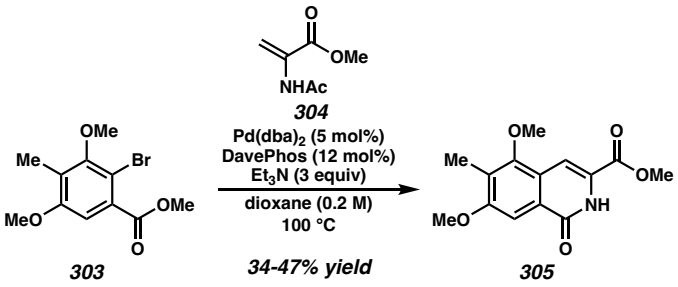
concentrated. The crude solid was purified with silica gel chromatography (0–10% EtOAc/hexanes) to yield ester **303** (303 mg, 1.05 mmol, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 3.77 (s, 3H), 2.20 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.0, 157.5, 156.5, 130.9, 125.7, 108.5, 108.4, 60.5, 55.9, 52.5, 10.1.

IR (neat film, NaCl): 2999, 2949, 2846, 1783, 1565, 1445, 1388 1329, 1377, 1329, 1242, 1122, 1035, 1007 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{11}H_{13}BrO_4$ $[M]^{+\bullet}$: 287.9992, found 287.9980.



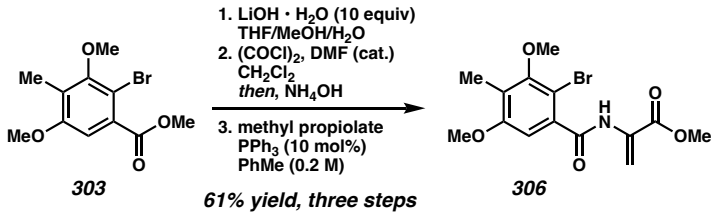
To a flame-dried vial was added $Pd(dba)_2$ (2.9 mg), DavePhos (4.7 mg) and dioxane (0.5 mL). The Pd stock solution was stirred for 20 minutes, then 0.25 mL of the stock solution was added to a separate vial containing ester **303** (14.5 mg, 0.05 mmol), enamide **304** (10.7 mg, 0.075 mmol, 1.5 equiv), and triethylamine (20 uL, 0.15 mmol, 3 equiv). The reaction vial was sealed and heated to 100 °C for 18 h, at which point the reaction was diluted with water and extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude oil was purified with silica gel chromatography (0–20% EtOAc/CH_2Cl_2) to yield isoquinolinone **305** (4.7 g, 0.017 mmol, 34% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.08 (s, 1H), 7.63 (s, 1H), 7.59 (s, 1H), 3.98 (s, 3H), 3.98 (s, 3H), 3.87 (s, 3H), 2.30 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.7, 161.4, 160.4, 156.0, 128.1, 126.6, 125.3, 124.4, 106.7, 103.0, 62.3, 56.3, 53.2, 9.9.

IR (neat film, NaCl): 2930, 1725, 1640, 1260 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{14}H_{15}NO_5$ $[M]^{+\bullet}$: 277.0945, found 277.0933.



To a round bottom flask was added ester **303** (230 mg, 0.8 mmol) and LiOH•H_2O (336 mg, 8.0 mmol, 10 equiv) in THF/MeOH/H_2O (3:1:1, 0.1 M overall). The reaction was stirred at room temperature for 18 h, then concentrated. The crude mixture was acidified with HCl (1 N), then extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and used without further purification.

To the crude acid in CH_2Cl_2 (3 mL, 0.27 M) and 1 drop of DMF at 0 °C was added oxalyl chloride (0.1 mL, 1.2 mmol, 1.5 equiv) dropwise. After 2 h, the crude acid chloride was added dropwise to a flask containing NH_4OH (33% aq, 3 mL) at 0 °C. After stirring for an hour, the reaction was extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to yield 215 mg of the benzamide intermediate. This intermediate was used without further purification.

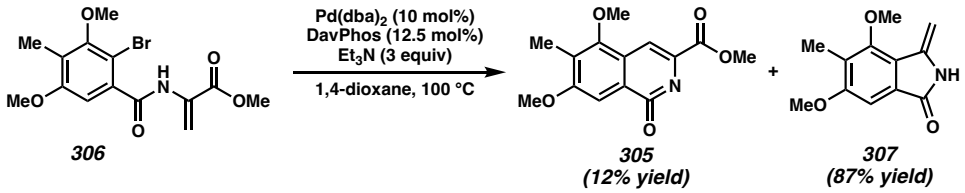
To a vial containing crude benzamide intermediate (110 mg, 0.4 mmol) was added triphenylphosphine (21 mg, 0.08 mmol, 20 mol%), PhMe (4 mL) and methyl propionate (43 uL, 0.48 mmol, 1.2 equiv). The mixture was sparged with N_2 for three minutes and heated to reflux for one hour, at which point the reaction had reached completion by TLC. The reaction was cooled, concentrated, and purified with silica gel chromatography (0–20% EtOAc/hexanes) to yield enamide **306** (87 mg, 0.24 mmol, 61% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 1H), 6.89 (s, 1H), 6.78 (s, 1H), 6.01 (d, *J* = 1.4 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 2.21 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.1, 164.5, 158.1, 156.2, 135.7, 131.0, 124.6, 109.7, 107.4, 105.9, 60.7, 56.0, 53.2, 10.0.

IR (neat film, NaCl): 3361, 2942, 1726, 1678, 1564, 1519, 1440, 1379, 1338, 1200, 1121, 905 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{14}H_{16}BrNO_5$ $[M]^{+\bullet}$: 357.0206, found 357.0199.



To a flame-dried vial was added $Pd(dba)_2$ (2.9 mg), DavePhos (4.9 mg) and dioxane (0.5 mL). The Pd stock solution was stirred for 20 minutes, then 0.25 mL of the stock solution was added to a separate vial containing enamide **306** (18 mg, 0.05 mmol) and triethylamine (20 uL, 0.15 mmol, 3 equiv) in dioxane (0.25 mL). The reaction vial was sealed and heated to 100 °C for 18 h, at which point the reaction was cooled, filtered through Celite with CH_2Cl_2 and concentrated. The reaction was purified with preparatory TLC, eluting with 50% ethyl acetate/hexanes, to isoquinolinone **305** (1.6 g, 0.006 mmol, 12% yield) and isoindolinone **307** (9.5 mg, 0.044 mmol, 87% yield).

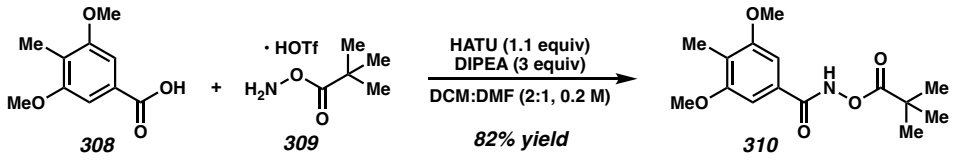
Spectral data for **307**:

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.12 (s, 1H), 5.42 (d, *J* = 1.2 Hz, 1H), 4.99 (d, *J* = 1.2 Hz, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 2.24 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.9, 160.5, 154.8, 138.3, 130.2, 125.8, 121.6, 100.5, 93.5, 60.2, 56.3, 9.5.

IR (neat film, NaCl): 3180, 1706, 1643, 1613, 1477, 1359, 1167, 1123, 1005 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{12}H_{13}NO_3$ $[M]^{+\bullet}$: 219.0890, found 219.0885.



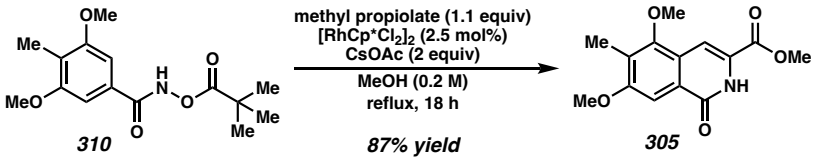
To a round bottom flask was added carboxylic acid **308** (1.76 g, 9.0 mmol), CH_2Cl_2 (30 mL), DMF (15 mL), hydroxylamine **309** (3.61 g, 13.5 mmol, 1.5 equiv), HATU (3.76 g, 9.9 mmol, 1.1 equiv), and DIPEA (4.7 mL, 27 mmol, 3 equiv). The mixture was stirred at 23 °c for 3 h, or until complete consumption of starting material by TLC. The crude mixture was diluted with water and extracted three times with ethyl acetate. The combined organics were washed three times with saturated aq. LiCl, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude oil was purified with silica gel chromatography (0–20% EtOAc/hexanes) to yield hydroxamate **301** (2.17 g, 7.35 mmol, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.46 (s, 1H), 6.94 (s, 2H), 3.83 (s, 6H), 2.09 (s, 3H), 1.36 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 177.5, 167.3, 158.4, 128.9, 120.2, 102.7, 56.0, 38.6, 27.2, 8.7.

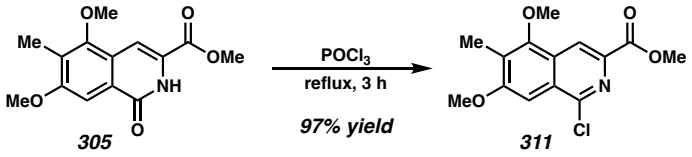
IR (neat film, NaCl): 3187, 2976, 1780, 1662, 1587, 1465, 1411, 1324, 1242, 1141, 1083, 845 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{15}H_{21}NO_5$ $[M]^{+\bullet}$: 295.1414, found 295.1429.



To a round bottom flask equipped with a reflux condenser was added hydroxamate **310** (1.97 g, 6.67 mmol), methanol (33 mL), CsOAc (2.56 g, 13.3 mmol, 2 equiv), $[RhCp^*Cl_2]_2$ (103 mg, 0.167 mmol, 2.5 mol%), and the alkyne (0.65 mL, 7.34 mmol, 1.1 equiv). The reaction was heated to 65 °C for 18 h, then cooled, filtered through Celite with acetone, and concentrated. The crude mixture was purified with silica gel chromatography (0–15% EtOAc/CH_2Cl_2) to yield isoquinolinone **305** (1.615 g, 5.82 mmol, 87% yield).

See above preparation for characterization of **305**.



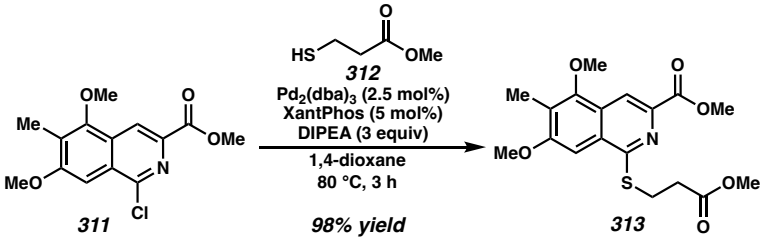
To a round bottom flask was added isoquinolinone **305** (4.15 g, 15 mmol) and $POCl_3$ (30 mL, 0.5 M). The reaction was heated to 90 °C for 4 h, then cooled, carefully poured over $NaHCO_3$ and ice, then transferred to a separatory funnel with ethyl acetate. The crude mixture was extracted three times with ethyl acetate, and the combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude oil was purified with silica gel chromatography (0–20% EtOAc/hexanes) to yield isoquinoline chloride **311** (4.31 g, 14.6 mmol, 97% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, J = 0.9 Hz, 1H), 7.39 (s, 1H), 4.05 (s, 3H), 4.04 (s, 3H), 3.94 (s, 3H), 2.37 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.7, 161.1, 155.4, 138.4, 128.6, 128.1, 126.8, 118.8, 99.8, 62.5, 56.3, 53.0, 10.1.

IR (neat film, NaCl): 2945, 2369, 2340, 1715, 1407, 1233 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{14}H_{14}ClNO_4$ $[M]^{+\bullet}$: 295.0606, found 295.0618.



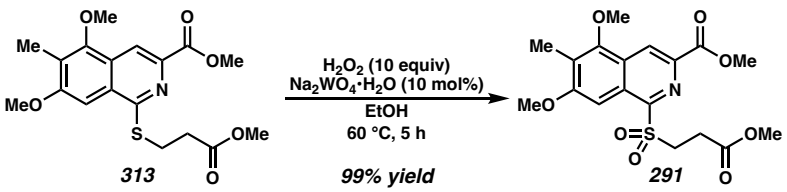
To a flame-dried two-neck round bottom flask equipped with a reflux condenser was added isoquinoline chloride **311** (296 mg, 1 mmol), $Pd_2(dba)_3$ (46 mg, 0.05 mmol, 5 mol%), and XantPhos (58 mg, 0.10 mmol, 10 mol%). The flask was backfilled with N_2 three times, then dioxane (5 mL) and DIPEA (0.52 mL, 3 mmol, 3 equiv) were added, followed by thiol **312** (0.13 mL, 1.2 mmol, 1.2 equiv). The reaction was heated to 80 °C for 3 h, or until starting material was consumed by TLC. The crude mixture was cooled to room temperature, diluted with water, and extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude oil was purified with silica gel chromatography (0–20% EtOAc/hexanes) to yield isoquinoline **313** (373 g, 0.98 mmol, 98% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 1H), 7.13 (s, 1H), 3.98 (s, 4H), 3.97 (s, 3H), 3.89 (s, 3H), 3.71 (s, 4H), 3.68 (t, J = 6.8 Hz, 2H), 2.96 (t, J = 6.8 Hz, 2H), 2.31 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.0, 166.6, 160.0, 157.1, 155.4, 138.8, 128.3, 125.4, 125.3, 115.4, 98.1, 62.3, 56.1, 52.5, 51.9, 34.2, 25.3, 9.9.

IR (neat film, NaCl): 2953, 1731, 1618, 1435, 1299, 1231, 1132, 997, 896 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{18}H_{21}NSO_6$ $[M]^{+\bullet}$: 379.1084, found 379.1094.



To a round bottom flask was thioether **313** (529 mg, 1.39 mmol), ethanol (10 mL) and $Na_2WO_4•H_2O$ (46 mg, 0.14 mmol, 10 mol%). H_2O_2 (33% aq, 1.22 mL, 13.9 mmol, 10 equiv) was added slowly, and the reaction was heated to reflux. After 3 h, the reaction was cooled to room temperature and concentrated behind a blast shield. The crude mixture was partitioned between water and ethyl acetate and extracted three times with ethyl acetate. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude oil was purified with silica gel chromatography (0–20% EtOAc/hexanes) to yield isoquinoline sulfone **291** (563 mg, 1.37 mmol, 99% yield).

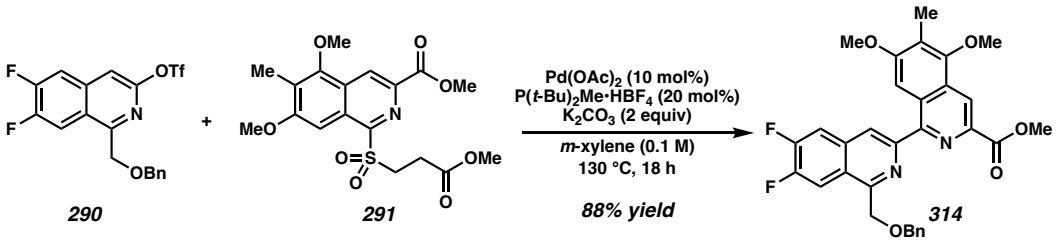
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (d, *J* = 0.9 Hz, 1H), 7.99 (s, 1H), 4.14 (dd, *J* = 8.0, 7.2 Hz, 2H), 4.05 (s, 3H), 4.02 (s, 3H), 3.93 (d, *J* = 0.7 Hz, 3H), 3.76 (s, 3H), 3.18 (dd, *J* = 8.1, 7.0 Hz, 2H), 2.38 (s, 3H), 1.57 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3, 165.2, 161.8, 155.4, 153.8, 136.9, 128.9, 127.5, 125.0, 122.3, 98.2, 62.6, 56.5, 52.9, 52.4, 48.4, 28.6, 10.2.

IR (neat film, NaCl): 2951, 1737, 1613, 1435, 1306, 1235, 1135, 992, 897 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{18}H_{21}NSO_8$ $[M]^{+\bullet}$: 411.0982, found 411.0990.

A7.6.2.3 Synthesis of Non-Natural Analogs



To a flame-dried two neck round bottom flask equipped with a reflux condenser was added freshly powdered K_2CO_3 (612 mg, 4.43 mmol, 2 equiv), sulfone **291** (1.094 g, 2.66 mmol, 1.5 equiv), $Pd(OAc)_2$ (50 mg, 0.222 mmol, 10 mol%), and $P(t\text{-Bu})_2Me{\bullet}HBF_4$ (110 mg, 0.443 mmol, 20 mol%). The flask was backfilled with N_2 three times, and isoquinoline triflate **290** (960 mg, 2.22 mmol, 1 equiv) in *m*-xylene (20 mL) was added, rinsing with 2 mL. The reaction was heated to 140 °C overnight, or until complete by TLC. The crude mixture was filtered through Celite with CH_2Cl_2 and acetone (1:1, x mL) and concentrated. The crude solid was purified with silica gel chromatography (15% EtOAc/hexanes + 3% Et_3N) to yield bis-isoquinoline **314** (981 mg, 1.80 mmol, 81% yield). Note: on 0.1 mmol scale, 88% yield could be reliably obtained.

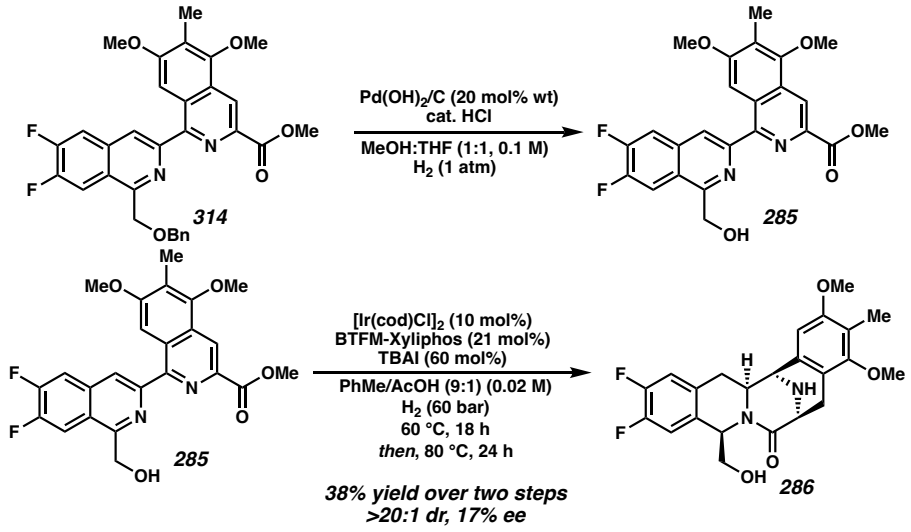
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (d, *J* = 1.0 Hz, 1H), 8.48 (d, *J* = 0.9 Hz, 1H), 8.19 (ddd, *J* = 11.1, 7.9, 0.9 Hz, 1H), 8.06 (s, 1H), 7.73 (dd, *J* = 10.3, 7.7 Hz, 1H), 7.40 – 7.27 (m, 5H), 5.17 (s, 2H), 4.65 (s, 2H), 4.06 (s, 3H), 3.96 (s, 3H), 3.80 (s, 3H), 2.37 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.74, 160.26, 154.95, 153.24 (dd, *J* = 230.4, 15.9 Hz), 151.65 (d, *J* = 2.8 Hz), 150.70 (dd, *J* = 227.3, 15.7 Hz), 138.97, 137.52, 135.53 (d, *J* = 8.4 Hz), 128.68, 128.49, 128.16, 125.37, 124.21 – 124.03 (m), 122.47 (dd, *J* = 5.1, 2.2 Hz), 119.07, 114.11 (d, *J* = 17.2 Hz), 112.74 (d, *J* = 18.4 Hz), 101.41, 73.37, 73.23, 65.76 – 51.57 (m), 9.93.

^{19}F NMR (282 MHz, $CDCl_3$): δ -129.26 (ddd, *J* = 18.7, 10.3, 7.8 Hz), -131.28 (ddd, *J* = 20.0, 11.1, 7.7 Hz).

IR (neat film, NaCl): 2951, 2361, 1716, 1619, 1577, 1512, 1451, 1398, 1311, 1230, 1100, 1071, 996, 901 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{31}H_{26}F_2N_2O_5$ $[M]^{+\bullet}$: 544.1804, found 544.1804.



To a round bottom flask containing bis-isoquinoline **314** (240 mg, 0.44 mmol, 1 equiv) dissolved in MeOH and THF (14 mL, 1:1) and HCl (1 drop) was added $Pd(OH)_2/C$ (24 mg, 20% wt). The backfilled with H_2 five times and then allowed to continue for 5 h, or until ~95% complete by LC/MS. The mixture was then filtered through Celite, washing with acetone, and concentrated. The crude solid was then dissolved in 4:1 $CHCl_3$:IPA and washed with sat. $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude solid was used without further purification.

A flame-dried round bottom flask with crude alcohol **285** (180 mg, 0.386 mmol, 1 equiv) was placed into a Parr bomb and brought into a nitrogen-filled glovebox, with the exception of the pressure gauge. To the flask of **285** was added TBAI (88 mg, 0.238 mmol, 0.6 equiv), PhMe (3 mL) and AcOH (1 mL). In as separatre vial, a solution of SL-J008-2 (BTFM-xyliphos) (89.0 mg, 0.098 mmol, 0.24 equiv) and $[Ir(cod)Cl]_2$ (27 mg, 0.04 mmol, 0.10 equiv) in PhMe (5 mL) was prepared and allowed to stand for 10 minutes, then transferred to the reaction flask, rinsing with PhMe (2 mL). After sealing the flask with a rubber septum that was pierced with three 16-gauge (purple) needles, each bent at a 90º angle, the flask was placed inside the bomb, and the top was covered tightly with plastic

wrap secured by a rubber band, and the bomb was then removed from the glovebox. The pressure gauge was quickly screwed into place and tightened. The bomb was charged to 5-10 bar H_2 and slowly released three times, then charged to 60 bar H_2 and heated to 60 °C. After 18 h, the reaction was heated to 80 °C and continued for an additional 36 h, at which point it was cooled, opened to air, and basified to pH > 7 with saturated aq. K_2CO_3. The biphasic mixture was transferred to a separatory funnel, and the aqueous was extracted five times with ethyl acetate. The combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated, and purified using reverse-phase (C18) chromatography (30 g RediSep Rf Gold column, 0.4% AcOH in H_2O/MeCN, 10–40% MeCN over 10 minutes, then 95% MeCN for 8 minutes) to afford bis-THIQ **286** (72.4 mg, 0.168 mmol, 38% over two steps, 17% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (ddd, J = 10.9, 7.6, 3.3 Hz, 2H), 6.33 (s, 1H), 5.31 (t, J = 5.5 Hz, 1H), 4.13 (d, J = 3.3 Hz, 1H), 4.10 (d, J = 5.6 Hz, 1H), 3.95 (dt, J = 12.5, 2.9 Hz, 1H), 3.83 (s, 3H), 3.68 (s, 3H), 3.29 (d, J = 5.5 Hz, 2H), 3.13 (dd, J = 17.4, 1.5 Hz, 1H), 3.02 (dd, J = 17.4, 6.4 Hz, 1H), 2.80 (dd, J = 14.7, 2.6 Hz, 1H), 2.73 – 2.54 (m, 3H, overlapped with OH and NH), 2.14 (s, 3H)

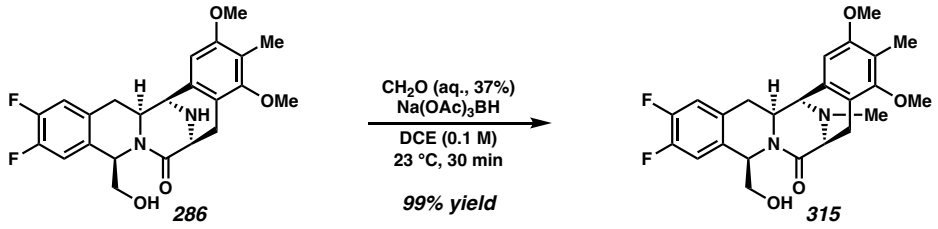
^{13}C NMR (101 MHz, $CDCl_3$): δ 172.3, 157.8, 156.8, 149.6 (dd, J = 243.6, 7.3 Hz), 149.5 (dd, J = 246.3, 11.2 Hz), 132.1 (dd, J = 6.1, 3.9 Hz), 130.6, 130.70 – 130.48 (m), 120.1, 119.7, 117.1 (d, J = 17.8 Hz), 116.6 (d, J = 17.4 Hz), 106.1, 68.2, 61.0, 60.5, 57.5, 56.0, 54.9, 54.3, 33.0, 30.0, 9.3

^{19}F NMR (282 MHz, $CDCl_3$): δ -138.67 – -139.26 (m), -139.30 – -139.75 (m)

IR (neat film, NaCl): 3288, 2941, 1634, 1513, 1455, 1407, 1371, 1335, 1310, 1296, 1274, 1214, 1125, 1061, 753 cm^{-1}.

HRMS (FD+): m/z calc'd for $C_{23}H_{24}F_2N_2O_4$ $[M]^{+\bullet}$: 430.1699, found 430.1709.

SFC: 10% IPA/hexanes, 1.0 mL/min, Chiralcel OD-H column, $\lambda = 220$ nm, t_R (min): major = 6.73, minor = 7.77.



To bis-THIQ **286** (724 mg, 0.168 mmol, 1 equiv) in DCE (3.5 mL) was added formaldehyde (37% aq., 23 uL, 0.311 mmol, 1.85 equiv). After stirring for 10 minutes, $Na(OAc)_3BH$ (178 mg, 0.841 mmol, 5 equiv). After 30 minutes, the reaction was complete by LC/MS. Citric acid monohydrate (265 mg, 1.26 mmol, 7.5 equiv) was added, along with H_2O (3 mL), and the biphasic mixture was stirred for 10 minutes. The pH was then adjusted to pH > 7 with sat. aq. K_2CO_3. The layers were separated, and then the aqueous was extracted twice with ethyl acetate. The combined organics were dried over anhydrous Na_2CO_3, filtered, and dried under reduced pressure to deliver methylated bis-THIQ **315** (73.6 mg, 0.166 mmol, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 – 6.96 (m, 2H), 6.32 (s, 1H), 5.24 (t, *J* = 5.7 Hz, 1H), 4.06 – 3.90 (m, 1H), 3.82 (s, 3H), 3.78 – 3.72 (m, 2H), 3.66 (s, 3H), 3.39 – 3.27 (m, 1H), 3.10 (dd, *J* = 17.8, 6.5 Hz, 1H), 2.87 (d, *J* = 17.7 Hz, 1H), 2.72 (dd, *J* = 14.7, 2.6 Hz, 1H), 2.57 (t, *J* = 13.7 Hz, 1H), 2.44 (s, 3H), 2.12 (s, 3H).

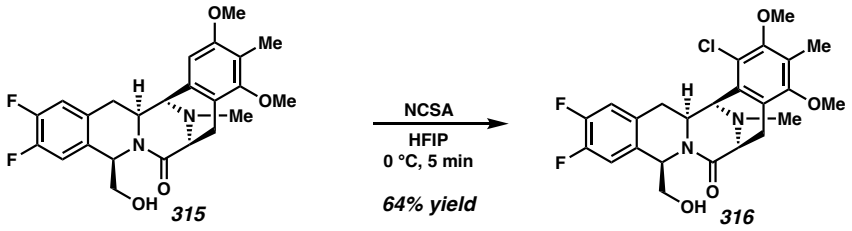
^{13}C NMR (101 MHz, $CDCl_3$): δ 172.5, 157.3, 156.8, 149.4 (dd, *J* = 245.0, 9.1 Hz), 149.2 (dd, *J* = 246.2, 11.6 Hz), 132.2 (dd, *J* = 6.0, 3.7 Hz), 130.6 (d, *J* = 2.1 Hz), 128.4, 119.8, 118.7, 117.1 (d, *J* = 17.9 Hz), 116.4 (d, *J* = 17.4 Hz), 106.8, 67.5, 61.1, 60.3, 60.0, 57.8, 57.2, 55.8, 40.0, 32.8, 23.7, 9.1.

Note: ^{13}C spectra contaminated with aliphatic grease.

^{19}F NMR (282 MHz, $CDCl_3$): δ 139.37 (dt, *J* = 19.0, 8.4 Hz), -139.76 – -139.94 (m).

IR (neat film, NaCl): 2940, 1643, 1513, 1443, 1271, 1168, 1123, 910, 731, 679 cm^{-1}.

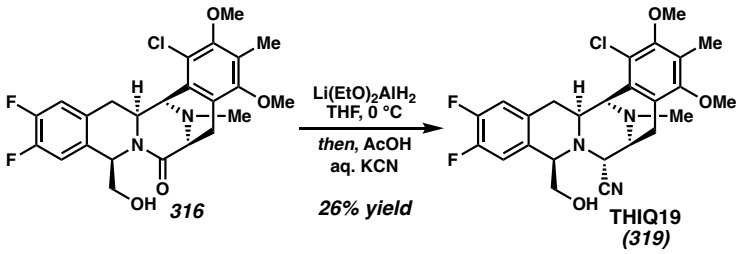
HRMS (FD+): m/z calc'd for $C_{24}H_{27}F_2N_2O_4$ $[M+H]^+$: 445.1933, found 445.1940.



To a solution of **315** (14.7 mg, 0.034 mmol, 1 equiv) in HFIP (1.5 mL, 0.02 M) at 0 °C was added *N*-chlorosaccharin (7.7 mg, 0.035 mmol, 1.05 equiv), after which the cloudy white mixture turned yellow and became homogeneous. After complete addition, the LC/MS showed complete consumption of **315**, so the reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$. The resulting mixture was transferred to a separatory funnel and diluted with CH_2Cl_2 and water, creating a triphasic system with HFIP on bottom, CH_2Cl_2 in the middle, and the aqueous phase on top. The bottom two phases were collected. The aqueous phase was basified with saturated aqueous K_2CO_3 solution and extracted with CH_2Cl_2. The organic phases were combined, concentrated, and azeotropically dried twice with benzene. The crude solid was purified with preparatory TLC (5% MeOH/CH_2Cl_2) to afford chlorinated bis-THIQ **316** (10.3 mg, 0.021 mmol, 64% yield).

^1H NMR (400 MHz, $CDCl_3$): δ 7.01 (dd, *J* = 10.3, 7.6 Hz, 2H), 5.40 (t, *J* = 5.9 Hz, 1H), 4.44 (dd, *J* = 3.7, 1.2 Hz, 1H), 4.09 (ddd, *J* = 12.8, 3.7, 2.6 Hz, 1H), 3.81 (s, 3H), 3.77 (dt, *J* = 6.9, 1.2 Hz, 1H), 3.71 (s, 3H), 3.48 – 3.19 (m, 3H), 3.12 (dd, *J* = 18.2, 6.8 Hz, 1H), 2.97 (dd, *J* = 18.2, 1.2 Hz, 1H), 2.43 (s, 3H), 2.39 (t, *J* = 13.9 Hz, 1H), 2.26 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.86, 156.21, 153.80, 152.27 – 148.21 (m), 149.38 (dd, *J* = 246.7, 11.7 Hz), 132.42 – 132.26 (m), 130.03 – 129.85 (m), 128.48, 127.69, 126.39, 124.49, 123.69, 116.87 (dd, *J* = 19.6, 17.7 Hz), 68.65, 60.52, 60.37, 59.39, 59.05, 57.59, 56.81, 40.28, 31.70, 24.52, 10.11.



In an oven-dried vial, $LiAlH_4$ solution (1.0 M in THF, 0.5 mL, 0.5 mmol) was cooled to 0 ºC. A solution of ethyl acetate (57 µL, 0.58 mmol) in 0.5 mL THF was added slowly, and the resulting solution was stirred 30 min at 0 ºC, providing a 0.47 M solution of $Li(EtO)_2AlH_2$ in THF. Chlorinated bis-THIQ **316** (10.3 mg, 0.0215 mmol, 1 equiv) was dissolved in THF (1 mL, 0.02 M) and the resulting solution was cooled to 0 ºC. A solution of $Li(EtO)_2AlH_2$ (0.47 M in THF, 0.7 mL, 0.32 mmol, 15 equiv) was added slowly, resulting in extensive evolution of H_2. After stirring 30 min, the LC/MS showed complete consumption of **316**, so the reaction was quenched with acetic acid (26 µL, 0.45 mmol, 21 equiv) and aqueous potassium cyanide (4.8 M, 27 µL, 0.13 mmol, 6 equiv) was added, followed by Celite and anhydrous Na_2SO_4 (roughly 250 mg each). The solution was diluted with 3 mL THF and stirred at 50 °C overnight. Upon full consumption of iminium by LC/MS, additional Celite and K_2CO_3 (1 g) were added, and the suspension was filtered through Celite, rinsing with EtOAc. The filtrate was transferred to a round bottom flask and concentrated, and the crude product was purified with reverse phase C18 chromatography (0.4% AcOH in H_2O/MeCN, 40–90% MeCN over 9 minutes, then 100%

MeCN for 1 min, t_R = 8.5 min) to afford amino nitrile **THIQ19** (**319**) (2.7 mg, 0.0055 mmol, 26% yield).

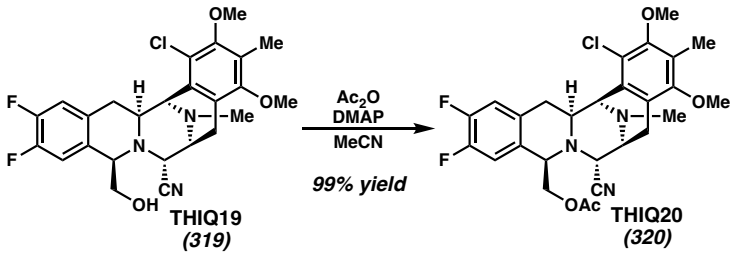
$[\alpha]_D^{25}$ = 0.193 (*c* = 0.1)

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 – 6.83 (m, 2H), 4.34 (dd, *J* = 3.0, 1.2 Hz, 1H), 4.08 (d, *J* = 2.6 Hz, 1H), 3.83 (m, *J* = 4.4 Hz, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.62 (dt, *J* = 11.1, 4.0 Hz, 1H), 3.50 – 3.39 (m, 2H), 3.31 – 3.20 (m, 1H), 3.08 (dd, *J* = 18.6, 7.9 Hz, 1H), 2.99 (dd, *J* = 15.5, 2.7 Hz, 1H), 2.53 (d, *J* = 18.6 Hz, 1H), 2.31 (s, 3H), 2.25 (s, 3H), 2.22 – 2.09 (m, 1H), 1.70 (dd, *J* = 8.4, 3.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.89, 153.44, 131.70, 129.76 (d, *J* = 4.4 Hz), 128.77, 125.60, 125.02, 124.22, 117.56, 116.76 (d, *J* = 17.0 Hz), 115.71 (d, *J* = 17.6 Hz), 67.00, 62.50, 60.70, 60.53, 60.04, 59.17, 57.00, 54.97, 41.93, 31.36, 21.87, 10.08.

Note: ^{13}C signal intensity low; peaks missing.

HRMS (FD+): m/z calc'd for $C_{25}H_{27}ClF_2N_3O_3$ $[M+H]^+$: 490.1704, found 490.1712.



In a 1-dram vial, **THIQ19** (1.6 mg, 0.003 mmol, 1 equiv) and DMAP (0.001 mg, 0.01 mmol, equiv) were dissolved in acetonitrile (150 μL, 0.02 M) and acetic anhydride (1 μL, 0.01 μmol, 3 equiv) was added neat. After 30 minutes, LC/MS showed complete consumption of **THIQ19**. The reaction was concentrated, and the crude material was purified using reverse-phase (C18) preparative HPLC (0.4% acetic acid in water/MeCN, 5.0 mL/min, monitor wavelength = 260 nm, 60–90% MeCN over 6 min, ramp to 95 over

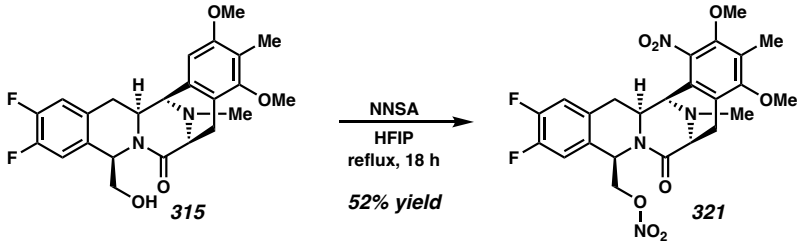
0.5 min, hold at 95% for 1.5 min) to afford acylated bis-THIQ analog **THIQ20** as a colorless solid (1.6 mg, 0.003 mmol, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92 (ddd, *J* = 13.3, 10.5, 7.7 Hz, 2H), 4.28 (dd, *J* = 3.1, 1.2 Hz, 1H), 4.06 (d, *J* = 2.6 Hz, 1H), 4.03 (dd, *J* = 11.0, 5.1 Hz, 1H), 3.89 (t, *J* = 5.1 Hz, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.65 (dd, *J* = 11.0, 5.1 Hz, 1H), 3.43 – 3.33 (m, 2H), 3.08 – 2.97 (m, 2H), 2.52 (d, *J* = 18.5 Hz, 1H), 2.28 (s, 3H), 2.25 (s, 3H), 2.20 – 2.08 (m, 1H), 1.82 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.42, 154.78, 153.09, 128.65, 125.72, 125.18, 123.86, 117.79, 116.46 (dd, *J* = 69.3, 17.6 Hz), 68.27, 61.05, 60.51 (d, *J* = 4.0 Hz), 59.80, 59.18, 57.30, 54.99, 41.90, 31.53, 21.60, 20.67, 10.07.

Note: ^{13}C signal intensity low; peaks missing.

HRMS (ESI+): m/z calc'd for $C_{27}H_{29}ClF_2N_3O_4$ $[M+H]^+$: 532.1809, found 532.1811.



A vial containing bis-THIQ **315** (73.6 mg, 0.166 mmol, 1 equiv) and *N*-nitrosaccharin (453 mg, 1.99 mmol, 12 equiv) was backfilled with argon three times. HFIP (1.1 mL) was added, and the reaction was heated to 60 °C for 18 h, or until full conversion to nitroester **321** by LC/MS. The reaction was quenched with sat. aq. $NaHCO_3$, extracted three times with ethyl acetate, and the combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude oil was purified with silica gel chromatography (0–20% ethyl acetate/CH_2Cl_2 + 1% Et_3N) to afford nitroester **321** (45.9 mg, 0.086 mmol, 52% yield).

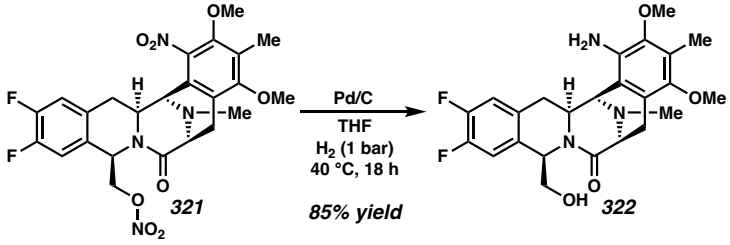
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 (dd, *J* = 10.2, 7.6 Hz, 1H), 6.97 (dd, *J* = 10.1, 7.4 Hz, 1H), 5.48 (t, *J* = 3.6 Hz, 1H), 5.01 (dd, *J* = 11.9, 3.9 Hz, 1H), 4.33 (dd, *J* = 3.5, 1.2 Hz, 1H), 3.99 (ddd, *J* = 11.8, 7.6, 3.9 Hz, 2H), 3.89 (s, 3H), 3.78 (s, 3H), 3.14 (dd, *J* = 18.4, 7.0 Hz, 1H), 2.86 (dd, *J* = 18.4, 1.1 Hz, 1H), 2.65 – 2.46 (m, 2H), 2.43 (s, 3H), 2.29 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.23, 159.23, 150.76, 149.91 (dd, *J* = 250.4, 12.3 Hz), 149.66 (dd, *J* = 248.8, 12.9 Hz), 142.96, 132.44 (dd, *J* = 6.4, 3.9 Hz), 128.14 (dd, *J* = 5.8, 3.9 Hz), 126.98, 124.19, 122.18, 117.50 (d, *J* = 17.7 Hz), 116.18 (d, *J* = 18.1 Hz), 74.01, 62.80, 60.32, 58.89, 58.68, 55.88, 52.75 (d, *J* = 1.5 Hz), 39.85, 31.23, 23.04, 10.16.

^{19}F NMR (282 MHz, $CDCl_3$): δ -139.02 – -140.35 (m), -140.78 – -142.25 (m).

IR (neat film, NaCl): 2944, 2357, 1649, 1520, 1446, 1363, 1275, 1106, 1003, 859, 731, 680 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{24}H_{25}F_2N_4O_8$ $[M+H]^+$: 535.1635, found 535.1562.



To a vial of nitroester **321** (21.6 mg, 0.04 mmol, 1 equiv) in THF (0.75 mL, 0.05 M) with conc. HCl (1 drop) was added Pd/C (5% wt, 20 mg). The vial was sealed, bubbled through with H_2 for three minutes, and heated to 40 °C under 1 atm H_2. After 18 h, the reaction was complete by LC/MS. The reaction was cooled, and the crude solution was passed through a short bed of Celite, eluting with methanol. The solution was concentrated under reduced pressure and purified via preparatory TLC (3% MeOH/CH_2Cl_2 + 1% Et_3N) to deliver **322** (15.7 mg, 0.034 mmol, 85% yield).

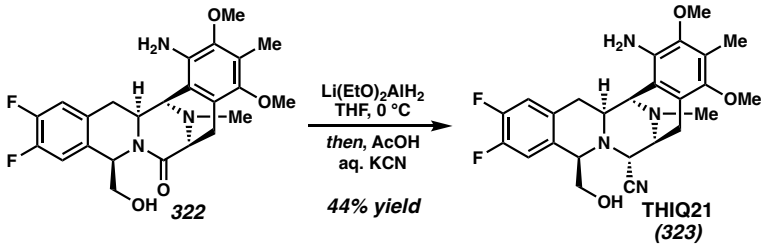
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04 – 6.91 (m, 2H), 5.36 – 5.29 (m, 1H), 4.06 (dt, *J* = 12.8, 3.0 Hz, 1H), 3.98 – 3.92 (m, 1H), 3.77 – 3.68 (m, 4H), 3.64 (m, 4H), 3.38 – 3.24 (m, 2H), 3.16 – 2.76 (m, 4H), 2.53 (dd, *J* = 15.1, 12.6 Hz, 1H), 2.46 (s, 3H), 2.21 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.83, 149.50 (dd, *J* = 245.2, 9.3 Hz), 149.28, 149.27 (dd, *J* = 246.3, 11.6 Hz), 145.23, 134.46, 132.50 (dd, *J* = 6.2, 3.7 Hz), 130.30 (dd, *J* = 6.0, 3.7 Hz), 124.00, 122.18, 116.78 (dd, *J* = 17.6, 10.9 Hz), 115.15, 70.68, 68.13 (d, *J* = 3.3 Hz), 60.41, 59.74, 59.61, 58.70, 56.74 (d, *J* = 49.6 Hz), 45.93, 40.56, 32.07, 24.77 (d, *J* = 2.8 Hz), 9.59.

^{19}F NMR (282 MHz, $CDCl_3$): δ -138.13 – -139.56 (m), -139.82 (m).

IR (neat film, NaCl): 2925, 2857, 1748, 1633, 1453, 1168, 680 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{24}H_{28}F_2N_3O_4$ $[M+H]^+$: 460.2042, found 460.2043.



In an oven-dried vial, $LiAlH_4$ solution (1.0 M in THF, 1.0 mL, 0.5 mmol) was cooled to 0 ºC. A solution of ethyl acetate (115 µL, 1.18 mmol) in 1.0 mL THF was added slowly, and the resulting solution was stirred 30 min at 0 ºC, providing a 0.47 M solution of $Li(EtO)_2AlH_2$ in THF. Aminated bis-THIQ **322** (15.7 mg, 0.034 mmol, 1 equiv) was dissolved in THF (1.7 mL, 0.02 M) and the resulting solution was cooled to 0 ºC. A solution of $Li(EtO)_2AlH_2$ (0.47 M in THF, 1.1 mL, 0.52 mmol, 15 equiv) was added slowly, resulting in extensive evolution of H_2. After stirring 30 min, the LC/MS showed complete consumption of **322**, so the reaction was quenched with acetic acid (41 µL, 0.727 mmol, 21 equiv) and aqueous potassium cyanide (4.8 M, 43 µL, 0.21 mmol, 6 equiv) was added,

followed by Celite and anhydrous Na_2SO_4 (roughly 250 mg each). The solution was diluted with 2 mL THF and allowed to warm to 23 °C and continued overnight.

After 18 h, some residual iminium remained by LC/MS. Additional Na_2SO_4 (roughly 200 mg) was added, and the reaction was heated to 50 °C. After two hours, only trace iminium remained by LC/MS. Solid K_2CO_3 was added to the suspension, and the mixture was filtered through Celite, rinsing with EtOAc. The filtrate was concentrated under reduced pressure, and the crude product was purified with reverse phase C18 chromatography (0.4% AcOH in H_2O/MeCN, 45–70% MeCN over 5 minutes, then 95% MeCN for 3 min, t_R = 4.91 min) to afford amino nitrile **THIQ21** (**323**) (7.1 mg, 0.015 mmol, 44% yield).

^{1}H NMR (400 MHz, C_6D_6): δ 6.33 (dd, *J* = 10.7, 7.8 Hz, 1H), 6.26 (dd, *J* = 10.8, 7.8 Hz, 1H), 3.46 (s, 3H), 3.40 – 3.34 (m, 1H), 3.33 – 3.30 (m, 1H), 3.25 (s, 3H), 3.22 (m, 1H), 3.13 (m, 1H), 3.04 (dd, *J* = 11.0, 4.1 Hz, 1H), 2.79 (dd, *J* = 11.1, 4.2 Hz, 1H), 2.76 – 2.65 (m, 2H), 2.12 (s, 3H), 2.10 – 2.03 (m, 2H), 2.00 (s, 3H).

^{13}C NMR (101 MHz, C_6D_6): δ 149.5 (d, *J* = 216.6 Hz), 149.4 (d, *J* = 249.1 Hz), 148.4, 144.8, 135.0, 132.0 (m), 130.9 (dd, *J* = 5.6, 3.5 Hz), 123.4, 123.1, 117.6, 116.5 (d, *J* = 16.9 Hz), 116.0 (d, *J* = 17.5 Hz), 115.7, 67.0, 62.4, 60.4, 59.7, 58.9, 57.7, 57.1, 55.1, 41.7, 31.5, 21.9, 9.6.

^{19}F NMR (282 MHz, C_6D_6): δ -140.26 – -140.51 (m), -140.70 (m).

IR (neat film, NaCl): 3464, 2927, 1615, 1517, 1464, 1320, 1100, 1055, 880, 679 cm^{-1}.

HRMS (ESI+): m/z calc'd for $C_{25}H_{29}F_2N_4O_3$ $[M+H]^+$: 471.2202, found 471.2221.

A7.7 REFERENCES AND NOTES

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