CHAPTER 3

An Enantioselective Spirocyclization of Pd-Enolates and Isocyanates†

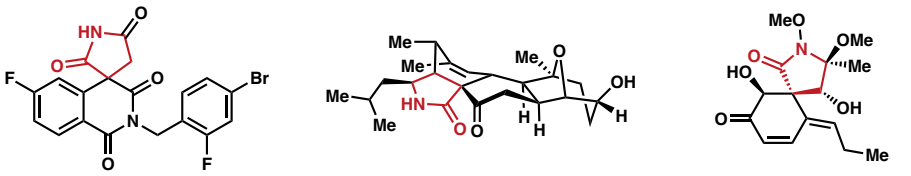
3.1 INTRODUCTION

Since their first description by von Baeyer over 120 years ago,[1] spirocyclic compounds have found widespread utility as chiral ligands,[2] pharmaceuticals,[3] and optoelectronic materials.[4] Spirocyclic frameworks are also found within nature and feature in a variety of bioactive natural products.[5] Due to their inherently high fraction of sp^3 carbon atoms (Fsp^3) and their ability to project functionality along multiple distinct spatial vectors, spiranes are of increased interest in modern medicinal chemistry campaigns.[3] While the development of new stereoselective methods for the construction of spirocyclic compounds remains an ongoing challenge, many new asymmetric technologies have been developed for the synthesis of spirocyclic oxindoles.[5] In comparison, there are far fewer asymmetric methods for the synthesis of saturated spirocyclic γ-lactams, despite the

† This work was performed in collaboration with Dr. Kaylin N. Flesch, Dr. Melinda Chan, Hannah R. Ang, and Dr. Brian M. Stoltz. Portions of this chapter have been reproduced with permission from Barbor, J. P.; Flesch, K. N.; Chan, M.; Ang, H.R.; Stoltz, B. M. An Enantioselective Spirocyclization of Pd-Enolates and Isocyanates. *Angew. Chem. Int. Ed.* **2025**, e202502583.

prevalence of this motif in a range of biologically active small molecules and natural products (Figure 3.1).[6,7]

Figure 3.1 *Natural products and pharmaceutical compounds bearing a spirocyclic lactam.*

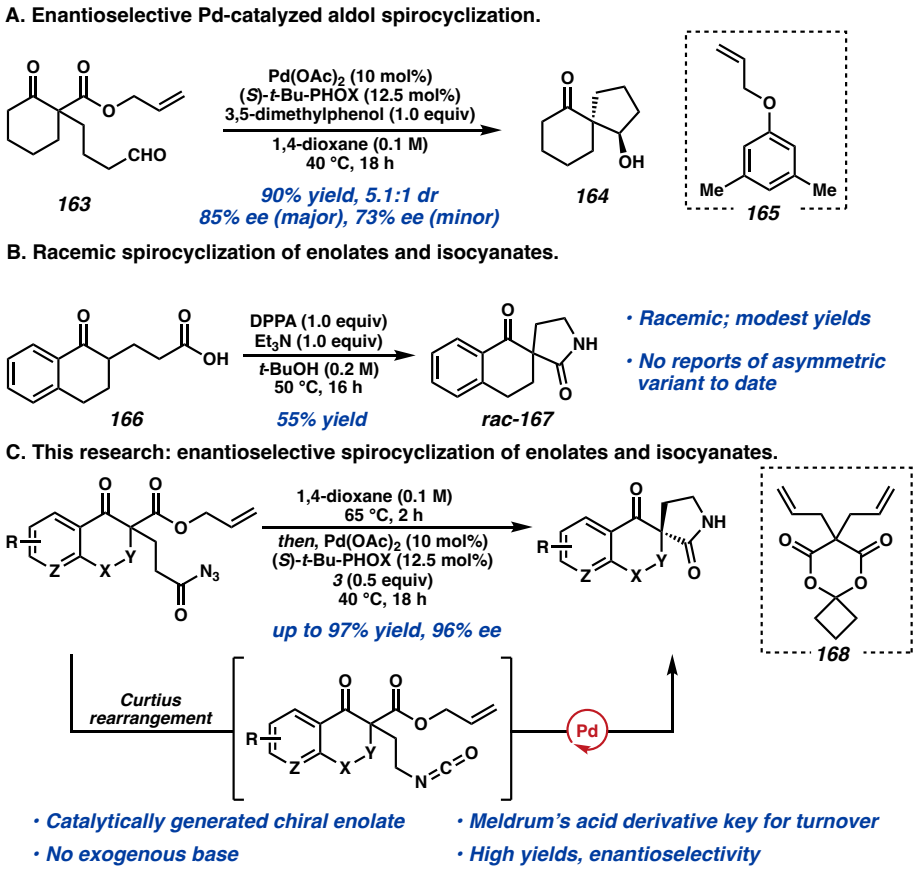


In 2020, our group disclosed an enantioselective Pd-catalyzed aldol cyclization, enabling the general asymmetric construction of spiranes bearing a 1,3-dioxygenation pattern (Scheme 3.1a).[8] Following decarboxylative enolate formation, chiral Pd enolates can undergo an intramolecular aldol cyclization, which upon further oxidation delivers a variety of 1,3-diketospiranes in good yields and enantioselectivity. Bronsted acidic additives, namely phenols, were found to be essential for catalyst turnover, serving as a proton-donor for the putative Pd-alkoxide and facilitating Pd reduction by trapping the allyl group. Following this report, we sought to expand this strategy toward other classes of electrophiles and hypothesized that we may be able to achieve similar success with isocyanates, enabling access to chiral spirocyclic lactams.

An uncatalyzed and racemic variant of our targeted reaction was reported by Xue and coworkers in 2015 (Scheme 3.1b).[9] Upon treatment with DPPA and triethylamine, δ-keto acids could undergo a Curtius rearrangement and subsequent nucleophilic cyclization, delivering spirocyclic lactams in modest to good yields. Within the context of catalysis, isocyanates are well-precedented to undergo a variety of polymerization reactions in the presence of transition metal catalysts,[10] and there is a well-established body of literature pertaining to the reactions of isocyanates with Pd π-allyl intermediates.[11] However, there

appears to be a general lack of research into controlled, stereoselective additions of metal enolates and isocyanates. In fact, we have been unable to find any general reports detailing the stereoselective addition of an enolate to an isocyanate,[12] which we attribute to the unforgiving propensity of isocyanates to decompose or self-condense and their inherent incompatibility with many strong bases.[10c] Given the mild, base-free, and regiospecific nature under which we can generate chiral Pd enolates from allyl β-keto esters, we envisioned that this decarboxylative enolate formation would be an appropriate manifold for the development of a general asymmetric spirocyclization of Pd enolates and isocyanates (Scheme 3.1c).

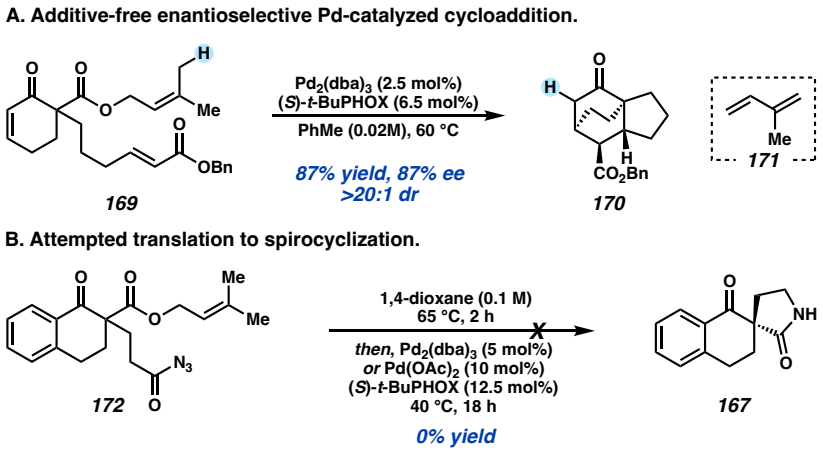
Scheme 3.1 *Construction of spiranes via enolate addition.*



3.2 REACTION DESIGN AND OPTIMIZATION

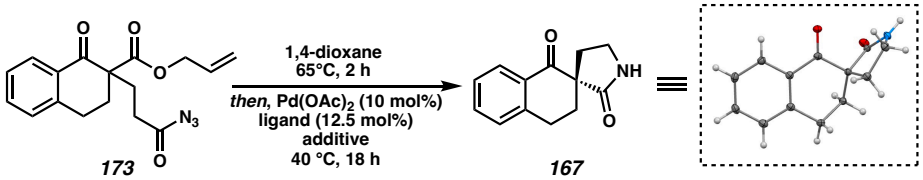
Inspired by a recent disclosure from our group, we decided to first explore reactivity with a prenyl β-keto ester. In 2023, our group reported an asymmetric decarboxylative Pd-catalyzed [4+2] cycloaddition.[13] Rather than adding an exogenous additive, we found that use of a prenylated β-keto ester enabled proton-transfer from the prenyl group following cycloaddition, generating isoprene and turning over the catalytic cycle (Scheme 3.2a). Unfortunately, subjecting prenylated starting material **172** to a Curtius rearrangement followed by treatment with a Pd/PHOX catalyst resulted in a complex mixture of undesired byproducts (Scheme 3.2b).

Scheme 3.2 *Attempted additive-free spirocyclization.*

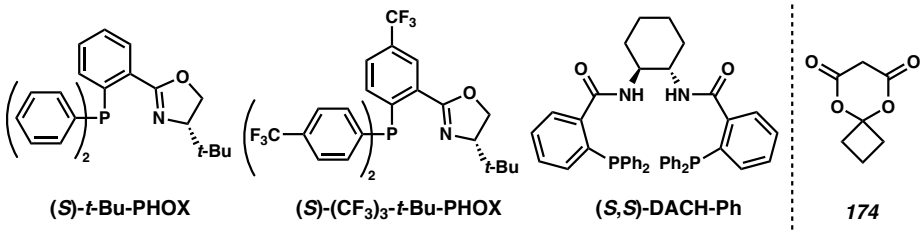


Alternatively, Curtius rearrangement of allyl β-keto ester **173** followed by treatment with a Pd/PHOX catalyst generated the desired product **167** in 89% ee, albeit in a modest 10% yield (Table 3.1, entry 1). Akin to the previously developed aldol spirocyclization, we did not observe reductive elimination of the allyl group onto the amidate following cyclization.[8] Unable to force reductive elimination of the allyl, we decided to explore alternative strategies to achieve turnover.

Table 3.1 *Reaction optimization.*[a]



entry	ligand	additive	result
1	(*S*)-*t*-Bu-PHOX	–	10% yield, 89% ee
2	(*S*)-*t*-Bu-PHOX	phenol (1.0 equiv)	17% yield, 39% ee
3	(*S*)-*t*-Bu-PHOX	Meldrum's acid (0.5 equiv)	59% yield, 93% ee
4	(*S*)-*t*-Bu-PHOX	Meldrum's acid (1.0 equiv)	19% yield, 85% ee
5	(*S*)-*t*-Bu-PHOX	dimedone (0.5 equiv)	43% yield, 31% ee
6	(*S*)-*t*-Bu-PHOX	acacH (0.5 equiv)	32% yield, 58% ee
7	(*S*)-*t*-Bu-PHOX	*174* (0.5 equiv)	99(93[b])% yield, 96% ee
8	(*S*)-$(CF_3)_3$-*t*-Bu-PHOX	*174* (0.5 equiv)	89% yield, 83% ee
9	(*S*,*S*)-DACH-Ph	*174* (0.5 equiv)	99% yield, 10% ee
10[c]	(*S*)-*t*-Bu-PHOX	*174* (0.5 equiv)	85% yield, 98% ee



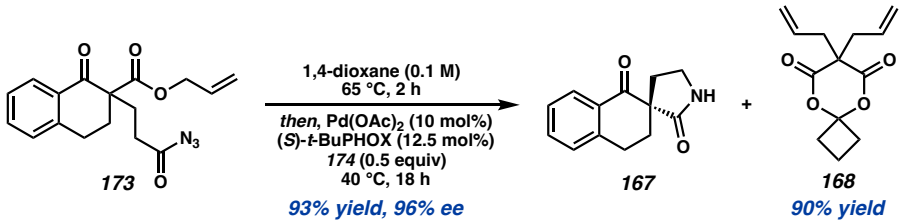
[a] Reactions performed on 0.05 mmol scale and yields determined by ^{1}H NMR integration against an internal standard (1,3,5-trimethoxybenzene). [b] 0.2 mmol scale, isolated yield. [c] 1.0 mmol scale, isolated yield.

Drawing inspiration from the previously developed aldol spirocyclization, we decided to explore phenol as an additive.[8] Predictably, inclusion of phenol in this reaction generated significant amounts of carbamate side products, with only a marginally improved 17% yield of our desired product (Table 3.1, entry 2).[14,15] Pursuing alternative additives that may be less reactive toward the isocyanate, we decided to assess the use of Meldrum's acid, as we have previously demonstrated that this additive can be used for enantioselective protonation.[16]

Gratifyingly, inclusion of 50 mol% of Meldrum's acid delivered a 59% yield of product **167** in 93% ee, highlighting that cyclization to form the γ-lactam kinetically outcompetes protonation of the enolate (Table 3.1, entry 3). Increasing equivalents of

Meldrum's acid resulted in lower conversion (Table 3.1, entry 4). Use of similar 1,3-dicarbonyl compounds, like dimedone or acacH, also resulted in poorer reaction performance, with the ee of the product dropping significantly (Table 3.1, entries 5 and 6); however, use of Meldrum's acid derivative **174** resulted in near quantitative yield of the desired product and excellent 96% ee (Table 3.1, entry 7).[16] (*S*)-*t*-Bu-PHOX was found to be the optimal ligand for this transformation, with a more electron-deficient PHOX ligand or DACH-Ph affording diminished ee (Table 3.1, entry 8, 9). Additionally, we were pleased to find that the reaction also performs well on scale, with a 1.0 mmol scale reaction generating an 85% yield of product with 98% ee (Table 3.1, entry 10). From a 0.2 mmol scale reaction of our model substrate, 90% of **174** added to the reaction could be reisolated as the diallylated byproduct (**168**), confirming the ultimate fate of **174** and the allyl group (Scheme 3.3).

Scheme 3.3. *Isolation of reaction byproduct.*

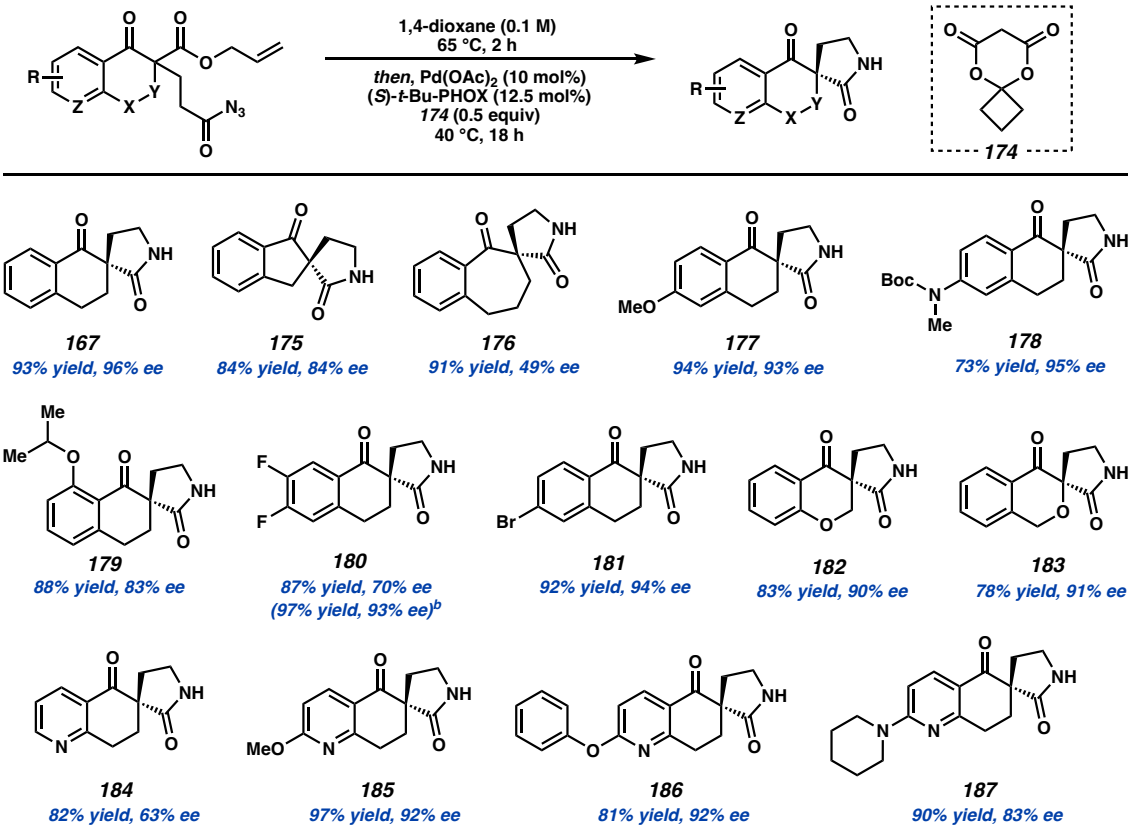


3.3 SUBSTRATE SCOPE

With optimized reaction conditions in hand, we explored the scope of the transformation (Table 3.2). Ring contraction from the model system to an indanone derived substrate (**175**) was well tolerated. Ring-expanded benzosuberone product **176** was formed in an excellent 91% yield, albeit in a diminished 49% ee. Electron donating groups para to the ketone performed well (**177** and **178**). Additionally, incorporation of an *ortho*-isopropyl

ether (**179**) was successful, demonstrating that this reaction can accommodate a moderate amount of steric bulk near the ketone. Gratifyingly, a compound bearing an aryl bromide can withstand the reaction conditions without any evidence of protodehalogenation, generating **181** in 92% yield and 94% ee. Heterocyclic chromanone **182** and isochromanone **183** were also competent substrates. Saturated ketone, α,β-unsaturated ketone, or *N*-benzoylated lactam starting materials all furnished product in good to excellent yield but suffered from low enantioselectivity under these reaction conditions.

Table 3.2 *Substrate scope.*[a]



[a] Reactions performed on 0.2 mmol scale, isolated yield. [b] Reaction performed on 0.05 mmol scale with (*S*)-$(CF_3)_3$-*t*-Bu-PHOX, isolated yield.

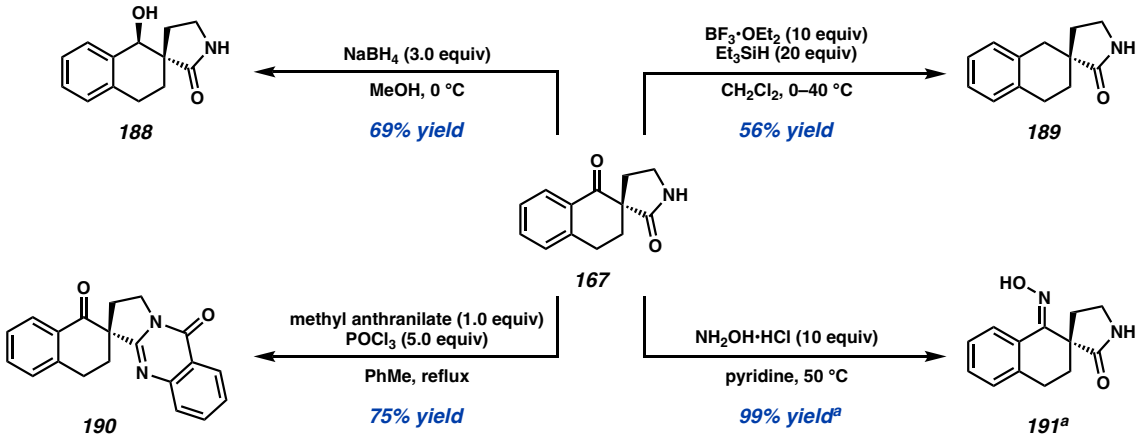
Although di-fluorinated (**180**) and pyridine-containing (**184**) compounds were able to be synthesized in excellent yields, the ee of these products was notably diminished.

Increasing electron density by substitution of the pyridine derivative with a methoxy (**185**), phenoxy (**186**), or piperidine (**187**) enabled the synthesis of these complex heterocyclic spiranes in excellent yields and enantioselectivities. Given the overall trends of the scope of this reaction, we postulate that it is necessary for substrates to be electron rich to obtain products with high ee using (*S*)-*t*-Bu-PHOX. Excitingly, **180** could be synthesized in 97% yield and 93% ee with the more electron-deficient (*S*)-$(CF_3)_3$-*t*-Bu-PHOX, indicating that further tuning of the catalyst can potentially improve the performance of this reaction across electronically diverse substrates.[17]

3.4 PRODUCT DERIVATIZATIONS

To highlight the utility of these spirocyclic compounds, we explored various transformations to further diversify the products obtained from the reaction (Scheme 3.4).

Scheme 3.4 *Product derivatizations.*



[a] Oxime geometry not determined.

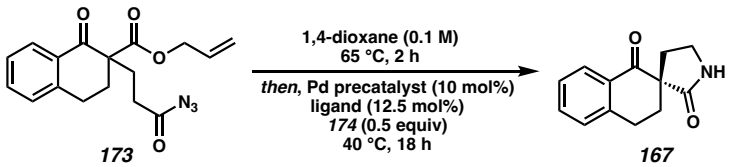
Diastereoselective reduction of the ketone with $NaBH_4$ to alcohol **188** can be achieved in 69% yield and >20:1 dr. Selective ketone reduction with BF_3•Et_2O and Et_3SiH yielded lactam **189** in 56% yield. Owing to the fact that this reaction affords unprotected lactam

products, **167** could directly undergo a heterocyclic annulation to deliver pentacyclic pyrimidone **190** in 75% yield. Furthermore, oxime **191** can be selectively formed as a single stereoisomer in 99% yield.

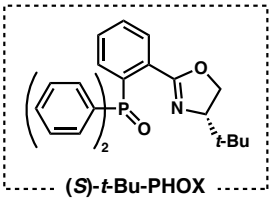
3.5 MECHANISTIC STUDIES

Throughout the development of this reaction, we observed a stark correlation between the choice of Pd-precatalyst and enantioselectivity (Table 3.3).

Table 3.3 *Investigation of reaction dependence on Pd-precatalyst.*[a]



entry	Pd precatalyst	ligand	additive	yield (%)	ee (%)
1	$Pd(OAc)_2$	(*S*)-*t*-Bu-PHOX	—	99	96
2[b]	$Pd_2(dba)_3$	(*S*)-*t*-Bu-PHOX	—	99	15
3[b]	$Pd_2(dba)_3$	(*S*)-*t*-Bu-PHOX	$[NBu_4]OAc$ (20 mol%)	94	3
4	$Pd(dba)_2$	(*S*)-*t*-Bu-PHOX	—	97	15
5	[Pd((*S*)-*t*-BuPHOX)dba]	—	—	98	11
6	$Pd(OAc)_2$	(*S*)-*t*-Bu-PHOX/ (*S*)-*t*-Bu-PHOX=O (1:1)	—	39	83
7[c]	$Pd(OAc)_2$	(*S*)-*t*-Bu-PHOX	—	94	84
8	$Pd(OAc)_2$	(*S*)-*t*-Bu-PHOX (40 mol%)	—	19	90
9	$Pd(TFA)_2$	(*S*)-*t*-Bu-PHOX	—	9	76
10	$Pd(TFA)_2$ (8 mol%)/ $Pd_2(dba)_3$ (1 mol%)	(*S*)-*t*-Bu-PHOX	—	96	74



[a] Reactions performed on 0.05 mmol scale and yields determined by ^1H NMR integration against an internal standard (1,3,5-trimethoxybenzene). [b] 5 mol% $Pd_2(dba)_3$. [c] O_2 balloon.

Interestingly, use of $Pd_2(dba)_3$ in place of $Pd(OAc)_2$ under otherwise identical reaction conditions affords a similarly excellent yield of product but with a severely diminished 15%

ee (Table 3.3, entries 1 and 2). To further probe this effect, we first explored the impact of the ancillary ligands for each of these precatalysts.

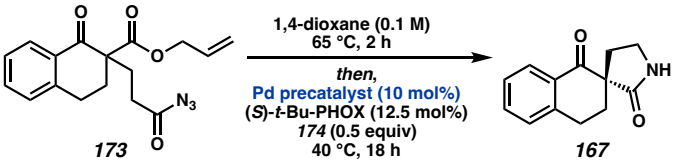
Addition of acetate in the form of [N(*n*-Bu)$_4$]OAc to a reaction utilizing Pd$_2$(dba)$_3$ did not restore ee (Table 3.3, entry 3); likewise, alteration of the amount of dibenzylideneacetone (dba) did not have any significant impact on reaction performance (Table 3.3, entries 4 and 5), indicating that neither of these ancillary ligands alter the enantioselectivity of the reaction. Because reduction of Pd(OAc)$_2$ to Pd(0) with a phosphine ligand necessitates the formation of the corresponding phosphine oxide with adventitious water,[18] we were curious if the oxidized variant of our ligand played a supporting role in the reaction mechanism. Yet, utilizing a 1:1 ratio of (*S*)-*t*-Bu-PHOX to the oxidized derivative, (*S*)-*t*-Bu-PHOX=O, resulted in diminished product ee and significant unreacted starting material (Table 3.3, entry 6), eliminating the possibility that (*S*)-*t*-Bu-PHOX=O might serve some beneficial function as a supporting ligand.

We were surprised that use of such a small excess of PHOX ligand with Pd(OAc)$_2$ afforded product in both high yield and ee, as typically, full reduction of Pd(OAc)$_2$ to Pd(0) requires three to four times the amount of phosphine relative to Pd(II),[18] and previous research within our group has demonstrated that a 1:4 ratio of Pd(OAc)$_2$ to PHOX ligand is required for high enantioselectivity in allylic alkylation reactions utilizing Pd(OAc)$_2$.[19] To probe whether this reaction might be a Pd(II)-only mechanism, we performed an experiment with an O$_2$ balloon (Table 3.2, entry 7). While we only obtained a 19% yield of product, indicating that the reaction is likely not a Pd(II)-only mechanism, we observed a similar 90% ee. Conversely, increasing equivalents of (*S*)-*t*-BuPHOX in an effort to force the reduction of Pd(OAc)$_2$ to Pd(0) resulted in diminished ee (Table 3.3, entry 8).

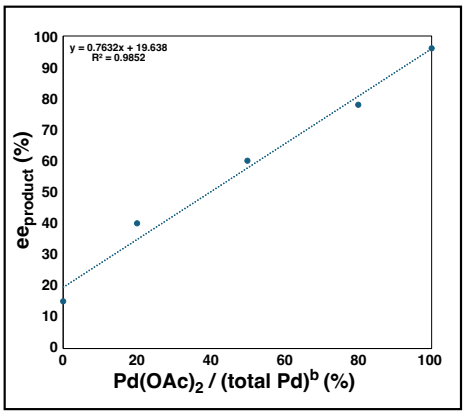
We decided to survey alternative Pd(II) precatalysts that might also be effective, and we found that while $Pd(TFA)_2$ alone affords only a 9% yield of product, enantioselectivity was improved to 76% ee as compared to the nearly racemic $Pd_2(dba)_3$ reactions (Table 3.3, entry 9). Curiously, replacing a small amount of the total palladium loading with $Pd_2(dba)_3$ restored the yield to 96% while maintaining 74% ee (Table 3.3, entry 10).

Table 3.4 *Exploration of mixed precatalysts.*[a]

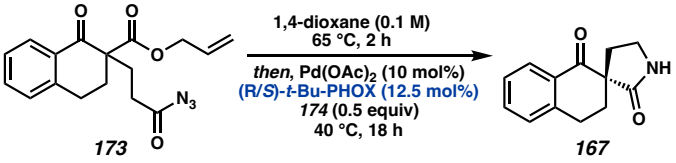
A. Exploration of mixed precatalysts.



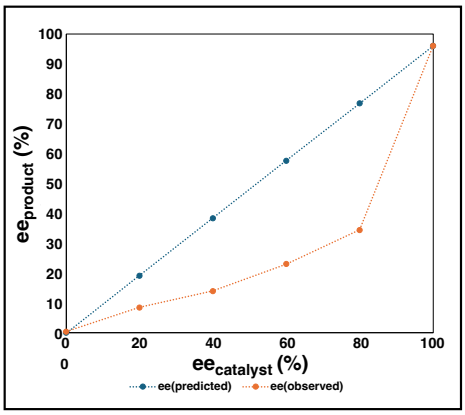
entry	$Pd(OAc)_2$ (mol%)	$Pd_2(dba)_3$ (mol%)	yield (%)	ee (%)
1	0	5	99	15
2	2	4	95	40
3	5	2.5	96	60
4	8	1	98	78
5	10	0	99	96



B. Nonlinearity experiment.



entry	ee_{cat} (%)	$ee_{predicted}$ (%)	$ee_{observed}$ (%)
1	100	96	96
2	80	77	34
3	60	58	23
4	40	38	14
5	20	19	9
6	0	0	0



[a] Reactions performed on 0.05 mmol scale and yields determined by ^1H NMR integration against an internal standard (1,3,5-trimethoxybenzene). [b] Total Pd is the molar amount of Pd by combination of $Pd(OAc)_2$ and $Pd_2(dba)_3$.

To explore this effect further, we mixed varying amounts of $Pd(OAc)_2$ and $Pd_2(dba)_3$, keeping the total Pd concentration at 10 mol%, and we observed a nearly linear

relationship between increased $Pd(OAc)_2$ loading and product ee (Table 3.4a). In a more traditional nonlinearity experiment,[20] we observed a negative nonlinear effect (Table 3.4b). Taken together, we posit that it is mechanistically important for some amount of Pd(II) to be present in the reaction mixture to obtain product with high ee, and these findings implicate the formation of catalytically relevant higher-order species. These results suggest a remarkable mechanistic departure from previously studied decarboxylative Pd enolate reactions and warrant further investigation to determine if this pathway is more generalizable.

3.6 CONCLUSIONS

In conclusion, we have developed a novel asymmetric cyclization of isocyanates and Pd enolates for the synthesis of spirocyclic γ-lactams. To the best of our knowledge, this transformation is the first example of an asymmetric enolate addition to an isocyanate. This reaction tolerates a variety of functional groups, including aryl bromides and electron-rich heterocyclic motifs. The importance of the Pd(II) precatalyst was explored through preliminary mechanistic investigations, which revealed both a negative non-linear effect and strong correlation between the presence of Pd(II) in the reaction and high enantioselectivity. In the future, we intend to perform additional mechanistic studies, both kinetic and computational, to obtain a deeper understanding of this unusual catalytic cycle. Ultimately, we aim to leverage these findings for the development of new reactions derived from this decarboxylative Pd enolate formation.

3.7 EXPERIMENTAL SECTION

3.7.1 Materials and Methods

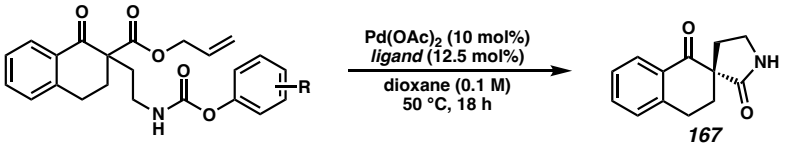
Unless otherwise stated, reactions were performed in flame-dried glassware under a nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[21] Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 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.[22] 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 Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm

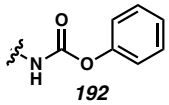
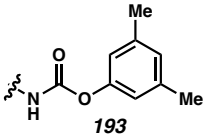
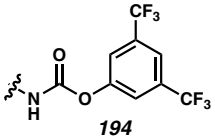
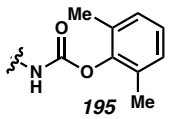
path-length cell. Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system or an Agilent 1260 Infinity II supercritical CO_2 analytical chromatography system utilizing utilizing Chiralpak (IC-3, AD-3, ID- 3, IF-3, IG-3, IH-3) or Chiralcel (OD-3, OJ-3) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. 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 $M^{+\bullet}$). The Caltech Chemistry Division Mass Spectrometry laboratory acknowledges DOW Chemical Company (DOW Next Generation Instrumentation Grant) and the NSF CRIF program for providing funds that enabled the purchase of this instrumentation.

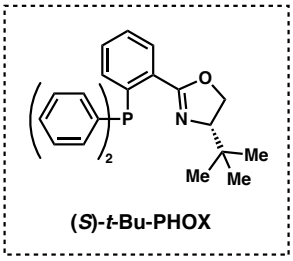
Reagents were purchased from commercial sources and used as received unless otherwise stated. Compound **174** was prepared according to a literature procedure.[23]

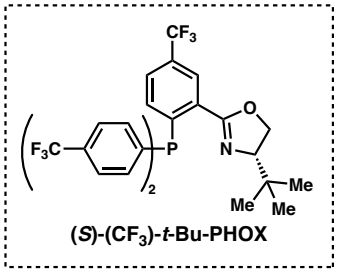
3.7.2 ADDITIONAL OPTIMIZATION DATA

Table 3.5 *Assessment of alternative carbamate electrophiles.*[a]



substrate	(*S*)-*t*-Bu-PHOX	(*S*)-(CF$_3$)-*t*-Bu-PHOX
 *192*	*15% yield 46% ee*	*0% yield*
 *193*	*trace yield ND ee*	*0% yield*
 *194*	*16% yield 32% ee*	*64% yield 14% ee*
 *195*	*trace yield ND ee*	*0% yield*

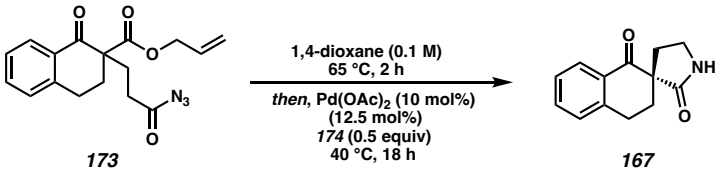




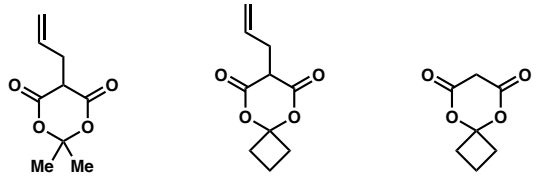
[a] Yields determined by ^{1}H NMR integration against an internal standard.

Note: adding various bases to encourage blocked isocyanate reactivity was unsuccessful;[24] in a few instances, we observed improved enantioselectivity that was found to be irreproducible.

Table 3.6 *Assessment of alternative additives.*[a]

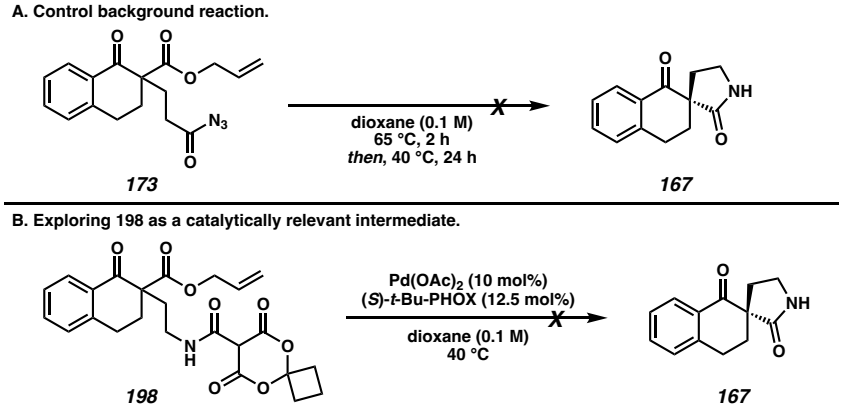


entry	additive	result
1	acac	32% yield, 58% ee
2	dimethyl malonate	0% yield, ND ee
3	methylsulfonylacetone	0% yield, ND ee
4	*197* (1.0 equiv)	98% yield, 54% ee
5	*198* (1.0 equiv)	91% yield, 57% ee
6	*199* (1.0 equiv)	93% yield, 92% ee

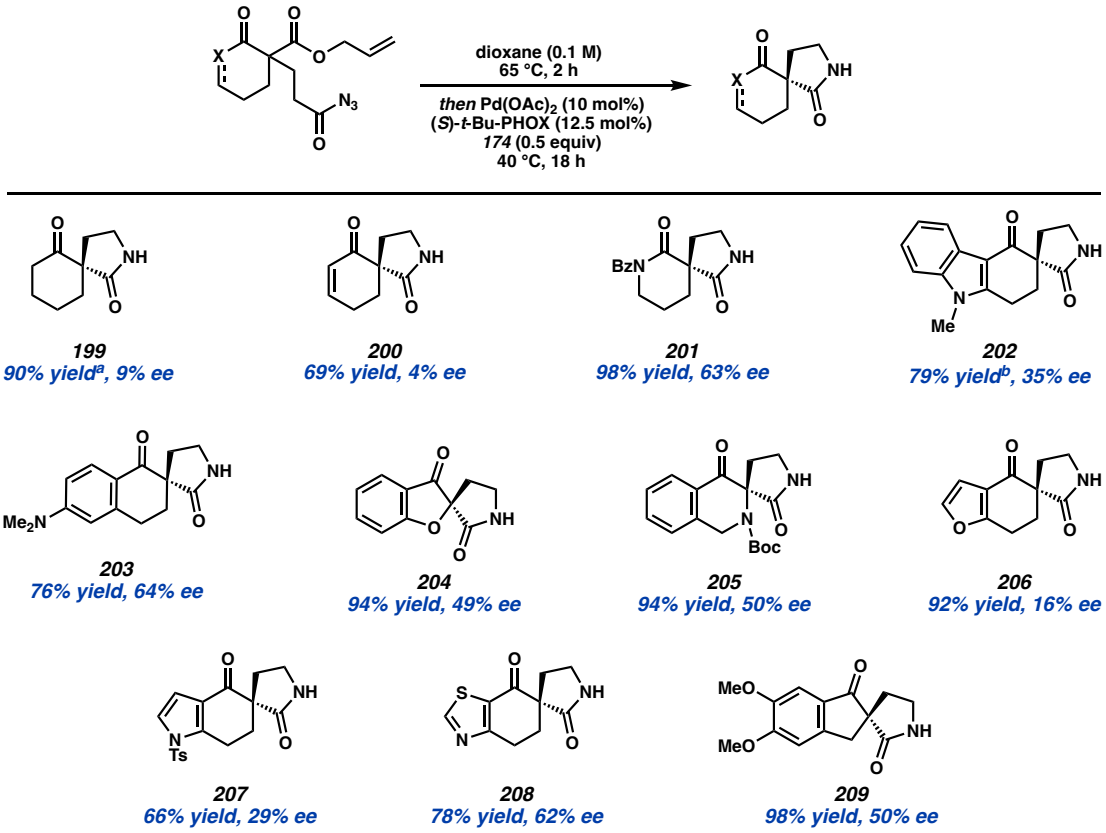


[a] Yields determined by ^{1}H NMR integration against an internal standard.

Scheme 3.5 *Control reactions.*



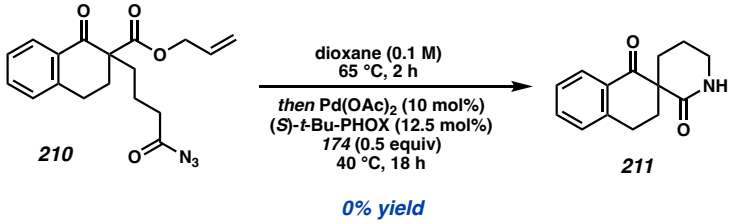
Scheme 3.6 *Failed substrates.*



[a] Yield determined by ^{1}H NMR integration against internal standard (1,3,5-trimethoxybenzene); **199** was found to be volatile.

[b] Reaction performed at 50 °C.

Scheme 3.7 *Failed δ-lactam synthesis.*[a]



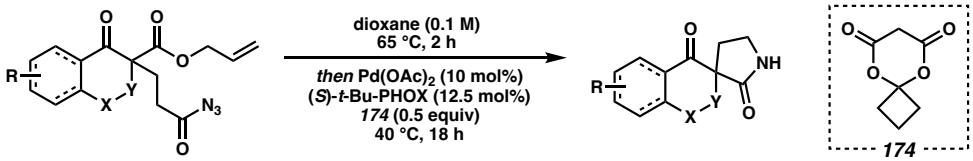
[a] Reaction performed on 0.05 mmol scale.

Note: only protonation of the enolate was observed; resulting isocyanate unstable to purification, confirmed identity via IR.

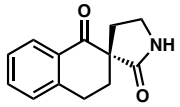
3.7.3 EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

3.7.3.1 Pd-Catalyzed Decarboxylative Spirocyclization

General Procedure A: *Asymmetric Pd-Catalyzed Decarboxylative Spirocyclization*



In a nitrogen-filled glovebox, an oven-dried 2-dram vial was charged with a stir bar, acyl azide (0.2 mmol), and dioxane (0.8 mL, 0.25 M). The vial was sealed with a Teflon-lined cap, removed from the glovebox, and stirred at 65 °C. After 2 h, the solution was cooled and pumped into the glovebox. To a separate oven-dried 2-dram vial, $Pd(OAc)_2$ (0.02 mmol, 10 mol%) and (*S*)-*t*-Bu-PHOX (0.025 mmol, 12.5 mol%) was taken up in dioxane (0.8 mL, 0.25 M) and stirred at 23 °C for 20 minutes. The reaction vial is charged with a solution of **174** (0.1 mmol, 0.5 equiv) in dioxane (0.4 mL, 0.5 M) and the Pd stock solution (0.8 mL), sealed, removed from the glovebox, and heated to 40 °C for 18 h. The reaction mixture was then cooled, concentrated under reduced pressure, and purified on silica gel chromatography to afford the spirocyclic product.



167

3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-1,2'-dione (167)

Prepared from **173** following General Procedure A. Purification by flash column chromatography (0–10% acetone/dichloromethane) afforded the title compound as a light yellow solid (40.0 mg, 0.19 mmol, 93% yield, 96% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.49 (td, *J* = 7.5, 1.5 Hz, 1H), 7.42 – 7.29 (m, 1H), 7.25 (d, *J* = 7.1 Hz, 1H), 6.42 (s, 1H), 3.51 (dt, *J* = 9.7, 7.5 Hz, 1H), 3.45 – 3.36 (m, 1H), 3.29 (ddd, *J* = 16.8, 6.5, 4.7 Hz, 1H), 2.96 (ddd, *J* = 16.9, 9.4, 4.7 Hz, 1H), 2.61 (m, 2H), 2.19 – 2.02 (m, 2H).

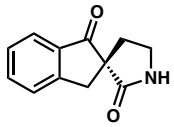
^{13}C NMR (100 MHz, $CDCl_3$): δ 196.5, 177.1, 144.0, 134.0, 131.1, 128.8, 128.3, 127.0, 55.1, 39.5, 32.0, 31.4, 25.7.

IR (neat film, NaCl): 3238, 1701, 1570, 1598, 1360, 1290, 1229, 1071 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{13}H_{14}NO_2$ $[M+H]^+$: 216.1019, found 216.1018.

Optical Rotation: $[\alpha]_D^{24}$ = 82.20 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 3.35, t_R (min): minor = 4.27.



175

spiro[indene-2,3'-pyrrolidine]-1,2'(3*H*)-dione (175)

Prepared from **212** following General Procedure A. Purification by flash column chromatography (0–50% ethyl acetate/dichloromethane) afforded the title compound as a light yellow solid (33.8 mg, 0.17 mmol, 84% yield, 81% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.7 Hz, 1H), 7.61 (td, *J* = 7.4, 1.3 Hz, 1H), 7.48 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.43 – 7.34 (m, 1H), 6.65 (s, 1H), 3.81 – 3.68 (m, 2H), 3.41 (tdd, *J* = 9.1, 3.0, 1.1 Hz, 1H), 2.99 (d, *J* = 17.1 Hz, 1H), 2.63 (ddd, *J* = 12.9, 7.6, 3.0 Hz, 1H), 2.25 (ddd, *J* = 12.8, 8.8, 7.9 Hz, 1H).

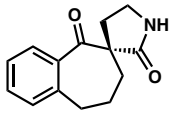
^{13}C NMR (100 MHz, $CDCl_3$): δ 204.7, 176.7, 153.8, 135.5, 135.1, 127.9, 126.5, 124.8, 58.0, 40.0, 37.8, 32.7.

IR (neat film, NaCl): 3246, 1693, 1278 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{12}H_{12}NO_2$ $[M+H]^+$: 202.0863, found 202.0859.

Optical Rotation: $[\alpha]_D^{24}$ = 114.40 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 3.76, t_R (min): minor = 4.05.



176

8,9-dihydrospiro[benzo[7]annulene-6,3'-pyrrolidine]-2',5(7*H*)-dione (176)

Prepared from **213** following General Procedure A. Purification by flash column chromatography (0–100% ethyl acetate/hexanes) afforded the title compound as an off-white solid (41.5 mg, 0.18 mmol, 91% yield, 49% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.41 (td, *J* = 7.5, 1.5 Hz, 1H), 7.30 (td, *J* = 7.5, 1.2 Hz, 1H), 7.13 (dd, *J* = 7.5, 1.1 Hz, 1H), 6.17 (s, 1H), 3.77 – 3.55 (m, 1H), 3.39 (dddd, *J* = 9.4, 8.5, 3.9, 1.0 Hz, 1H), 2.90 (ddd, *J* = 14.3, 6.2, 4.1 Hz, 1H), 2.75 (ddd, *J* = 14.3, 10.5, 6.8 Hz, 1H), 2.59 (dddd, *J* = 12.0, 8.0, 4.0, 1.6 Hz, 1H), 2.31 – 2.12 (m, 2H), 2.07 – 1.85 (m, 2H), 1.77 (dddd, *J* = 14.7, 5.4, 3.8, 1.2 Hz, 1H).

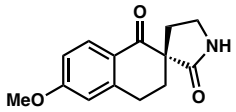
^{13}C NMR (100 MHz, $CDCl_3$): δ 209.8, 177.8, 139.8, 137.7, 132.2, 128.6, 128.0, 127.2, 58.2, 39.8, 39.8, 31.8, 31.1, 29.8, 29.7, 22.1.

IR (neat film, NaCl): 3228, 2942, 1698, 1671, 1597, 1448, 1348, 1280, 1254, 1066, 960 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{14}H_{16}NO_2$ $[M+H]^+$: 230.1176, found 230.1174.

Optical Rotation: $[\alpha]_D^{24}$ = 36.40 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 3.07, t_R (min): minor = 4.03.



177

6-methoxy-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-1,2'-dione (177)

Prepared from **214** following General Procedure A. Purification by flash column chromatography (0–10% acetone/dichloromethane) afforded the title compound as an off-white solid (46.0 mg, 0.188 mmol, 94% yield, 93% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.8 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.69 (d, *J* = 2.6 Hz, 1H), 6.14 (s, 1H), 3.86 (s, 3H), 3.61 – 3.46 (m, 1H), 3.39 (dddd, *J* = 9.4, 8.4, 3.5, 1.0 Hz, 1H), 3.27 (ddd, *J* = 16.8, 6.7, 4.7 Hz, 1H), 2.91 (ddd, *J* = 16.7, 9.3, 4.6 Hz, 1H), 2.66 – 2.53 (m, 2H), 2.14 – 2.01 (m, 2H).

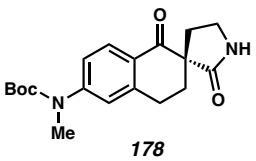
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 177.3, 164.1, 146.6, 130.8, 124.7, 113.7, 112.6, 55.6, 54.7, 39.5, 32.2, 31.6, 26.1.

IR (neat film, NaCl): 3320, 2921, 1695, 1661, 1598, 1230 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{14}H_{16}NO_3$ $[M+H]^+$: 246.1125, found 246.1123.

Optical Rotation: $[\alpha]_D^{24}$ = 71.93 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 4.15, t_R (min): minor = 8.66.



178

***tert*-butyl (*S*)-(1,2'-dioxo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidin]-6-yl)(methyl)carbamate (178)**

Prepared from **216** following General Procedure A. Purification by flash column chromatography (20% acetone/CH_2Cl_2) afforded the title compound as an off-white solid (51.0 mg, 0.15 mmol, 73% yield, 95% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.5 Hz, 1H), 7.22 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.19 (d, *J* = 2.2 Hz, 1H), 5.70 (s, 1H), 3.57 – 3.49 (m, 1H), 3.40 (dddd, *J* = 9.3, 8.3, 3.4, 1.0 Hz, 1H), 3.30 (s, 4H), 2.94 (ddd, *J* = 16.8, 9.2, 4.7 Hz, 1H), 2.66 – 2.56 (m, 2H), 2.15 – 2.04 (m, 2H), 1.49 (s, 9H).

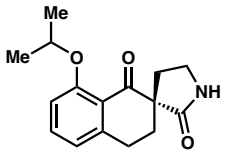
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.6, 176.8, 154.2, 148.7, 144.7, 128.9, 127.5, 123.8, 123.1, 81.4, 54.7, 39.4, 36.9, 32.2, 31.6, 28.4, 25.9.

IR (Neat Film, NaCl): 3228, 2940, 1702, 1670, 1601, 1352, 1152 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{19}H_{24}N_2O_4$ $[M+H]^+$: 345.1800, found 345.1800.

Optical Rotation: $[\alpha]_D^{21}$ 64.12 (c 1.0, $CHCl_3$).

SFC conditions: 25% IPA, 2.5 mL/min, Chiralpak AD3 column, λ = 210 nm, t_R (min): minor = 5.10, major = 3.38.



179

(*S*)-8-isopropoxy-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-1,2'-dione (179)

Prepared from **217** following General Procedure A. Purification by flash column chromatography (0–40% ethyl acetate/dichloromethane) afforded the title compound as an off-white solid (48.1 mg, 0.18 mmol, 88% yield, 82% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (dd, *J* = 8.5, 7.4 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.80 – 6.66 (m, 1H), 6.42 (s, 1H), 4.55 (p, *J* = 6.1 Hz, 1H), 3.60 – 3.49 (m, 1H), 3.42 – 3.30 (m, 1H), 3.19 (ddd, *J* = 16.4, 6.4, 4.5 Hz, 1H), 2.87 (ddd, *J* = 15.9, 10.1, 4.4 Hz, 1H), 2.63 (ddd, *J* = 12.9, 7.7, 3.1 Hz, 1H), 2.58 – 2.43 (m, 1H), 2.10 – 1.92 (m, 2H), 1.37 (dd, *J* = 9.7, 6.0 Hz, 6H).

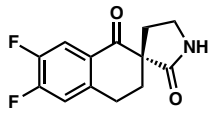
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.1, 177.7, 159.8, 146.6, 134.3, 121.8, 120.5, 113.9, 113.8, 71.8, 56.6, 56.6, 39.6, 32.8, 31.5, 26.9, 22.2, 22.1.

IR (neat film, NaCl): 3217, 2977, 2931, 2361, 2246, 1698, 1592, 1462, 1271, 1207, 1113, 919, 730 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{16}H_{20}NO_3$ $[M+H]^+$: 274.1438, found 274.1434.

Optical Rotation: $[\alpha]_D^{24}$ = 127.86 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 210 nm, t_R (min): major = 2.81, t_R (min): minor = 3.46.



180

6,7-difluoro-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-1,2'-dione (180)

Prepared from **218** following General Procedure A. Purification by flash column chromatography (0–10% acetone/dichloromethane) afforded the title compound as an off-white solid (43.5 mg, 0.17 mmol, 87% yield, 68% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 10.6, 8.3 Hz, 1H), 7.05 (dd, *J* = 10.4, 7.1 Hz, 1H), 6.06 (s, 1H), 3.68 – 3.47 (m, 1H), 3.41 (dddd, *J* = 9.4, 8.3, 3.9, 1.0 Hz, 1H), 3.38 – 3.25 (m, 1H), 3.03 – 2.85 (m, 1H), 2.68 (ddd, *J* = 12.9, 7.8, 3.9 Hz, 1H), 2.58 (ddd, *J* = 13.2, 8.1, 4.8 Hz, 1H), 2.16 – 2.04 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.4, 176.4, 157.5 – 151.6 (dd, *J* = 259.0, 13.5 Hz), 149.7 (dd, *J* = 249.7, 13.2 Hz), 141.9 (dd, *J* = 7.4, 3.6 Hz), 128.2, 117.3 (d, *J* = 17.5 Hz), 117.0 (dd, *J* = 17.8, 2.2 Hz), 54.3, 39.4, 31.9, 31.5, 25.2.

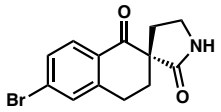
^{19}F NMR (282 MHz, $CDCl_3$): δ -128.25, -138.98.

IR (neat film, NaCl): 3248, 1698, 1674, 1616, 1509, 1355, 1330, 1283 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{13}H_{12}F_2NO_2$ $[M+H]^+$: 252.0831, found 252.0830.

Optical Rotation: $[\alpha]_D^{24}$ = 68.40 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 280 nm, t_R (min): major = 4.28, t_R (min): minor = 4.61.



181

(*S*)-6-bromo-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidine]-1,2'-dione (181)

Prepared from **219** following General Procedure A. Purification by flash column chromatography (0–20% acetone/dichloromethane) afforded the title compound as an off-white solid (54.3 mg, 0.18 mmol, 92% yield, 94% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 – 7.86 (m, 1H), 7.53 – 7.41 (m, 2H), 6.52 (s, 1H), 3.56 – 3.45 (m, 1H), 3.45 – 3.19 (m, 2H), 2.91 (ddd, *J* = 17.0, 8.7, 4.7 Hz, 1H), 2.71 – 2.51 (m, 2H), 2.15 – 2.01 (m, 2H).

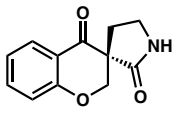
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.7, 176.7, 145.8, 131.8, 130.5, 130.0, 129.9, 129.3, 54.9, 39.5, 31.9, 31.3, 25.5.

IR (neat film, NaCl): 3233, 2930, 2893, 2362, 1701, 1672, 1586, 1430, 1353, 1289, 1226, 1079, 911, 735 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{13}H_{13}NO_2Br$ $[M+H]^+$: 294.0124, found 294.0125.

Optical Rotation: $[\alpha]_D^{24}$ = 85.81 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 4.28, t_R (min): minor = 7.28.



182

(*R*)-spiro[chromane-3,3'-pyrrolidine]-2',4-dione (182)

Prepared from **220** following General Procedure A. Purification by flash column chromatography (75% EtOAc/hexanes) afforded the title compound as an off-white solid (35.9 mg, 0.17 mmol, 83% yield, 90% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.52 (ddd, *J* = 8.4, 7.2, 1.8 Hz, 1H), 7.06 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H), 7.01 (dd, *J* = 8.4, 1.3 Hz, 1H), 5.89 (s, 1H), 4.78 (d, *J* = 11.7 Hz, 1H), 4.39 (d, *J* = 11.8 Hz, 1H), 3.53 (dtd, *J* = 9.6, 7.6, 0.7 Hz, 1H), 3.44 (dddd, *J* = 9.6, 8.6, 3.2, 1.1 Hz, 1H), 2.52 (ddd, *J* = 13.4, 7.6, 3.2 Hz, 1H), 2.30 (ddd, *J* = 13.4, 8.5, 7.7 Hz, 1H).

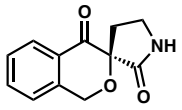
^{13}C NMR (100 MHz, $CDCl_3$): δ 190.6, 173.7, 161.5, 136.6, 128.0, 122.0, 119.7, 118.1, 72.4, 54.4, 39.4, 30.0.

IR (Neat Film, NaCl): 3247, 2902, 1704, 1680, 1605, 1477, 1301 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{12}H_{11}NO_3$ $[M+H]^+$: 218.0812, found 218.0811.

Optical Rotation: $[\alpha]_D^{21}$ 62.22 (c 1.0, $CHCl_3$).

SFC conditions: 20% IPA, 2.5 mL/min, Chiralpak AD3 column, λ = 210 nm, t_R (min): minor = 4.59, major = 4.22.



183

(*R*)-spiro[isochromane-3,3'-pyrrolidine]-2',4-dione (183)

Prepared from **221** following General Procedure A. Purification by flash column chromatography (0–50% ethyl acetate/dichloromethane) afforded the title compound as an off-white solid (34.1 mg, 0.16 mmol, 78% yield, 91% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.58 (td, *J* = 7.6, 1.4 Hz, 1H), 7.49 – 7.37 (m, 1H), 7.19 (s, 1H), 5.98 (s, 1H), 5.63 (d, *J* = 15.3 Hz, 1H), 4.88 (d, *J* = 15.3 Hz, 1H), 3.52 (td, *J* = 6.6, 1.0 Hz, 2H), 2.91 (dt, *J* = 13.3, 6.8 Hz, 1H), 2.30 (dt, *J* = 13.3, 6.4 Hz, 1H).

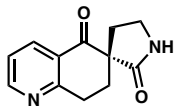
^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 173.3, 141.6, 134.6, 128.6, 127.9, 127.1, 124.5, 83.9, 64.4, 39.2, 32.3.

IR (neat film, NaCl): 3252, 2954, 2901, 2246, 1706, 1684, 1603, 1441, 1284, 1222, 1123, 1055, 886, 755 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{12}H_{12}NO_3$ $[M+H]^+$: 218.0812, found 218.0807.

Optical Rotation: $[\alpha]_D^{24}$ = 50.98 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 3.27, t_R (min): minor = 3.65.



184

7',8'-dihydro-5'*H*-spiro[pyrrolidine-3,6'-quinoline]-2,5'-dione (184)

Prepared from **222** following General Procedure A. Purification by flash column chromatography (0–30% acetone/dichloromethane) afforded the title compound as an off-white solid (35.3 mg, 0.16 mmol, 82% yield, 63% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (dd, *J* = 4.8, 1.9 Hz, 1H), 8.29 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.29 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.59 (s, 1H), 3.67 – 3.46 (m, 2H), 3.42 (dddd, *J* = 9.5, 8.3, 4.1, 1.0 Hz, 1H), 3.12 (ddd, *J* = 17.7, 8.4, 5.0 Hz, 1H), 2.78 – 2.43 (m, 2H), 2.33 – 2.02 (m, 2H).

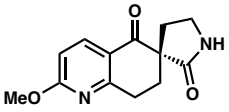
^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 176.4, 163.3, 154.0, 136.0, 126.9, 122.5, 54.8, 54.8, 46.1, 39.4, 31.6, 30.3, 30.3, 28.9.

IR (neat film, NaCl): 2930, 2603, 2496, 1645, 1396, 1035 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{12}H_{13}N_2O_2$ $[M+H]^+$: 217.0972, found 217.0971.

Optical Rotation: $[\alpha]_D^{24}$ = 81.71 (c 0.42, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack ID-3 column, λ = 280 nm, t_R (min): major = 2.61, t_R (min): minor = 3.55.



185

2'-methoxy-7',8'-dihydro-5'*H*-spiro[pyrrolidine-3,6'-quinoline]-2,5'-dione (185)

Prepared from **223** following General Procedure A. Purification by flash column chromatography (0–50% ethyl acetate/dichloromethane) afforded the title compound as an off-white solid (48.0 mg, 0.195 mmol, 97% yield, 92% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.7 Hz, 1H), 6.65 (dd, *J* = 8.7, 0.7 Hz, 1H), 6.34 (s, 1H), 3.99 (s, 3H), 3.51 (dddd, *J* = 9.5, 7.8, 7.1, 0.8 Hz, 1H), 3.45 – 3.30 (m, 2H), 2.97 (ddd, *J* = 17.8, 8.4, 5.0 Hz, 1H), 2.70 – 2.53 (m, 2H), 2.16 – 2.01 (m, 2H).

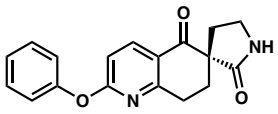
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 176.8, 166.6, 163.7, 138.6, 121.4, 110.4, 54.4, 54.2, 39.5, 31.8, 30.5, 28.9.

IR (neat film, NaCl): 3305, 2942, 1700, 1669, 1591, 1412, 1347, 1329, 1266, 1235, 1013, 906, 734 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{13}H_{15}N_2O_3$ $[M+H]^+$: 247.1077, found 247.1073.

Optical Rotation: $[\alpha]_D^{24}$ = 92.99 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 2.76, t_R (min): minor = 3.56.



186

(*S*)-2'-phenoxy-7',8'-dihydro-5'*H*-spiro[pyrrolidine-3,6'-quinoline]-2,5'-dione (186)

Prepared from **224** following General Procedure A. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as an off-white solid (50.1 mg, 0.16 mmol, 81% yield, 95% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.7 Hz, 1H), 7.41 (tt, *J* = 7.6, 2.2 Hz, 2H), 7.30 – 7.19 (m, 1H), 6.74 (d, *J* = 8.6 Hz, 2H), 6.47 (s, 1H), 3.62 – 3.45 (m, 1H), 3.43 – 3.18

(m, 2H), 2.93 (ddd, *J* = 17.9, 8.2, 5.0 Hz, 1H), 2.66 (ddd, *J* = 12.9, 7.9, 4.1 Hz, 1H), 2.57 (ddd, *J* = 13.5, 8.2, 5.1 Hz, 1H), 2.07 (dddd, *J* = 18.4, 8.3, 7.2, 4.5 Hz, 2H).

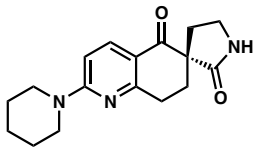
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.1, 176.6, 166.1, 164.1, 153.3, 139.8, 129.9, 125.5, 122.7, 121.6, 109.8, 54.5, 39.5, 31.7, 30.4, 28.8.

IR (neat film, NaCl): 3227, 2939, 1698, 1672, 1509, 1488, 1452, 1346, 1260, 1201, 934, 909, 774, 727 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{18}H_{17}N_2O_3$ $[M+H]^+$: 309.1234, found 309.1243.

Optical Rotation: $[\alpha]_D^{24}$ = 86.14 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 3.58, t_R (min): minor = 4.53.



187

(*S*)-2'-(piperidin-1-yl)-7',8'-dihydro-5'*H*-spiro[pyrrolidine-3,6'-quinoline]-2,5'-dione (187)

Prepared from **225** following General Procedure A. Purification by flash column chromatography (0–75% ethyl acetate/hexanes) afforded the title compound as an off-white solid (53.6 mg, 0.18 mmol, 90% yield, 82% ee).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 9.1 Hz, 1H), 6.52 (d, *J* = 9.1 Hz, 1H), 6.25 (s, 1H), 3.70 (dd, *J* = 6.3, 4.4 Hz, 4H), 3.57 – 3.44 (m, 1H), 3.37 (dddd, *J* = 9.4, 8.4, 3.7, 1.0 Hz, 1H), 3.21 (ddd, *J* = 17.4, 6.6, 4.9 Hz, 1H), 2.86 (ddd, *J* = 17.3, 9.3, 4.9 Hz, 1H), 2.64 – 2.50 (m, 2H), 2.13 – 1.97 (m, 2H), 1.80 – 1.66 (m, 2H), 1.63 (m, 4H).

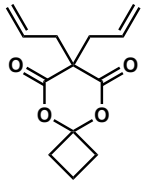
^{13}C NMR (100 MHz, $CDCl_3$): δ 194.5, 177.6, 164.4, 159.9, 137.3, 116.5, 105.0, 54.2, 45.8, 39.6, 32.2, 30.6, 29.2, 25.8, 24.8.

IR (neat film, NaCl): 3226, 2932, 2855, 2239, 1697, 1653, 1587, 1496, 1345, 1239, 1126, 1021, 913, 728 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{17}H_{22}N_3O_2$ $[M+H]^+$: 300.1707, found 300.1709.

Optical Rotation: $[\alpha]_D^{24}$ = 77.89 (c 1.0, $CHCl_3$).

SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 230 nm, t_R (min): major = 3.52, t_R (min): minor = 9.73.



168

7,7-diallyl-5,9-dioxaspiro[3.5]nonane-6,8-dione (168)

Isolated from a reaction with **173** following General Procedure A. Purification by flash column chromatography (0–10% acetone/dichloromethane) afforded the title compound as a clear oil (21.0 mg, 0.09 mmol, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.65 (ddt, *J* = 17.3, 10.1, 7.4 Hz, 2H), 5.23 – 5.13 (m, 4H), 2.72 – 2.66 (m, 4H), 2.65 – 2.57 (m, 4H), 1.89 (tt, *J* = 9.8, 7.2 Hz, 2H).

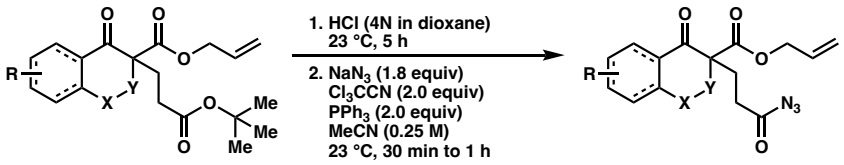
^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 130.6, 121.4, 104.5, 53.6, 41.4, 37.7, 10.7.

IR (neat film, NaCl): 2956, 1782, 1750, 1285, 1246, 1157, 995, 929 cm^{-1}.

HMRS (FD+): *m/z* calc'd for $C_{13}H_{16}O_4$ $[M]^{+\bullet}$: 236.1043, found 236.1041.

3.7.3.2 Preparation of Acyl Azide Starting Materials

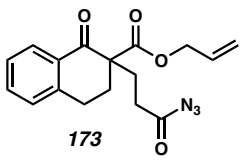
General Procedure B: Synthesis of Acyl Azides



To a flask containing ester intermediate was added HCl (4N in dioxane) at 23 °C. The resultant solution was stirred for 5 h, or until full consumption of starting material by TLC analysis. The crude mixture was concentrated under reduced pressure, then dissolved in ethyl acetate, washed with water twice, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude carboxylic acid intermediate was used without further purification.

Acyl azides were synthesized according to a modified literature procedure.[25] To a solution of the carboxylic acid intermediate in acetonitrile (0.25 M) at 23 °C was added sodium azide (1.8 equiv) and triphenylphosphine (2.0 equiv). Trichloroacetonitrile (2.0 equiv) was added dropwise, and the reaction was stirred for 30 minutes to an hour, or until starting material was consumed by TLC analysis. The crude reaction mixture was concentrated under reduced pressure, then dissolved in ethyl acetate and washed with water, saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and concentrated again under reduced pressure. The product was purified by silica gel chromatography.

Note: occasionally, upon addition of trichloroacetonitrile, the reaction gently exotherms, in which case the reaction flask was cooled with an ice bath at 0 °C until completion of the dropwise addition.



173

allyl 2-(3-azido-3-oxopropyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (173)

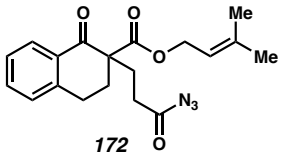
Prepared from **226** following General Procedure B. Purification by flash column chromatography (0–30% ethyl acetate/hexanes) afforded the title compound as a clear oil (642 mg, 1.96 mmol, 64% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (m, 1H), 7.48 (m, 1H), 7.36 – 7.28 (m, 1H), 7.25 – 7.18 (m, 1H), 5.78 (ddt, *J* = 17.5, 10.2, 5.6 Hz, 1H), 5.17 (m, 1H), 5.16 – 4.97 (m, 1H), 4.58 (ddt, *J* = 5.6, 3.4, 1.4 Hz, 2H), 3.21 – 2.84 (m, 2H), 2.73 – 2.41 (m, 3H), 2.38 – 2.17 (m, 2H), 2.11 (ddd, *J* = 13.6, 9.8, 5.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.1, 180.1, 171.3, 142.8, 133.9, 133.9, 132.0, 131.4, 128.9, 128.2, 128.2, 127.1, 127.1, 118.9, 118.8, 66.0, 56.7, 32.7, 31.7, 28.8, 26.0.

IR (neat film, NaCl): 3735, 2939, 2268, 2137, 1731, 1686, 1600, 1454, 1180, 929, 743 cm^{-1}.

HMRS (FD+): *m/z* calc'd for $C_{17}H_{17}N_3O_4$ $[M]^{+\bullet}$: 327.1214, found 327.1211.



172

3-methylbut-2-en-1-yl 2-(3-azido-3-oxopropyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2- carboxylate (172)

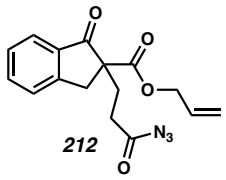
Prepared from **227** following General Procedure B. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (881 mg, 2.48 mmol, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.51 – 7.42 (m, 1H), 7.32 – 7.28 (m, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 5.20 (ddt, *J* = 7.2, 5.9, 1.4 Hz, 1H), 4.63 – 4.48 (m, 2H), 3.14 – 2.84 (m, 2H), 2.76 – 2.38 (m, 3H), 2.36 – 2.13 (m, 2H), 2.08 (ddd, *J* = 13.5, 10.2, 4.9 Hz, 1H), 1.68 (s, 3H), 1.58 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.3, 180.1, 171.5, 142.8, 133.7, 132.1, 130.2, 128.8, 128.1, 126.9, 117.9, 62.4, 56.6, 32.7, 31.9, 28.9, 26.0, 25.7, 18.1.

IR (neat film, NaCl): 2930, 2264, 2136, 1717, 1599, 1457, 1185, 1-71, 957, 766 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{19}H_{21}N_3O_4Na$ $[M+Na]^+$: 378.1424, found 378.1412.



212

allyl 2-(3-azido-3-oxopropyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (212)

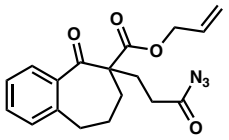
Prepared from **228** following General Procedure B. Purification by flash column chromatography (10–15% EtOAc/hexanes) afforded the title compound (191 mg, 0.50 mmol, 51% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.8 Hz, 1H), 7.65 (td, *J* = 7.4, 1.2 Hz, 1H), 7.49 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.42 (td, *J* = 7.4, 0.9 Hz, 1H), 5.82 (ddt, *J* = 17.3, 10.6, 5.5 Hz, 1H), 5.26 – 5.15 (m, 2H), 4.59 (dt, *J* = 5.5, 1.5 Hz, 2H), 3.70 (d, *J* = 17.3 Hz, 1H), 3.06 (d, *J* = 17.3 Hz, 1H), 2.61 – 2.51 (m, 1H), 2.51 – 2.30 (m, 2H), 2.27 (ddd, *J* = 14.0, 10.6, 4.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.8, 179.8, 170.5, 152.6, 135.8, 135.1, 131.5, 128.3, 126.6, 125.2, 118.7, 66.3, 59.3, 37.8, 32.5, 29.5.

IR (Neat Film, NaCl): 3423, 2269, 2137, 1713, 1173 cm^{-1}.

HRMS (MM: FD+): *m/z* calc'd for $C_{16}H_{15}NO_4$ $[M+H]^+$: 286.1074, found 286.1067.



213

allyl 6-(3-azido-3-oxopropyl)-5-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-6-carboxylate (213)

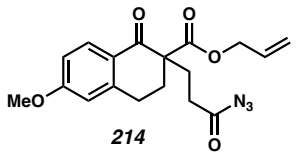
Prepared from **229** following General Procedure B. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (184 mg, 0.54 mmol, 49% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (m, 1H), 7.36 (m, 1H), 7.26 (m, 1H), 7.12 (m, 1H), 5.65 (ddd, *J* = 17.2, 10.3, 5.9 Hz, 1H), 5.28 – 5.03 (m, 2H), 4.46 (dd, *J* = 5.9, 1.3 Hz, 1H), 2.89 (dddd, *J* = 53.8, 15.7, 8.3, 4.2 Hz, 2H), 2.67 – 2.28 (m, 4H), 2.28 – 2.13 (m, 1H), 2.03 (m, 1H), 1.77 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.2, 180.0, 171.7, 140.0, 138.7, 131.5, 131.3, 129.3, 129.2, 126.7, 119.3, 66.2, 61.1, 33.1, 33.0, 32.5, 30.9, 23.9.

IR (neat film, NaCl): 2937, 2265, 2137, 1784, 1685, 1598, 1447, 1182, 959, 743 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{18}H_{20}N_1O_4$ $[M–N_2+H]^+$: 314.3487, found 314.3478.



214

allyl 2-(3-azido-3-oxopropyl)-6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (214)

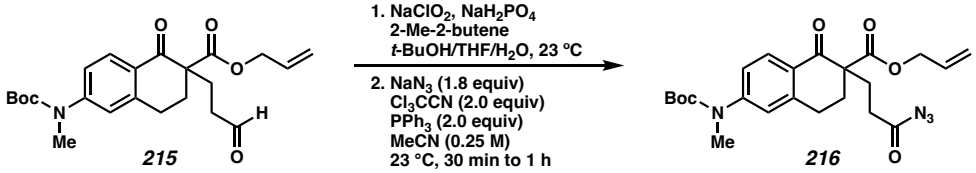
Prepared from **230** following General Procedure B. Purification by flash column chromatography (0–40% ethyl acetate/hexanes) afforded the title compound as a clear oil (513 mg, 1.44 mmol, 59% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.8 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.65 (d, *J* = 2.5 Hz, 1H), 5.87 – 5.73 (m, 1H), 5.25 – 5.11 (m, 2H), 4.58 (m, 2H), 3.85 (s, 3H), 3.11 – 2.80 (m, 2H), 2.74 – 2.39 (m, 3H), 2.38 – 2.14 (m, 2H), 2.15 – 1.95 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 180.2, 171.5, 164.0, 145.4, 131.5, 130.7, 125.5, 118.7, 113.8, 112.6, 66.0, 56.5, 55.6, 32.7, 31.6, 28.8, 26.3.

IR (neat film, NaCl): 2940, 2268, 2137, 1726, 1675, 1599, 1442, 1352, 1256, 1187, 1076, 931 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{18}H_{20}N_3O_5$ $[M+H]^+$: 330.1336, found 330.1337.



allyl 2-(3-azido-3-oxopropyl)-6-((*tert*-butoxycarbonyl)(methyl)amino)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (216)

To a solution of aldehyde **215** (1.28 g, 3.07 mmol, 1 equiv) and 2-Me-2-butene (4.9 mL, 46 mmol, 15 equiv) in *t*-BuOH/THF (1:1 ratio, 30 mL, 0.1 M total) was added $NaClO_2$ (833 mg, 3 equiv, 9.2 mmol) and NaH_2PO_4 (2.21 g, 18.4 mmol, 6 equiv) in H_2O (8 mL, 0.4 M). The reaction was stirred for 2 hours at 23 ºC until starting material was consumed by TLC analysis. The reaction was quenched with 1 N HCl and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate,

filtered, and concentrated under reduced pressure. The crude carboxylic acid intermediate was used without further purification.

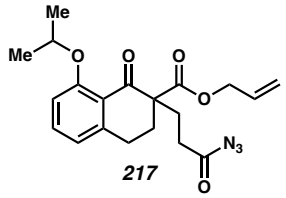
To a solution of the carboxylic acid intermediate in acetonitrile (16 mL, 0.25 M) at 23 °C was added sodium azide (242 mg, 3.7 mmol, 1.8 equiv) and triphenylphosphine (1.63 g, 6.2 mmol, 2.0 equiv). Trichloroacetonitrile (0.62 mL, 6.2 mmol, 2.0 equiv) was added dropwise, and the reaction was stirred for 30 minutes to an hour, or until starting material was consumed by TLC analysis. The crude reaction mixture was concentrated under reduced pressure, then dissolved in ethyl acetate and washed with water, saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and concentrated again under reduced pressure. Purification by flash column chromatography (20% EtOAc/hexanes) afforded the title compound as a clear oil (939 mg, 2.06 mmol, 66% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.6 Hz, 1H), 7.22 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.16 (d, *J* = 2.2 Hz, 1H), 5.80 (ddt, *J* = 17.1, 10.4, 5.6 Hz, 1H), 5.19 (dq, *J* = 9.8, 1.4 Hz, 1H), 5.15 (dq, *J* = 2.8, 1.4 Hz, 1H), 4.58 (dt, *J* = 5.6, 1.4 Hz, 2H), 3.28 (s, 3H), 3.02 (ddd, *J* = 17.3, 10.0, 4.8 Hz, 1H), 2.91 (dt, *J* = 17.4, 5.1 Hz, 1H), 2.69 – 2.42 (m, 3H), 2.35 – 2.16 (m, 2H), 2.09 (ddd, *J* = 13.6, 9.8, 4.9 Hz, 1H), 1.48 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.0, 180.1, 171.3, 154.1, 148.6, 143.4, 131.4, 128.8, 128.3, 123.8, 123.1, 118.8, 81.4, 66.0, 56.6, 36.9, 32.7, 31.6, 28.8, 28.4, 26.1.

IR (Neat Film, NaCl): 2976, 2935, 2264, 2139, 1704, 1601, 1356, 1153 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{23}H_{28}N_4O_6$ $[M+H]^+$: 457.2082, found 457.2078.



217

allyl 2-(3-azido-3-oxopropyl)-8-isopropoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (217)

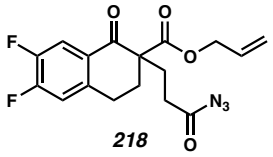
Prepared from **231** following General Procedure B. Purification by flash column chromatography (0–40% ethyl acetate/hexanes) afforded the title compound as a clear oil (343 mg, 0.89 mmol, 59% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.27 (m, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.73 (dd, *J* = 7.6, 1.0 Hz, 1H), 5.76 (ddt, *J* = 17.2, 10.5, 5.5 Hz, 1H), 5.22 – 5.09 (m, 2H), 4.65 – 4.47 (m, 3H), 3.27 – 2.75 (m, 2H), 2.63 (ddd, *J* = 16.9, 10.6, 5.4 Hz, 1H), 2.55 – 2.40 (m, 2H), 2.23 (dddd, *J* = 56.7, 14.1, 10.5, 5.4 Hz, 2H), 2.07 – 1.88 (m, 1H), 1.37 (dd, *J* = 16.1, 6.0 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.4, 180.3, 171.6, 159.2, 144.8, 133.8, 131.6, 123.4, 120.6, 118.5, 113.7, 71.8, 65.8, 57.7, 32.7, 31.1, 29.2, 26.6, 22.2, 22.1.

IR (neat film, NaCl): 2979, 2933, 2263, 2138, 1731, 1694, 1592, 1454, 1270, 1182, 1111, 922, 763 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{20}H_{23}N_3O_5Na$ $[M+Na]^+$: 408.1530, found 408.1515.



218

allyl 2-(3-azido-3-oxopropyl)-6,7-difluoro-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (218)

Prepared from **232** following General Procedure B. Purification by flash column chromatography (0–30% ethyl acetate/hexanes) afforded the title compound as a clear oil (416 mg, 1.14 mmol, 64% yield).

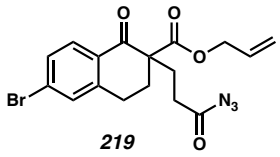
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (dd, *J* = 10.6, 8.2 Hz, 1H), 7.01 (dd, *J* = 10.3, 7.1 Hz, 1H), 5.79 (ddt, *J* = 17.6, 10.0, 5.7 Hz, 1H), 5.24 – 5.11 (m, 2H), 4.65 – 4.53 (m, 2H), 3.06 – 2.84 (m, 2H), 2.71 – 2.38 (m, 3H), 2.36 – 2.15 (m, 2H), 2.10 (ddd, *J* = 13.7, 10.3, 5.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 192.90, 179.93, 170.85, 153.95 (dd, *J* = 258.9, 13.6 Hz), 149.76 (dd, *J* = 250.2, 13.1 Hz), 140.37 (dd, *J* = 7.3, 3.6 Hz), 131.21, 130.04 – 126.31 (m), 119.17, 117.28 (d, *J* = 17.5 Hz), 116.94 (dd, *J* = 17.9, 2.2 Hz), 66.26, 56.18, 32.54, 31.74, 28.82, 25.57.

^{19}F NMR (282 MHz, $CDCl_3$): δ -128.23, -138.48.

IR (neat film, NaCl): 3067, 2937, 2269, 2139, 1731, 1619, 1511, 1356, 1284, 1170, 1072, 919, 786 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{17}H_{16}F_2O_4$ $[M–N_3+H]^+$: 321.0933, found 321.0936.



219

allyl 2-(3-azido-3-oxopropyl)-6-bromo-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (219)

Prepared from **233** following General Procedure B. Purification by flash column chromatography (0–30% ethyl acetate/hexanes) afforded the title compound as a clear oil (484 mg, 1.19 mmol, 67% yield).

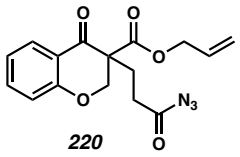
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.4 Hz, 1H), 7.46 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.40 (s, 1H), 5.79 (m, *J* = 17.2, 9.9, 5.6 Hz, 1H), 5.22 – 5.13 (m, 2H), 4.58 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.16 – 2.79 (m, 2H), 2.64 (ddd, *J* = 16.6, 10.3, 5.5 Hz, 1H), 2.55 (dt, *J* = 13.7, 4.8

Hz, 1H), 2.46 (ddd, *J* = 16.7, 10.1, 5.5 Hz, 1H), 2.26 (dddd, *J* = 40.0, 14.1, 10.2, 5.5 Hz, 2H), 2.13 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.2, 180.0, 171.0, 144.5, 131.8, 131.3, 130.9, 130.6, 129.9, 129.1, 119.1, 66.2, 56.6, 32.6, 31.5, 28.8, 25.8.

IR (neat film, NaCl): 2939, 2271, 2138, 1728, 1688, 1587, 1443, 1349, 1183, 1071, 905 cm^{-1}.

HMRS (FD+): *m/z* calc'd for $C_{17}H_{16}N_3O_4Br$ $[M]^{+\bullet}$: 405.0319, found 405.0329.



220

allyl 3-(3-azido-3-oxopropyl)-4-oxochromane-3-carboxylate (220)

A solution of **234** (507 mg, 1.41 mmol, 1 equiv) in acetone (0.5 M, 2.8 mL) was cooled to 0 ºC. Concentrated HCl (2.8 mL) was added. Upon complete consumption of starting material (as determined by TLC), the reaction mixture was diluted with brine and extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the crude carboxylic acid which was used directly in the next step.

To a solution of the carboxylic acid intermediate in acetonitrile (0.25 M) at 23 °C was added sodium azide (1.8 equiv) and triphenylphosphine (2.0 equiv). Trichloroacetonitrile (2.0 equiv) was added dropwise, and the reaction was stirred for 30 minutes to an hour, or until starting material was consumed by TLC analysis. The crude reaction mixture was concentrated under reduced pressure, then dissolved in ethyl acetate and washed with water, saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and concentrated again under reduced pressure. Purification by flash column chromatography

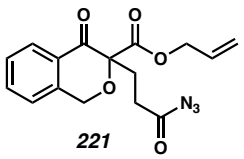
(15% EtOAc/hexanes) afforded the title compound as a clear oil (148 mg, 0.45 mmol, 64% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.50 (ddd, *J* = 8.6, 7.2, 1.7 Hz, 1H), 7.06 (td, *J* = 7.7, 1.1 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 5.81 (ddt, *J* = 17.1, 10.2, 5.6 Hz, 1H), 5.25 – 5.17 (m, 2H), 4.80 (d, *J* = 11.7 Hz, 1H), 4.68 – 4.59 (m, 2H), 4.31 (d, *J* = 11.7 Hz, 1H), 2.70 – 2.50 (m, 2H), 2.31 (ddd, *J* = 14.2, 10.1, 5.8 Hz, 1H), 2.15 (ddd, *J* = 14.3, 10.3, 5.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 189.7, 179.6, 169.0, 161.0, 136.5, 131.1, 128.0, 122.2, 120.1, 119.0, 117.9, 72.1, 66.5, 56.3, 32.4, 25.0.

IR (Neat Film, NaCl): 3076, 2937, 2264, 2136, 1713, 1606, 1458, 1220 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{16}H_{15}NO_5$ $[M+H]^+$: 302.1023, found 302.1012.



221

allyl 3-(3-azido-3-oxopropyl)-4-oxoisochromane-3-carboxylate (221)

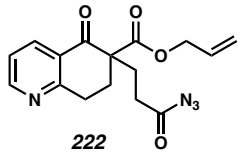
Prepared from **235** following General Procedure B. Purification by flash column chromatography (0–30% ethyl acetate/hexanes) afforded the title compound as a clear oil (400 mg, 1.22 mmol, 64% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.58 (m, 1H), 7.41 (m, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 5.92 – 5.76 (m, 1H), 5.41 – 5.16 (m, 2H), 4.90 (d, *J* = 16.1 Hz, 1H), 4.63 (m, 2H), 2.64 – 2.38 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.0, 179.8, 167.8, 141.0, 134.7, 131.0, 128.4, 128.0, 127.4, 124.4, 119.3, 84.1, 66.6, 64.3, 31.2.

IR (neat film, NaCl): 2948, 2270, 2139, 1741, 1701, 1603, 1449, 1287, 1210, 1051, 756 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{16}H_{15}NO_5Na$ $[M–N_2+Na]^+$: 324.0842, found 324.0831.



222

allyl 6-(3-azido-3-oxopropyl)-5-oxo-5,6,7,8-tetrahydroquinoline-6-carboxylate (222)

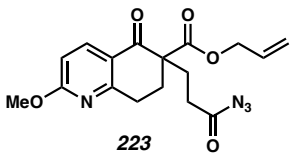
Prepared from **236** following General Procedure B. Purification by flash column chromatography (0–40% ethyl acetate/hexanes) afforded the title compound as a clear oil (0.193 mg, 0.59 mmol, 27% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (dd, *J* = 4.8, 1.9 Hz, 1H), 8.34 – 8.26 (m, 1H), 7.31 (dd, *J* = 7.9, 4.7 Hz, 1H), 5.78 (ddt, *J* = 17.6, 10.0, 5.7 Hz, 1H), 5.22 – 5.13 (m, 2H), 4.58 (dt, *J* = 5.2, 1.4 Hz, 2H), 3.29 – 3.09 (m, 2H), 2.74 – 2.56 (m, 2H), 2.47 (ddd, *J* = 16.7, 10.1, 5.4 Hz, 1H), 2.29 (dddd, *J* = 42.9, 14.1, 10.3, 5.4 Hz, 2H), 2.15 (ddd, *J* = 13.9, 9.6, 6.1 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.8, 179.9, 170.8, 162.0, 154.0, 136.0, 131.2, 127.9, 122.6, 119.3, 66.3, 56.5, 32.5, 30.6, 29.3, 28.8.

IR (neat film, NaCl): 2949, 2272, 2138, 1713, 1694, 1584, 1442, 1181, 1089, 943, 759 cm^{-1}.

HMRS (FD+): *m/z* calc'd for $C_{16}H_{16}N_4O_4$ $[M]^{+\bullet}$: 328.1166, found 328.1154.



223

allyl 6-(3-azido-3-oxopropyl)-2-methoxy-5-oxo-5,6,7,8-tetrahydroquinoline-6-carboxylate (223)

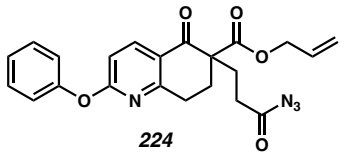
Prepared from **237** following General Procedure B. Purification by flash column chromatography (0–30% ethyl acetate/hexanes) afforded the title compound as a clear oil (259 mg, 0.72 mmol, 42% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.7 Hz, 1H), 6.66 (d, *J* = 8.7 Hz, 1H), 5.81 (ddt, *J* = 17.4, 10.2, 5.7 Hz, 1H), 5.26 – 5.15 (m, 2H), 4.59 (d, *J* = 5.6 Hz, 2H), 3.98 (s, 3H), 3.14 – 2.94 (m, 2H), 2.78 – 2.54 (m, 2H), 2.48 (ddd, *J* = 16.8, 10.1, 5.5 Hz, 1H), 2.32 (ddd, *J* = 14.1, 10.1, 5.6 Hz, 1H), 2.21 (ddd, *J* = 14.2, 10.4, 5.5 Hz, 1H), 2.14 – 1.97 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 180.1, 171.2, 166.5, 162.4, 138.5, 131.4, 122.1, 119.0, 110.6, 66.2, 56.1, 54.2, 32.6, 30.5, 29.2, 28.7.

IR (neat film, NaCl): 2945, 2267, 2139, 1727, 1592, 1480, 1329, 1267, 1183, 1072, 1020, 842, 784 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{=17}H_{19}N_2O_5$ $[M–N_2+H]^+$: 331.1288, found 331.1301.



224

allyl 6-(3-azido-3-oxopropyl)-5-oxo-2-phenoxy-5,6,7,8-tetrahydroquinoline-6-carboxylate (224)

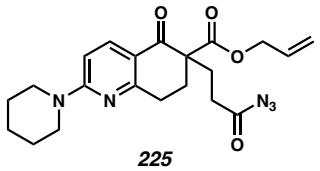
Prepared from **238** following General Procedure B. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (164 mg, 0.39 mmol, 44% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.6 Hz, 1H), 7.47 – 7.33 (m, 2H), 7.26 (s, 1H), 7.19 – 7.11 (m, 2H), 6.76 (d, *J* = 8.7 Hz, 1H), 5.81 (m, 1H), 5.22 (dd, *J* = 8.4, 1.4 Hz, 1H), 5.19 (m, 1H), 4.59 (m, 2H), 3.18 – 2.86 (m, 2H), 2.75 – 2.38 (m, 3H), 2.27 (dddd, *J* = 43.3, 14.1, 10.2, 5.5 Hz, 2H), 2.09 (ddd, *J* = 13.9, 9.8, 5.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5, 180.0, 171.0, 166.1, 162.8, 153.3, 139.8, 131.3, 129.9, 125.6, 123.5, 121.6, 119.1, 110.0, 66.2, 56.2, 32.6, 30.5, 29.1, 28.7.

IR (neat film, NaCl): 2946, 2266, 2137, 1727, 1579, 1489, 1451, 1414, 1314, 1257, 1196, 1071, 941, 777 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{22}H_{21}N_2O_5$ $[M–N_2+H]^+$: 393.1445, found 393.1446.



225

allyl 6-(3-azido-3-oxopropyl)-5-oxo-2-(piperidin-1-yl)-5,6,7,8-tetrahydroquinoline-6-carboxylate (225)

Prepared from **239** following General Procedure B. Purification by flash column chromatography (0–30% ethyl acetate/hexanes) afforded the title compound as a clear oil (1.18 g, 2.87 mmol, 66% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 9.1 Hz, 1H), 6.53 (d, *J* = 9.1 Hz, 1H), 5.92 – 5.76 (m, 1H), 5.34 – 5.14 (m, 2H), 4.64 – 4.56 (m, 2H), 3.70 (m, 4H), 3.02 – 2.77 (m, 2H), 2.69 – 2.40 (m, 3H), 2.38 – 2.19 (m, 2H), 2.13 – 1.86 (m, 1H), 1.76 – 1.66 (m, 2H), 1.67 – 1.57 (m, 4H).

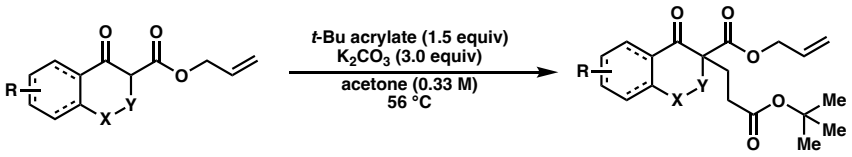
^{13}C NMR (100 MHz, $CDCl_3$): δ 192.8, 180.3, 171.8, 163.4, 159.8, 137.3, 131.7, 118.7, 117.1, 105.1, 66.0, 56.0, 45.8, 32.8, 30.5, 29.5, 28.8, 25.9, 24.8.

IR (neat film, NaCl): 2938, 2855, 2266, 2137, 1729, 1662, 1589, 1498, 1408, 1249, 1088, 1024, 941, 817 cm^{-1}.

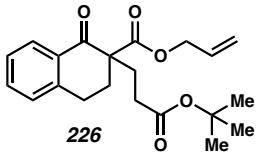
HMRS (ESI+): *m/z* calc'd for $C_{21}H_{26}N_5O_4$ $[M+H]^+$: 412.2132, found 412.2113.

3.7.3.3 Preparation of *tert*-Butyl Ester Intermediates

General Procedure C: Michael Addition of tert-Butyl Acrylate



To a flask containing the allyl β-keto ester intermediate was added acetone (0.33 M), *t*-butyl acrylate (1.5 equiv) and K_2CO_3 (3.0 equiv). The reaction was heated to 56 °C for 5 h, or until complete consumption of starting material by TLC analysis. The reaction was cooled, filtered through a small Celite plug, concentrated, and purified via silica gel chromatography to afford the *tert*-butyl ester products.



226

allyl 2-(3-(*tert*-butoxy)-3-oxopropyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (226)

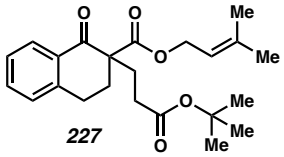
Prepared from **240** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (11.65 g, 32.5 mmol, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (m, 1H), 7.46 (m, 1H), 7.30 (m, 1H), 7.20 (m, 1H), 5.86 – 5.71 (m, 1H), 5.21 – 5.09 (m, 2H), 4.65 – 4.51 (m, 2H), 3.11 – 2.89 (m, 2H), 2.57 (m, 1H), 2.51 – 2.39 (m, 1H), 2.38 – 2.04 (m, 4H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 172.5, 171.5, 142.9, 133.7, 132.1, 131.6, 128.8, 128.2, 127.0, 118.4, 80.5, 65.8, 56.9, 31.2, 31.1, 29.0, 28.2, 25.9.

IR (neat film, NaCl): 2974, 2365, 1729, 1686, 1601, 1365, 1228, 1154, 947 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{21}H_{26}O_5Na$ $[M+Na]^+$: 381.1672, found 381.1676.



227

3-methylbut-2-en-1-yl 2-(3-(*tert*-butoxy)-3-oxopropyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (227)

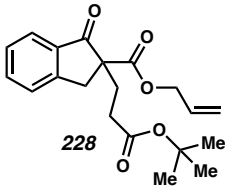
Prepared from **241** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (1.18 g, 3.10 mmol, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (dt, *J* = 8.0, 1.3 Hz, 1H), 7.58 – 7.38 (m, 1H), 7.32 (d, *J* = 1.4 Hz, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 5.22 (ddt, *J* = 7.2, 5.8, 1.4 Hz, 1H), 4.65 – 4.49 (m, 2H), 3.10 – 2.87 (m, 2H), 2.60 – 2.39 (m, 2H), 2.38 – 2.20 (m, 2H), 2.20 – 1.97 (m, 2H), 1.68 (s, 3H), 1.58 (s, 3H), 1.43 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.4, 172.6, 171.8, 143.0, 139.9, 133.6, 132.3, 128.8, 128.2, 126.9, 118.2, 80.5, 62.3, 56.9, 31.5, 31.2, 29.2, 28.2, 26.0, 25.8, 18.1.

IR (neat film, NaCl): 2974, 2361, 1729, 1691, 1601, 1454, 1367, 1226, 1164, 941, 741 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{23}H_{30}O_5Na$ $[M+Na]^+$: 409.1985, found 409.1977.



228

allyl 2-(3-(*tert*-butoxy)-3-oxopropyl)-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (228)

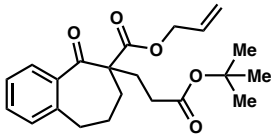
Prepared from **242** following General Procedure C. Purification by flash column chromatography (20% EtOAc/hexanes) afforded the title compound as a clear oil (772 mg, 2.24 mmol, 39% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.63 (td, *J* = 7.5, 1.2 Hz, 1H), 7.48 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.40 (td, *J* = 7.2, 0.9 Hz, 1H), 5.83 (ddt, *J* = 17.3, 10.5, 5.5 Hz, 1H), 5.23 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.18 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.60 (dt, *J* = 5.5, 1.5 Hz, 2H), 3.70 (d, *J* = 17.4 Hz, 1H), 3.09 (d, *J* = 17.3 Hz, 1H), 2.38 – 2.21 (m, 4H), 1.44 (s, 2H), 1.41 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.1, 172.1, 170.7, 152.8, 135.6, 135.3, 131.7, 128.1, 126.5, 125.0, 118.5, 80.7, 66.2, 59.7, 37.3, 31.1, 30.0, 28.2.

IR (Neat Film, NaCl): 3427, 2980, 2340, 1715, 1605, 1453, 1368, 1168 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{20}H_{24}O_5$ $[M+Na]^+$: 367.1516, found 367.1527.



229

allyl 6-(3-(*tert*-butoxy)-3-oxopropyl)-5-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-6-carboxylate (229)

Prepared from **243** following General Procedure C. Purification by flash column chromatography (0–10% ethyl acetate/hexanes) afforded the title compound as a clear oil (409 mg, 1.10 mmol, 79% yield).

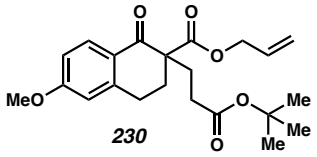
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (m, 1H), 7.35 (m, 1H), 7.29 – 7.20 (m, 3H), 7.11 (m, 1H), 5.66 (ddt, *J* = 17.3, 10.4, 5.8 Hz, 1H), 5.23 – 5.10 (m, 2H), 4.47 (dt, *J* = 5.7, 1.1 Hz,

2H), 3.09 – 2.61 (m, 2H), 2.58 – 2.12 (m, 5H), 2.10 – 1.95 (m, 1H), 1.92 – 1.72 (m, 2H), 1.43 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.4, 172.4, 171.9, 140.2, 138.8, 131.5, 131.3, 129.3, 129.2, 126.6, 119.0, 80.6, 66.0, 61.4, 33.1, 32.8, 31.6, 30.9, 28.2, 24.0.

IR (neat film, NaCl): 2935, 1730, 1685, 1449, 1366, 1253, 1153, 1090, 958 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{22}H_{29}O_5Na$ $[M+Na]^+$: 395.1829, found 395.1831.



230

allyl 2-(3-(*tert*-butoxy)-3-oxopropyl)-6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (230)

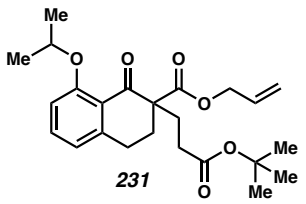
Prepared from **244** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (1.02 g, 2.62 mmol, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.8 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.65 (d, *J* = 2.5 Hz, 1H), 5.88 – 5.74 (m, 1H), 5.24 – 5.12 (m, 2H), 4.66 – 4.53 (m, 2H), 3.85 (s, 3H), 3.07 – 2.86 (m, 2H), 2.56 (ddd, *J* = 13.6, 5.9, 4.8 Hz, 1H), 2.50 – 2.01 (m, 5H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 172.6, 171.7, 163.9, 145.5, 131.7, 130.7, 125.6, 118.4, 113.7, 112.5, 80.5, 65.8, 56.7, 55.6, 31.2, 29.0, 28.2, 26.3.

IR (neat film, NaCl): 2934, 1729, 1600, 1450, 1366, 1257, 1155, 1080, 934, 850, 681 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{22}H_{28}O_6Na$ $[M+Na]^+$: 411.1778, found 411.1775.



231

allyl 2-(3-(*tert*-butoxy)-3-oxopropyl)-8-isopropoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (231)

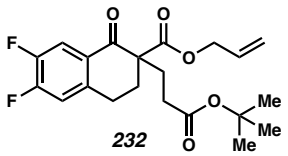
Prepared from **246** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (637 mg, 1.53 mmol, 86% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (dd, *J* = 8.3, 7.6 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.72 (dd, *J* = 7.6, 1.0 Hz, 1H), 5.77 (ddt, *J* = 17.3, 10.7, 5.4 Hz, 1H), 5.22 – 5.00 (m, 2H), 4.65 – 4.47 (m, 3H), 3.20 – 2.71 (m, 2H), 2.62 – 2.20 (m, 4H), 2.20 – 2.09 (m, 1H), 2.06 – 1.88 (m, 1H), 1.43 (s, 9H), 1.36 (dd, *J* = 14.1, 6.0 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 172.6, 171.8, 159.2, 145.0, 133.7, 131.7, 123.6, 120.6, 118.2, 113.7, 80.4, 71.8, 65.6, 58.0, 31.1, 30.6, 29.4, 28.2, 26.6, 22.2, 22.2.

IR (neat film, NaCl): 2976, 2932, 1780, 1693, 1592, 1453, 1367, 1270, 1154, 1112, 921, 848, 764 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{24}H_{33}O_6$ $[M+H]^+$: 417.2272, found 417.2274.



232

allyl 2-(3-(*tert*-butoxy)-3-oxopropyl)-6,7-difluoro-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (232)

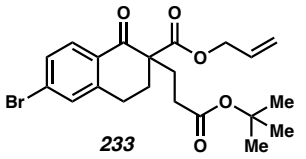
Prepared from **247** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (1.07 g, 2.71 mmol, 73% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (m, 1H), 7.00 (m, 1H), 5.86 – 5.72 (m, 1H), 5.23 – 5.11 (m, 2H), 4.65 – 4.51 (m, 2H), 3.05 – 2.84 (m, 2H), 2.55 (m, 1H), 2.50 – 2.37 (m, 1H), 2.36 – 2.16 (m, 3H), 2.16 – 2.05 (m, 1H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 192.99, 172.29, 171.03, 153.83 (dd, *J* = 258.5, 13.5 Hz), 149.68 (dd, *J* = 249.9, 13.3 Hz), 140.48 (dd, *J* = 7.3, 3.6 Hz), 131.38, 129.45 – 128.95 (m), 118.83, 117.22 (d, *J* = 17.5 Hz), 116.88 (dd, *J* = 17.7, 2.2 Hz), 80.68, 66.07, 56.42, 31.26, 30.97, 28.98, 28.18, 25.53.

IR (neat film, NaCl): 3434, 2935, 2356, 1750, 1435, 1213, 1097, 991, 665 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{21}H_{24}F_2O_5$ $[M+Na]^+$: 417.1484, found 417.1492.



233

allyl 6-bromo-2-(3-(*tert*-butoxy)-3-oxopropyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (233)

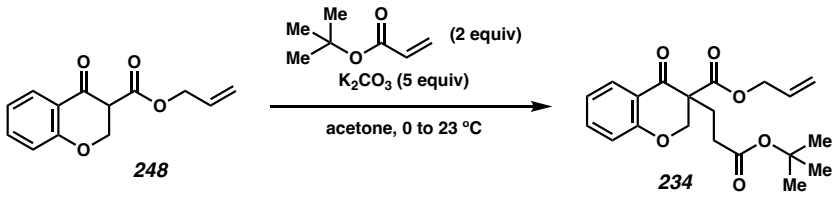
Prepared from **248** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (772 mg, 1.77 mmol, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.4 Hz, 1H), 7.47 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.42 (d, *J* = 1.9 Hz, 1H), 6.05 – 5.59 (m, 1H), 5.25 – 5.15 (m, 2H), 4.61 (dq, *J* = 5.6, 1.5 Hz, 2H), 3.11 – 2.89 (m, 2H), 2.58 (m, 1H), 2.52 – 2.39 (m, 1H), 2.41 – 2.09 (m, 4H), 1.45 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.3, 172.4, 171.2, 144.6, 131.8, 131.5, 131.0, 130.5, 129.9, 129.0, 118.8, 80.7, 66.0, 56.8, 31.1, 31.0, 29.0, 28.2, 25.8.

IR (neat film, NaCl): 2975, 2360, 1780, 1691, 1587, 1367, 1226, 1154, 1089 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{21}H_{25}BrO_5Na$ $[M+Na]^+$: 459.0778, found 459.0783.



allyl 3-(3-(*tert*-butoxy)-3-oxopropyl)-4-oxochromane-3-carboxylate (234)

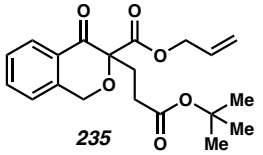
48 reactions performed in parallel and combined for purification. Yield significantly decreased at larger scale. A solution of β-ketoester **248** (20 mg, 0.09 mmol, 1 equiv) in acetone (0.3 mL, 0.3 M) was cooled to 0 ºC. To the reaction K_2CO_3 (59 mg, 0.43 mmol, 5 equiv) and *t*-Bu acrylate (25 mL, 0.17 mmol, 2 equiv) were added, and the reaction was slowly warmed to 23 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction was filtered over celite with acetone and concentrated. Purification by flash column chromatography (10% EtOAc/hexanes) afforded the title compound (500 mg, 1.38 mmol, 33% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.49 (ddd, *J* = 8.4, 7.2, 1.8 Hz, 1H), 7.05 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H), 6.97 (dd, *J* = 8.3, 1.0 Hz, 1H), 5.82 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.24 – 5.16 (m, 2H), 4.81 (d, *J* = 11.7 Hz, 1H), 4.70 – 4.58 (m, 2H), 4.32 (d, *J* = 11.6 Hz, 1H), 2.52 – 2.34 (m, 2H), 2.29 (ddd, *J* = 14.0, 10.1, 5.8 Hz, 1H), 2.12 (ddd, *J* = 14.1, 10.5, 5.4 Hz, 1H), 1.43 (s, 10H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 189.8, 171.9, 169.2, 161.0, 136.3, 131.3, 128.0, 122.1, 120.3, 118.8, 117.9, 80.9, 72.0, 66.4, 56.5, 30.9, 28.2, 25.5.

IR (Neat Film, NaCl): 3437, 2980, 2932, 1731, 1607, 1479, 1217 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{20}H_{24}O_6$ $[M+Na]^+$: 383.1465, found 383.1470.



235

allyl 3-(3-(*tert*-butoxy)-3-oxopropyl)-4-oxochromane-3-carboxylate (235)

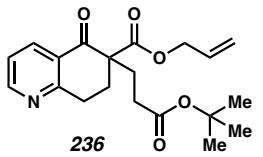
Prepared from **250** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (686 mg, 1.90 mmol, 39% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.56 (td, *J* = 7.5, 1.4 Hz, 1H), 7.44 – 7.35 (m, 1H), 7.16 (dt, *J* = 7.7, 0.9 Hz, 1H), 5.84 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.34 – 5.15 (m, 3H), 4.94 – 4.85 (m, 1H), 4.71 – 4.57 (m, 2H), 2.66 – 2.10 (m, 4H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.3, 172.1, 168.1, 141.1, 134.5, 131.2, 128.5, 127.9, 127.4, 124.4, 119.1, 84.6, 80.5, 66.4, 64.2, 30.5, 29.7, 28.2.

IR (neat film, NaCl): 2973, 1781, 1603, 1364, 1230, 1169, 707 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{20}H_{24}O_6Na$ $[M+Na]^+$: 383.1465, found 383.1467.



236

allyl 6-(3-(*tert*-butoxy)-3-oxopropyl)-5-oxo-5,6,7,8-tetrahydroquinoline-6-carboxylate (236)

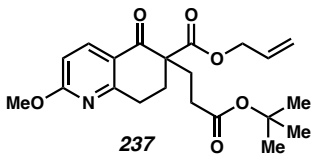
Prepared from **250** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (830 mg, 2.31 mmol, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (dd, *J* = 4.7, 1.9 Hz, 1H), 8.29 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.30 (dd, *J* = 7.9, 4.8 Hz, 1H), 5.86 – 5.72 (m, 1H), 5.23 – 5.13 (m, 2H), 4.59 (dq, *J* = 5.7, 1.5 Hz, 2H), 3.27 – 3.09 (m, 2H), 2.62 (dt, *J* = 13.9, 5.0 Hz, 1H), 2.54 – 2.41 (m, 1H), 2.38 – 2.26 (m, 2H), 2.26 – 2.10 (m, 2H), 1.44 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.9, 172.3, 171.0, 162.2, 153.9, 136.0, 131.4, 127.9, 122.5, 119.0, 80.7, 66.2, 56.7, 31.0, 30.2, 29.3, 29.0, 28.2.

IR (neat film, NaCl): 2977, 1729, 1697, 1584, 1456, 1367, 1229, 1171, 1155, 937 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{20}H_{26}NO_5$ $[M+H]^+$: 360.1805, found 360.1813.



237

allyl 6-(3-(*tert*-butoxy)-3-oxopropyl)-5-oxo-5,6,7,8-tetrahydroquinoline-6-carboxylate (237)

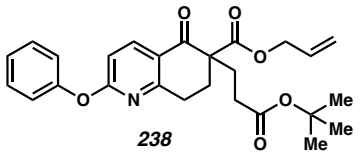
Prepared from **251** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (670 mg, 1.72 mmol, 61% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.7 Hz, 1H), 6.66 (d, *J* = 8.7 Hz, 1H), 5.82 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.26 – 5.14 (m, 2H), 4.60 (dt, *J* = 5.6, 1.5 Hz, 2H), 3.98 (s, 3H), 3.14 – 2.94 (m, 2H), 2.59 (dt, *J* = 13.8, 5.3 Hz, 1H), 2.50 – 2.02 (m, 5H), 1.43 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 172.4, 171.3, 166.4, 162.5, 138.6, 131.6, 122.2, 118.7, 110.4, 80.6, 66.0, 56.4, 54.2, 31.1, 30.1, 29.2, 28.9, 28.2.

IR (neat film, NaCl): 2977, 2365, 1780, 1683, 1480, 1415, 1329, 1265, 1154, 1020 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{21}H_{28}NO_6$ $[M+H]^+$: 390.1911, found 390.1913.



238

allyl 6-(3-(*tert*-butoxy)-3-oxopropyl)-5-oxo-2-phenoxy-5,6,7,8-tetrahydroquinoline-6-carboxylate (238)

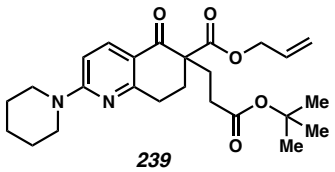
Prepared from **252** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (395 mg, 0.87 mmol, 96% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (dd, *J* = 8.7, 0.8 Hz, 1H), 7.42 (ddd, *J* = 8.4, 7.4, 0.8 Hz, 2H), 7.19 – 7.11 (m, 2H), 6.75 (d, *J* = 8.6 Hz, 1H), 5.82 (dddd, *J* = 11.4, 10.5, 5.2, 0.8 Hz, 1H), 5.27 – 5.15 (m, 2H), 4.60 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.10 – 2.90 (m, 2H), 2.62 – 2.02 (m, 6H), 1.43 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 172.4, 171.2, 166.0, 162.9, 153.3, 139.8, 131.5, 129.9, 125.5, 123.6, 121.6, 118.8, 109.9, 80.7, 66.1, 56.5, 31.0, 30.1, 29.1, 28.9, 28.2.

IR (neat film, NaCl): 2973, 2351, 1729, 1685, 1579, 1455, 1315, 1256, 1156 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{26}H_{30}NO_6$ $[M+H]^+$: 452.2068, found 452.2072.



239

allyl 6-(3-(*tert*-butoxy)-3-oxopropyl)-5-oxo-2-(piperidin-1-yl)-5,6,7,8-tetrahydroquinoline-6-carboxylate (239)

Prepared from **253** following General Procedure C. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (1.94 g, 4.39 mmol, 94% yield).

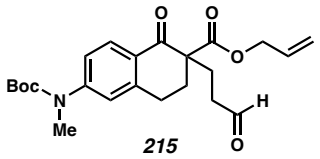
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 9.1 Hz, 1H), 6.52 (d, *J* = 9.1 Hz, 1H), 5.84 (ddt, *J* = 17.4, 10.7, 5.5 Hz, 1H), 5.34 – 5.13 (m, 2H), 4.59 (dd, *J* = 5.5, 1.5 Hz, 2H), 3.69 (m, 4H), 3.03 – 2.79 (m, 2H), 2.54 (ddd, *J* = 13.7, 6.1, 5.0 Hz, 1H), 2.47 – 2.21 (m, 3H), 2.22 – 2.11 (m, 1H), 2.06 (ddd, *J* = 13.9, 8.6, 5.2 Hz, 1H), 1.69 (d, *J* = 4.8 Hz, 2H), 1.66 – 1.54 (m, 6H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.0, 172.6, 171.9, 163.5, 159.8, 137.4, 131.8, 118.4, 117.2, 105.0, 80.4, 65.8, 56.2, 45.8, 31.2, 30.1, 29.5, 29.0, 28.2, 25.8, 24.8.

IR (neat film, NaCl): 2937, 2855, 1729, 1663, 1589, 1496, 1406, 1249, 1154, 1085, 1022, 949, 698 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{25}H_{35}N_2O_5$ $[M+H]^+$: 443.2540, found 443.2551.

Preparation of aldehyde S13.



215

allyl 6-((*tert*-butoxycarbonyl)(methyl)amino)-2-(3-hydroxy-3λ2-propyl)-1-oxo-1,2,3,4- tetrahydronaphthalene-2-carboxylate (215)

To a solution of **245** (1.42 g, 3.95 mmol) was added acrolein (0.4 mL, 5.9 mmol, 1.5 equiv) and triethylamine (80 uL, 0.6 mmol, 0.15 equiv) in DMF (3.2 mL, 1.2 M). The reaction was stirred at 23 °C until starting material was consumed by TLC, at which point the

reaction was quenched with water and extracted with diethyl ether (x3), dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (30% ethyl acetate/hexanes) afforded the title compound (1.33 g, 3.21 mmol, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.22 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.16 (d, *J* = 2.2 Hz, 1H), 5.81 (ddt, *J* = 17.3, 10.5, 5.6 Hz, 1H), 5.23 – 5.14 (m, 2H), 4.59 (dt, *J* = 5.6, 1.4 Hz, 2H), 3.29 (s, 3H), 3.09 – 2.97 (m, 1H), 2.92 (dt, *J* = 17.4, 5.2 Hz, 1H), 2.79 – 2.68 (m, 1H), 2.65 – 2.51 (m, 2H), 2.35 – 2.18 (m, 2H), 2.11 (ddd, *J* = 13.7, 9.8, 4.9 Hz, 1H), 1.49 (s, 9H).

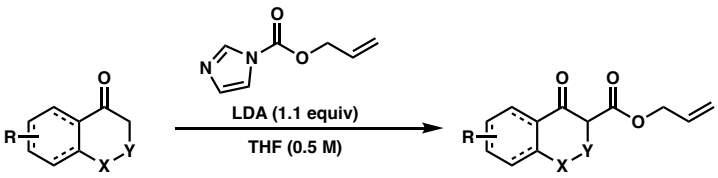
^{13}C NMR (100 MHz, $CDCl_3$): δ 201.3, 194.3, 171.6, 154.2, 148.6, 143.5, 131.5, 128.8, 128.4, 123.9, 123.1, 118.8, 81.5, 66.0, 56.6, 39.8, 36.9, 31.8, 28.4, 26.3, 26.2.

IR (Neat Film, NaCl): 2941, 2346, 1703, 1600, 1357, 1164 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{23}H_{29}NO_6$ $[M+H]^+$: 416.2068, found 416.2067.

3.7.3.4 Preparation of β-Keto Ester Intermediates

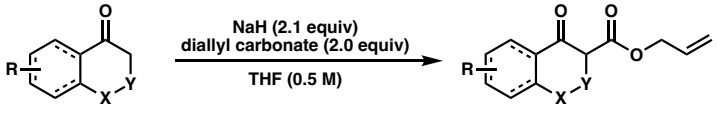
General Procedure D: Acylation of Ketones using N-Acyl Imidazole Reagent



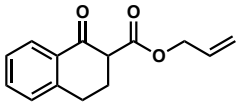
A flame dried round bottom flask was charged with *i*-Pr_2NH (1.1 equiv) and THF (1.75 M). The solution was cooled to 0 ºC and *n*-BuLi (2.5 M in hexanes, 1.05 equiv) was added dropwise. The resultant solution was stirred for 30 min at 0 ºC. Then, ketone (1.0 equiv) in THF (1.25 M) was added dropwise and stirring was continued at 0 ºC for 30 minutes. The solution was cooled to –78 ºC, and the N-acyl imidazole reagent (1.2 equiv) in THF (3.25 M) was added dropwise. After 2 h, the reaction was gradually warmed to 23 ºC and diluted

with 2 M aqueous HCl until reaching a pH < 7. The reaction mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography to afford the acylated ketone.

General Procedure E: Acylation of Ketones using Diallyl Carbonate



A flame dried round bottom flask was charged with NaH (2.1 equiv) and THF (0.625 M). Diallyl carbonate was added, followed by a solution of ketone (1.0 equiv) in THF (2.5 M) dropwise. The solution was heated to reflux for 2 h or until complete conversion by TLC, at which point the reaction was cooled and quenched with 1 M aqueous HCl until neutral. The reaction mixture was extracted three times with EtOAc, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel column chromatography to afford the acylated ketone.

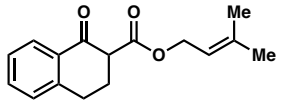


240

allyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (240)

Prepared from 3,4-dihydronaphthalen-1(2*H*)-one following General Procedure D. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (622 mg, 2.70 mmol, 54% yield). All characterization data match those reported in the literature.[26]

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (7:3) δ 12.39 (s, 0.7H), 8.05 (dd, *J* = 7.9, 1.5 Hz, 0.3H), 7.81 (dd, *J* = 7.5, 1.6 Hz, 1=0.7H), 7.50 (m, 0.3H), 7.42 – 7.27 (m, 2H), 7.21 – 7.10 (m, 0.7H), 6.14 – 5.82 (m, 1H), 5.52 – 5.34 (m, 1H), 5.33 – 5.07 (m, 1H), 4.83 – 4.52 (m, 2H), 3.65 (dd, *J* = 10.5, 4.7 Hz, 0.3H), 3.04 (dt, *J* = 13.6, 5.0 Hz, 0.6H), 2.82 (dd, *J* = 8.9, 6.6 Hz, 1.4H), 2.65 – 2.56 (m, 1.4H), 2.55 – 2.17 (m, 0.6H).



241

3-methylbut-2-en-1-yl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (241)

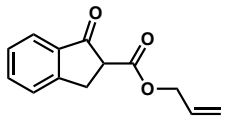
Prepared from 3,4-dihydronaphthalen-1(2*H*)-one following General Procedure D, using a prenyl variant of the N-acyl imidazole reagent instead. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (1.15 g, 4.75 mmol, 47% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (6:4) δ 12.46 (s, 0.6H), 8.05 (dd, *J* = 7.9, 1.4 Hz, 0.4H), 7.80 (dd, *J* = 7.4, 1.7 Hz, 0.6H), 7.49 (td, *J* = 7.5, 1.5 Hz, 0.4H), 7.36 – 7.22 (m, 2H), 7.21 – 7.11 (m, 0.6H), 5.48 – 5.25 (m, 1H), 4.85 – 4.48 (m, 2H), 3.61 (dd, *J* = 10.3, 4.7 Hz, 0.4H), 3.12 – 2.93 (m, 0.8H), 2.80 (dd, *J* = 8.9, 6.6 Hz, 1.2H), 2.57 (dd, *J* = 8.8, 6.6 Hz, 1.2H), 2.53 – 2.14 (m, 0.8H), 1.79 (s, 2.4H), 1.75 (s, 3.6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.4, 172.9, 170.4, 165.1, 143.8, 139.6, 139.6, 139.2, 134.0, 132.0, 130.6, 130.2, 128.9, 127.9, 127.5, 127.0, 126.7, 124.4, 118.8, 118.4, 118.3, 97.3, 64.7, 62.4, 61.6, 54.7, 27.9, 27.8, 26.6, 26.0, 25.9, 20.7, 18.3, 18.2.

IR (neat film, NaCl): 2938, 2342, 1739, 1643, 1453, 1392, 1268, 1210, 1082, 956, 759 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{16}H_{18}O_3Na$ $[M+Na]^+$: 281.1148, found 281.1140.

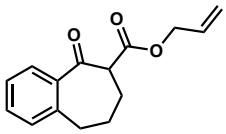


242

allyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (242)

Prepared from 2,3-dihydro-1*H*-inden-1-one following General Procedure D. Purification by flash column chromatography (5–10% EtOAc/hexanes) afforded the title compound as a clear oil (1.24 g, 5.72 mmol, 57% yield). All characterization data match those reported in the literature.[27]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.63 (td, *J* = 7.5, 1.3 Hz, 1H), 7.51 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.40 (ddd, *J* = 7.9, 7.1, 0.9 Hz, 1H), 5.94 (ddt, *J* = 17.3, 10.5, 5.7 Hz, 1H), 5.37 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.26 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.70 (tt, *J* = 5.9, 1.5 Hz, 2H), 3.76 (dd, *J* = 8.3, 4.1 Hz, 1H), 3.63 – 3.52 (m, 1H), 3.39 (dd, *J* = 17.3, 8.2 Hz, 1H).



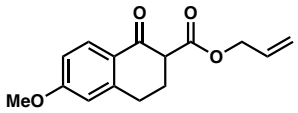
243

allyl 5-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-6-carboxylate (243)

Prepared from 6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one following General Procedure D. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (339 mg, 1.39 mmol, 28% yield). All characterization data match those reported in the literature.[28]

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (7:3) δ 12.59 (s, 0.7H), 7.75 (dd, *J* = 7.7, 1.5 Hz, 0.3H), 7.67 – 7.58 (m, 0.7H), 7.43 (td, *J* = 7.5, 1.5 Hz, 0.3H), 7.39 – 7.29 (m, 1.7H), 7.25 – 7.03 (m, 1H), 6.22 – 5.74 (m, 1H), 5.38 (m, 1H), 5.33 – 5.20 (m,

1H), 4.74 (m, 1.4H), 4.70 – 4.59 (m, 0.6H), 3.85 (dd, *J* = 10.5, 4.4 Hz, 0.3H), 3.01 – 2.90 (m, 0.6H), 2.65 (t, *J* = 6.8 Hz, 1.4H), 2.26 – 1.99 (m, 3.7H), 1.85 (ddd, *J* = 8.9, 6.8, 5.5 Hz, 0.3H).

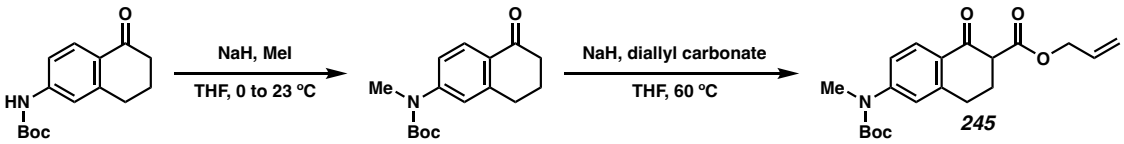


244

allyl 6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (244)

Prepared from 6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one following General Procedure D. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (751 mg, 2.89 mmol, 58% yield). All characterization data match those reported in the literature.[29]

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (3:7) δ 12.44 (s, 0.3H), 8.03 (d, *J* = 8.8 Hz, 0.7H), 7.74 (d, *J* = 8.6 Hz, 0.3H), 6.82 (ddd, *J* = 16.3, 8.7, 2.6 Hz, 1H), 6.70 (dd, *J* = 5.9, 2.5 Hz, 1H), 6.07 – 5.86 (m, 1H), 5.48 – 5.12 (m, 2H), 4.86 – 4.62 (m, 2H), 3.86 (s, 2H), 3.84 (s, 1H), 3.60 (dd, *J* = 10.3, 4.7 Hz, 0.7H), 3.16 – 2.91 (m, 1.4H), 2.79 (m, 0.6H), 2.63 – 2.56 (m, 0.6H), 2.54 – 2.26 (m, 1.4H).



245

allyl 6-((*tert*-butoxycarbonyl)(methyl)amino)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (245)

A solution of *tert*-butyl (5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)carbamate (466 mg, 1.8 mmol, 1 equiv) and THF (1.2 M, 1.5 mL) was cooled 0 ºC. NaH (60% dispersion in mineral oil, 86 mg, 2.1 mmol, 1.2 equiv) was added portion wise. Then MeI (0.13 mL, 2.1 mmol, 1.2 equiv) was added dropwise, and the reaction was slowly warmed to 23 ºC. Upon

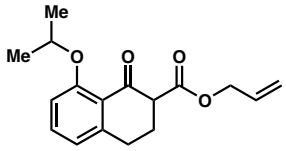
complete consumption of starting material (as determined by TLC), the reaction mixture was diluted with water and extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude *N*-Me aniline which was used directly in the next step. To NaH (60% dispersion in mineral oil, 150 mg, 3.7 mmol, 2.1 equiv) in THF (2.1 mL, 1.8 M) diallyl carbonate (0.51 mL, 3.6 mmol, 2 equiv) was added. Crude *N*-Me aniline in THF (1.5 mL, 1.2 M) was added, and the reaction was heated to 60 ºC. Upon complete consumption of starting material (as determined by TLC), the reaction mixture was cooled to 23 ºC and diluted with a saturated solution of NH_4Cl and extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (15% EtOAc/hexanes) afforded the title compound (376 mg, 1.05 mmol, 59% yield). Mixture of enol-keto tautomers. Used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 12.38 (s, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.22 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.20 (d, *J* = 2.1 Hz, 1H), 7.15 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.11 (d, *J* = 2.2 Hz, 1H), 6.06 – 5.88 (m, 2H), 5.36 (ddq, *J* = 16.8, 13.6, 1.6 Hz, 2H), 5.26 (ddq, *J* = 13.1, 10.5, 1.3 Hz, 2H), 4.73 (dt, *J* = 5.6, 1.5 Hz, 2H), 4.69 (ddt, *J* = 6.1, 4.7, 1.4 Hz, 1H), 3.62 (dd, *J* = 10.3, 4.8 Hz, 1H), 3.30 (s, 2H), 3.28 (s, 3H), 3.10 – 2.91 (m, 2H), 2.80 (dd, *J* = 8.9, 6.6 Hz, 2H), 2.65 – 2.57 (m, 2H), 2.57 – 2.45 (m, 1H), 2.36 (ddt, *J* = 13.5, 5.8, 4.7 Hz, 1H), 1.49 (s, 7H), 1.47 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 192.2, 172.4, 170.1, 165.3, 154.6, 154.2, 148.8, 145.9, 144.3, 140.2, 132.4, 131.9, 128.6, 128.3, 126.8, 124.9, 124.0, 123.1, 123.0, 118.6, 118.3, 96.5, 81.5, 80.9, 66.0, 65.2, 54.6, 37.2, 36.9, 34.8, 31.7, 28.5, 28.4, 28.0, 28.0, 26.5, 22.8, 20.7, 14.3.

IR (Neat Film, NaCl): 2976, 2937, 1738, 1704, 1602, 1433, 1352, 1150 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{20}H_{25}NO_5$ $[M+H]^+$: 360.1805, found 360.1806.



246

allyl 8-isopropoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (246)

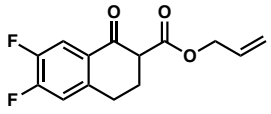
Prepared from 8-isopropoxy-3,4-dihydronaphthalen-1(2H)-one following General Procedure E. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (500 mg, 1.73 mmol, 98% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (4:6) δ 12.68 (s, 0.4H), 7.35 (dd, *J* = 8.4, 7.6 Hz, 0.6H), 7.22 (dd, *J* = 8.4, 7.4 Hz, 0.4H), 6.92 – 6.80 (m, 1H), 6.78 (m, 1H), 5.96 (m, H), 5.51 – 5.28 (m, 1H), 5.27 – 5.00 (m, 2H), 4.70 (ddt, *J* = 16.2, 5.6, 1.5 Hz, 2H), 4.55 (m, 1H), 3.61 (dd, *J* = 10.4, 4.9 Hz, 0.6H), 3.23 – 2.84 (m, 1H), 2.71 (dd, *J* = 8.8, 5.9 Hz, 1H), 2.53 – 2.47 (m, 1H), 2.46 – 2.18 (m, 1H), 1.44 – 1.32 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.6, 172.3, 170.4, 167.7, 159.5, 157.0, 146.1, 143.2, 134.2, 132.6, 132.1, 131.3, 122.6, 120.7, 120.6, 118.4, 118.1, 115.9, 113.7, 97.6, 72.8, 71.8, 65.8, 65.0, 56.5, 29.7, 28.8, 26.2, 22.3, 22.1, 22.1, 20.8.

IR (neat film, NaCl): 2975, 2937, 1740, 1684, 1592, 1463, 1383, 1267, 1116, 989, 922 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{16}H_{20}O_3$ $[M+H]^+$: 274.1438, found 274.1434.



247

allyl 6,7-difluoro-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (247)

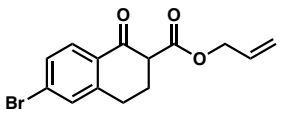
Prepared from 6,7-difluoro-3,4-dihydronaphthalen-1(2*H*)-one following General Procedure D. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (976 mg, 3.67 mmol, 56% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (7:3) δ 12.23 (s, 0.7H), 7.74 (dd, *J* = 10.5, 8.2 Hz, 0.3H), 7.49 (dd, *J* = 11.0, 8.1 Hz, 0.7H), 6.95 (dd, *J* = 10.4, 7.2 Hz, 0.3H), 6.87 (dd, *J* = 10.4, 7.5 Hz, 0.7H), 6.02 – 5.72 (m, 1H), 5.39 – 5.21 (m, 1H), 5.22 – 5.01 (m, 1H), 4.79 – 4.46 (m, 2H), 3.51 (dd, *J* = 9.9, 4.8 Hz, 0.3H), 2.88 (dt, *J* = 17.9, 7.4 Hz, 0.6H), 2.66 (dd, *J* = 9.1, 6.5 Hz, 1.4H), 2.49 (dd, *J* = 9.1, 6.6 Hz, 1.4H), 2.45 – 2.12 (m, 0.6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0, 172.2, 169.5, 163.5, 163.5, 163.5, 155.4, 155.3, 152.8, 152.8, 152.7, 152.6, 151.0, 150.9, 150.5, 150.4, 150.3, 150.1, 148.5, 148.4, 148.1, 148.0, 141.4, 141.4, 141.3, 141.3, 136.6, 136.5, 136.5, 136.5, 132.2, 132.1, 131.7, 128.9, 128.9, 128.8, 126.9, 126.8, 126.8, 126.8, 118.8, 118.5, 118.4, 117.5, 117.3, 117.3, 116.8, 116.8, 116.6, 116.6, 116.4, 113.9, 113.9, 113.8, 113.7, 97.1, 97.1, 68.1, 66.1, 65.4, 53.8, 50.1, 27.2, 27.1, 27.1, 27.1, 26.4, 20.5.

IR (neat film, NaCl): 2938, 2340, 1744, 1693, 1651, 1590, 1511, 1387, 1327, 1250, 1076, 926, 804 cm^{-1}.

HMRS (ESI–): *m/z* calc'd for $C_{14}H_{12}F2O_3$ $[M–H]^–$: 265.0682, found 265.0686.



248

allyl 6-bromo-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (248)

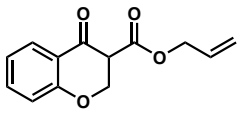
Prepared from 6-bromo-3,4-dihydronaphthalen-1(2*H*)-one following General Procedure E. Purification by flash column chromatography (0–10% ethyl acetate/hexanes) afforded the title compound as a clear oil (639 mg, 2.07 mmol, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (6:4) δ 12.35 (s, 0.6H), 7.91 (d, *J* = 8.3 Hz, 0.4H), 7.65 (d, *J* = 8.3 Hz, 0.6H), 7.52 – 7.38 (m, 1.4H), 7.34 (dt, *J* = 2.0, 0.9 Hz, 0.6H), 6.17 – 5.79 (m, 1H), 5.48 – 5.33 (m, 1H), 5.33 – 5.16 (m, 1H), 4.77 – 4.50 (m, 2H), 3.63 (dd, *J* = 10.1, 4.7 Hz, 0.4H), 3.14 – 2.89 (m, 0.8H), 2.80 (m, 1.2H), 2.67 – 2.53 (m, 1.2H), 2.54 – 2.25 (m, 0.8H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 192.3, 172.3, 169.7, 164.6, 145.4, 141.5, 132.2, 131.9, 131.8, 131.7, 130.7, 130.6, 129.9, 129.6, 129.4, 129.1, 126.1, 125.1, 119.1, 118.8, 118.4, 97.2, 68.6, 66.1, 65.4, 54.4, 27.6, 27.5, 26.3, 20.5.

IR (neat film, NaCl): 2341, 1613, 1259, 1212, 824 cm^{-1}.

HMRS (FD+): *m/z* calc'd for $C_{14}H_{13}BrO_3$ $[M]^{+\bullet}$: 308.0043, found 308.0052.



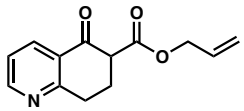
249

allyl 4-oxochromane-3-carboxylate (249)

Prepared from chroman-4-one following General Procedure D. Purification by flash column chromatography (0–5% ethyl acetate/hexanes) afforded the title compound as a clear oil (1.47 g, 6.3 mmol, 42% yield). All characterization data match those reported in the literature.[30]

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.95 (s, 0.4H), 7.93 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.66 (dd, *J* = 7.7, 1.7 Hz, 0.6H), 7.51 (ddd, *J* = 8.4, 7.2, 1.8 Hz, 1H), 7.33 (ddd, *J* = 8.2, 7.4, 1.7 Hz, 0.6H), 7.06 (ddd, *J* = 8.0, 7.2, 1.1 Hz, 1H), 7.02 – 6.97 (m, 1H), 6.87 (dd, *J* = 8.2, 1.1 Hz,

0.6H), 6.01 – 5.94 (m, 0.6H), 5.94 – 5.85 (m, 1H), 5.37 (dq, *J* = 17.2, 1.5 Hz, 0.6H), 5.34 – 5.28 (m, 1.6H), 5.24 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.99 (s, 1.2H), 4.81 (dd, *J* = 11.7, 8.4 Hz, 1H), 4.71 (m, 3.2H), 4.65 (dd, *J* = 11.6, 4.5 Hz, 1H), 3.78 (dd, *J* = 8.4, 4.4 Hz, 1H).



250

allyl 5-oxo-5,6,7,8-tetrahydroquinoline-6-carboxylate (250)

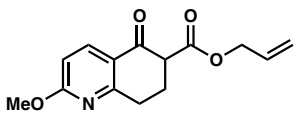
Prepared from 7,8-dihydroquinolin-5(6*H*)-one following General Procedure D. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a clear oil (580 mg, 2.56 mmol, 51% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (9:1) δ 12.29 (s, 0.9H), 8.71 (dd, *J* = 4.8, 1.9 Hz, 0.1H), 8.50 (dd, *J* = 4.9, 1.8 Hz, 0.9H), 8.30 (dd, *J* = 7.9, 1.9 Hz, 0.1H), 8.03 (dd, *J* = 7.8, 1.8 Hz, 0.9H), 7.31 (dd, *J* = 8.0, 4.7 Hz, 0.1H), 7.23 (dd, *J* = 7.8, 4.9 Hz, 0.9H), 6.00 (m, 1H), 5.39 (m, 1H), 5.30 (m, 1H), 4.75 (d, *J* = 5.6 Hz, 1.8H), 4.70 (ddd, *J* = 4.4, 2.9, 1.4 Hz, 0.2H), 3.69 (dd, *J* = 10.0, 4.8 Hz, 0.1H), 3.32 – 3.10 (m, 0.2H), 3.04 (dd, *J* = 8.8, 7.1 Hz, 1.8H), 2.73 (dd, *J* = 8.8, 7.1 Hz, 1.8H), 2.61 – 2.36 (m, 0.2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.0, 172.2, 169.5, 163.7, 162.9, 159.5, 154.2, 150.6, 135.7, 132.1, 131.7, 131.7, 127.7, 125.9, 122.6, 122.0, 118.9, 118.6, 97.6, 66.2, 65.5, 54.0, 30.7, 30.6, 25.1, 20.0.

IR (neat film, NaCl): 2948, 1743, 1692, 1654, 1380, 1321, 1269, 1209, 1085, 980, 805 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{13}H_{14}NO_3$ $[M+H]^+$: 232.0968, found 232.0969.



251

allyl 2-methoxy-5-oxo-5,6,7,8-tetrahydroquinoline-6-carboxylate (251)

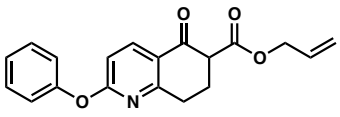
Prepared from 2-methoxy-7,8-dihydroquinolin-5(6*H*)-one following General Procedure E. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a yellow oil (1.504 g, 5.76 mmol, 91% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (15:85) δ 12.37 (s, 0.15H), 8.15 (d, *J* = 8.7 Hz, 0.85H), 7.91 (d, *J* = 8.5 Hz, 0.15H), 6.67–6.61 (m, 1H), 6.14 – 5.75 (m, 1H), 5.54 – 5.11 (m, 2H), 4.81 – 4.57 (m, 2H), 3.98 (s, 2.55H), 3.95 (s, 0.45H), 3.61 (dd, *J* = 10.1, 4.8 Hz, 0.85H), 3.19 – 2.95 (m, 1.7H), 2.94 – 2.62 (m, 0.6H), 2.57 – 2.25 (m, 1.7H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.9, 172.3, 169.9, 166.6, 165.1, 165.0, 163.3, 159.0, 138.2, 134.7, 132.3, 131.8, 122.1, 119.1, 118.7, 118.3, 110.5, 108.6, 94.5, 66.0, 65.2, 54.2, 53.9, 53.8, 30.7, 30.5, 25.2, 20.0.

IR (neat film, NaCl): 2945, 1740, 1681, 1591, 1479, 1331, 1267, 1200, 1023, 925, 834 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{14}H_{16}NO_4$ $[M+H]^+$: 262.1074, found 262.1070.



252

allyl 5-oxo-2-phenoxy-5,6,7,8-tetrahydroquinoline-6-carboxylate (252)

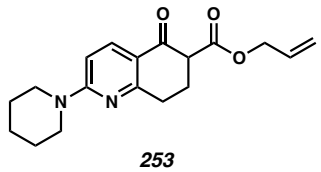
Prepared from 2-phenoxy-7,8-dihydroquinolin-5(6*H*)-one following General Procedure E. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a yellow oil (1.067 g, 3.30 mmol, 58% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (4:6) δ 12.35 (s, 0.4H), 8.27 (d, *J* = 8.6 Hz, 0.6H), 8.01 (d, *J* = 8.6 Hz, 0.4H), 7.42 (m, 2H), 7.31 – 7.21 (m, 1H), 7.16 (m, 1.8H), 6.76 (d, *J* = 8.7 Hz, 0.6H), 6.68 (t, *J* = 8.6 Hz, 0.6H), 6.16 – 5.86 (m, 1H), 5.45 – 5.35 (m, 1H), 5.33 – 5.22 (m, 1H), 4.77 – 4.62 (m, 2H), 3.62 (m, 0.6H), 3.35 – 2.96 (m, 1.6H), 2.97 – 2.86 (m, 0.4H), 2.69 (m, 0.4H), 2.60 – 2.29 (m, 1.6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.7, 169.7, 166.2, 163.6, 159.5, 153.9, 153.2, 139.7, 138.4, 135.8, 132.9, 132.1, 131.8, 130.0, 125.7, 125.3, 123.5, 121.6, 121.3, 118.9, 118.5, 110.7, 109.9, 108.4, 95.8, 67.5, 66.1, 66.0, 65.4, 53.8, 30.4, 30.0, 25.1, 19.9.

IR (neat film, NaCl): 2938, 1739, 1685, 1580, 1450, 1259, 1076, 990 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{19}H_{18}NO_4$ $[M+H]^+$: 324.1230, found 324.1229.



253

allyl 5-oxo-2-(piperidin-1-yl)-5,6,7,8-tetrahydroquinoline-6-carboxylate (253)

Prepared from 2-(piperidin-1-yl)-7,8-dihydroquinolin-5(6*H*)-one following General Procedure E. Purification by flash column chromatography (0–20% ethyl acetate/hexanes) afforded the title compound as a yellow oil (1.46 g, 4.64 mmol, 74% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (5:95) δ 12.41 (s, 0.05H), 7.95 (dd, *J* = 9.1, 1.5 Hz, 0.95H), 7.72 (dd, *J* = 8.9, 1.5 Hz, 0.05H), 6.48 (dd, *J* = 9.0, 1.5 Hz, 0.95H), 6.44 (dd, *J* = 8.8, 1.5 Hz, 0.05H), 6.05 – 5.73 (m, 1H), 5.30 (dt, *J* = 17.2, 1.6 Hz, 1H), 5.19 (dt, *J* = 10.5, 1.5 Hz, 1H), 4.80 – 4.43 (m, 2H), 3.78 – 3.57 (m, 3.75H), 3.59

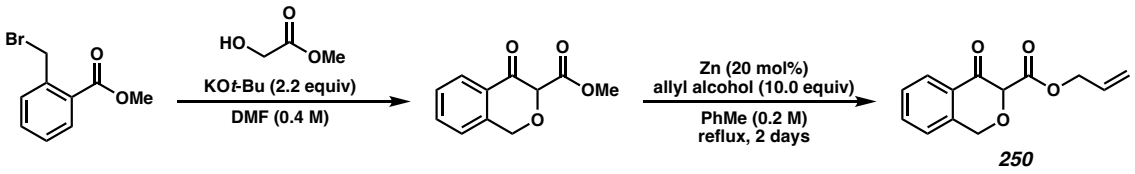
(t, *J* = 4.7 Hz, 0.25H), 3.51 (ddd, *J* = 10.3, 4.8, 1.5 Hz, 1H), 3.07 – 2.79 (m, 2H), 2.78 – 2.56 (m, 0.25H), 2.53 – 2.20 (m, 1.75H), 1.65 (m, 2H), 1.58 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 170.4, 164.1, 159.7, 136.8, 133.2, 132.5, 131.9, 118.3, 117.0, 104.8, 103.7, 92.3, 65.6, 64.7, 53.7, 45.6, 31.0, 25.7, 25.3, 24.6.

IR (neat film, NaCl): 2935, 2853, 1739, 1662, 1593, 1498, 1417, 1249, 1120, 1023 cm^{-1}.

HMRS (ESI+): *m/z* calc'd for $C_{18}H_{22}N_2O_3Na$ $[M+Na]^+$: 337.1523, found 337.1518.

Preparation of ß-Keto Ester **250**



250

A flame dried round bottom flask under N_2 was charged with KO*t*-Bu (2.2 equiv), methyl 2-(bromomethyl)benzoate (1.0 equiv, 10 mmol) and DMF (0.4 M). After cooling to 0 °C, methyl 2-hydroxyacetate was added. The ice bath was then removed, and the reaction was allowed to continue stirring for 18 h. The reaction was quenched with 1 N HCl, extracted with EtOAc three times, and the combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude methyl ester intermediate was used without further purification.

To the crude intermediate in PhMe (0.2 M) was added Zn powder (20 mol%) and allyl alcohol (5.0 equiv). The reaction was refluxed for 24 h, at which point more allyl alcohol (5.0 equiv) was added. After an additional day of refluxing, the reaction was cooled, filtered over Celite, and concentrated. The crude product was purified by flash silica gel column chromatography (0–15% ethyl acetate/hexanes) to afford the acylated ketone **250** (1.126 g, 4.84 mmol, 48% yield).

^{1}H NMR (400 MHz, $CDCl_3$): Mixture of enol/keto tautomers (1:1) δ 10.36 (s, 0.5H), 8.06 (dd, *J* = 7.9, 1.3 Hz, 0.5H), 7.73 – 7.64 (m, 0.5H), 7.60 (td, *J* = 7.6, 1.4 Hz, 0.5H), 7.49 – 7.40 (m, 0.5H), 7.40 – 7.32 (m, 1H), 7.21 (dt, *J* = 7.5, 0.9 Hz, 0.5H), 7.16 – 7.07 (m, 0.5H), 5.98 (dddt, *J* = 31.0, 17.1, 10.4, 5.9 Hz, 1H), 5.50 – 5.34 (m, 1H), 5.33 – 5.22 (m, 1.5H), 5.02 (s, 1H), 4.99 (s, 0.5H), 4.94 (s, 0.5H), 4.78 (ddt, *J* = 25.7, 5.8, 1.4 Hz, 2H).

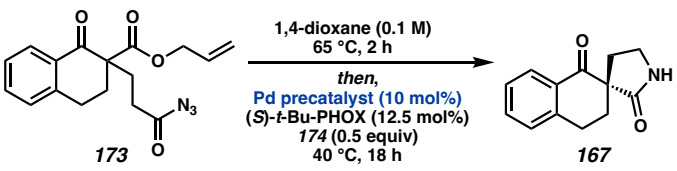
^{13}C NMR (100 MHz, $CDCl_3$): δ 188.5, 167.7, 166.1, 152.7, 141.2, 134.8, 133.0, 131.7, 131.3, 130.9, 130.7, 128.7, 128.4, 128.2, 127.7, 127.2, 127.1, 124.5, 124.3, 124.0, 123.5, 122.6, 119.8, 119.7, 119.4, 80.9, 68.4, 67.9, 66.6, 66.1, 62.3.

IR (neat film, NaCl): 1752, 1701, 1400, 1273, 744 cm^{-1}.

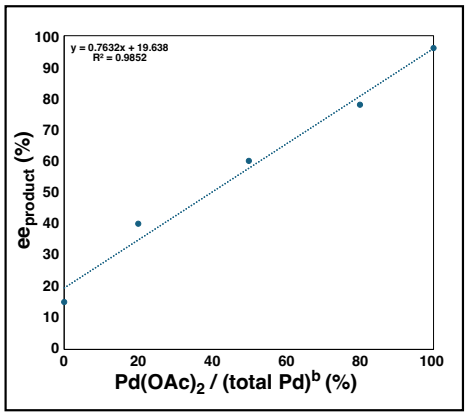
HMRS (ESI+): *m/z* calc'd for $C_{13}H_{14}NO_3$ $[M+H]^+$: 262.1074, found 262.1070.

3.7.3.5 Mechanistic Experiments

Mixed Precatalyst Experiment



entry	$Pd(OAc)_2$ (mol%)	$Pd_2(dba)_3$ (mol%)	yield (%)	ee (%)
1	0	5	99	15
2	2	4	95	40
3	5	2.5	96	60
4	8	1	98	78
5	10	0	99	96



In a nitrogen-filled glovebox, five oven-dried 1-dram vials were charged with a stir bar and **173** (16.4 mg, 0.05 mmol) in dioxane (0.2 mL), and each vial was heated to 65 °C for 2 h. After cooling, **174** (3.9 mg, 0.025 mmol) in dioxane (0.1 mL) was added. In a separate oven-dried 2-dram vial, $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) and (*S*)-*t*-BuPHOX (14.5 mg, 0.0375 mmol) in dioxane (1.2 mL) were stirred for 20 min at 23 °C. In another oven-dried

2-dram vial, $Pd_2(dba)_3$ (13.7 mg, 0.015 mmol) and (*S*)-*t*-BuPHOX (0.0375 mmol) in dioxane (1.2 mL) were stirred for 20 min at 23 °C. To each reaction vial containing **173** and **174** was added the corresponding volume of Pd-stock solutions, such that the mol% of Pd is as represented in the table and graph above:

Vial 01: Pd_2dba_3 solution (0.20 mL, 5 mol%)

Vial 02: Pd_2dba_3 solution (0.16 mL, 4 mol%), $Pd(OAc)_2$ solution (0.04 mL, 2 mol%)

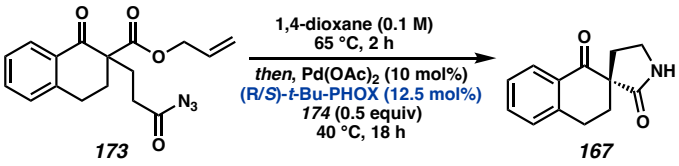
Vial 02: Pd_2dba_3 solution (0.10 mL, 2.5 mol%), $Pd(OAc)_2$ solution (0.10 mL, 5 mol%)

Vial 02: Pd_2dba_3 solution (0.04 mL, 1 mol%), $Pd(OAc)_2$ solution (0.16 mL, 8 mol%)

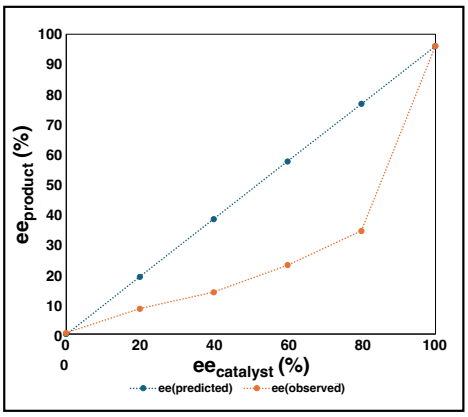
Vial 02: $Pd(OAc)_2$ solution (0.20 mL, 10 mol%)

The vials were sealed, removed from the glovebox, and heated to 40 °C for 18 h. The reaction mixtures were then cooled, 1,3,5-trimethoxybenzene (0.33 equiv) was added to each reaction, and the crude reactions mixtures were concentrated under reduced pressure. The yield was determined by ^{1}H NMR integration against 1,3,5-trimethoxybenzene as an internal standard, and the ee was determined utilizing SFC (30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 3.35, t_R (min): minor = 4.27).

Nonlinearity Experiment



entry	ee_{cat} (%)	$ee_{predicted}$ (%)	$ee_{observed}$ (%)
1	100	96	96
2	80	77	34
3	60	58	23
4	40	38	14
5	20	19	9
6	0	0	0



In a nitrogen-filled glovebox, five oven-dried 1-dram vials were charged with a stir bar and **173** (16.4 mg, 0.05 mmol) in dioxane (0.2 mL), and each vial was heated to 65 °C for 2 h. After cooling, **174** (3.9 mg, 0.025 mmol) in dioxane (0.1 mL) was added. In five separate oven-dried 1-dram vials was added $Pd(OAc)_2$ (2.2 mg, 0.01 mmol). Stock solutions were prepared of (*S*)-*t*-BuPHOX (19.4 mg, 0.05 mmol) in dioxane (1.6 mL) and (*R*)-*t*-BuPHOX (9.7 mg, 0.025 mmol) in dioxane (0.8 mL), and the corresponding volume of (*S*)- or (*R*)-*t*-BuPHOX stock solutions was added to each vial of $Pd(OAc)_2$, such that the ee of the resulting Pd solution is as represented in the table and graph above:

Vial 01: (*R*)-*t*-BuPHOX stock solution (0.04 mL, 1.25 mol%), (*S*)-*t*-BuPHOX stock solution (0.36 mL, 11.25 mol%)

Vial 02: (*R*)-*t*-BuPHOX stock solution (0.08 mL, 2.5 mol%), (*S*)-*t*-BuPHOX stock solution (0.32 mL, 10 mol%)

Vial 03: (*R*)-*t*-BuPHOX stock solution (0.12 mL, 3.75 mol%), (*S*)-*t*-BuPHOX stock solution (0.28 mL, 8.75 mol%)

Vial 04: (*R*)-*t*-BuPHOX stock solution (0.16 mL, 5 mol%), (*S*)-*t*-BuPHOX stock solution (0.24 mL, 7.5 mol%)

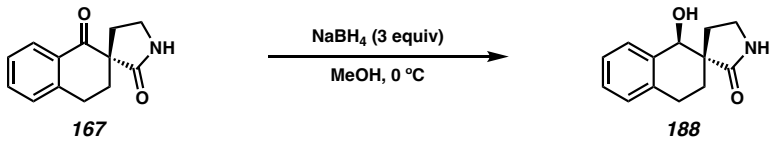
Vial 05: (*R*)-*t*-BuPHOX stock solution (0.20 mL, 6.25 mol%), (*S*)-*t*-BuPHOX stock solution (0.20 mL, 6.25 mol%)

The vials were sealed and stirred for 20 min at 23 °C. To each reaction vial, the corresponding Pd stock solution (0.2 mL) was added. The reaction vials were sealed, from the glovebox, and heated to 40 °C for 30 min, at which point the reactions were quenched by opening to air and concentrated. The ee of each reaction product was determined

utilizing SFC (30% IPA, 2.5 mL/min, Chiralpack AD-3 column, λ = 254 nm, t_R (min): major = 3.35, t_R (min): minor = 4.27).

3.7.3.6 Product Derivatizations

*Preparation of alcohol **188***



167 ***188***

(2*S*)-1-hydroxy-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidin]-2'-one (188)

A flame dried vial under N_2 was charged with **167** (1 equiv, 0.05 mmol, 10.8 mg) and MeOH (0.03 M, 1.8 mL) at 0 ºC. $NaBH_4$ (2 equiv, 0.1 mmol, 3.8 mg) was added to the reaction. After two hours, starting material was not consumed and additional $NaBH_4$ (1 equiv, 0.05 mmol, 1.9 mg) was added to the reaction. Following complete consumption of starting material as determined by TLC, the reaction was diluted with water. The reaction mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% acetone/CH_2Cl_2) afforded the title compound **188** as a white solid (7.5 mg, 0.035 mmol, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.24 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.24 – 7.15 (m, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 6.42 (s, 1H), 4.94 (s, 1H), 4.59 (s, 1H), 3.45 – 3.30 (m, 2H), 3.04 (ddd, *J* = 17.8, 7.1, 2.3 Hz, 1H), 2.00 (ddd, *J* = 13.1, 7.3, 3.8 Hz, 1H), 1.81 (dt, *J* = 13.2, 8.3 Hz, 1H), 1.71 (dd, *J* = 13.6, 5.9 Hz, 1H).

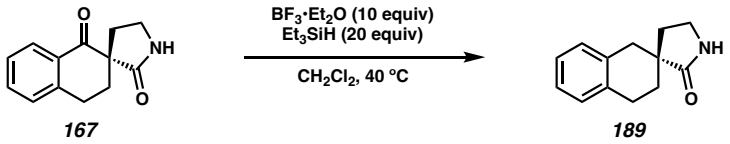
^{13}C NMR (100 MHz, $CDCl_3$): δ 182.8, 135.5, 135.4, 130.6, 129.2, 128.4, 126.3, 72.9, 44.8, 39.1, 29.3, 25.0, 22.8.

IR (Neat Film, NaCl): 3300, 2929, 1684, 1456, 1285 cm^{-1}.

HRMS (MM: ESI+): *m/z* calc'd for $C_{13}H_{15}NO_2$ $[M+Na]^+$: 240.0995, found 240.0985.

Optical Rotation: $[\alpha]_D^{21}$ –36.0 (c 0.75, $CHCl_3$).

*Preparation of lactam **189***



167 ***189***

(R)-3,4-dihydro-1H-spiro[naphthalene-2,3'-pyrrolidin]-2'-one (189)

A flame dried vial under N_2 was charged with ketone **167** (1 equiv, 0.05 mmol, 10.8 mg) and CH_2Cl_2 (0.1 M, 0.5 mL) at 0 ºC. Et_3SiH (10 equiv, 0.5 mmol, 62 µL) then BF_3•Et_2O (20 equiv, 1 mmol, 0.16 mL) was added to the reaction. The reaction was heated to 40 ºC. Following complete consumption of starting material as determined by TLC, the reaction was cooled to 23 ºC and diluted with saturated aqueous $NaHCO_3$. The reaction mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% acetone/CH_2Cl_2) afforded the title compound **189** as a white solid (5.6 mg, 0.028 mmol, 56% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 – 7.05 (m, 4H), 6.18 (s, 1H), 3.37 (ddd, J = 7.6, 6.1, 0.9 Hz, 2H), 3.10 (d, J = 16.4 Hz, 1H), 2.94 (ddd, J = 17.3, 6.5, 2.7 Hz, 1H), 2.84 (dddd, J = 17.4, 12.1, 5.9, 1.6 Hz, 1H), 2.63 (dd, J = 16.4, 2.3 Hz, 1H), 2.14 – 1.99 (m, 2H), 1.94 (dt, J = 12.7, 6.0 Hz, 1H), 1.74 (ddt, J = 13.3, 5.9, 2.5 Hz, 1H).

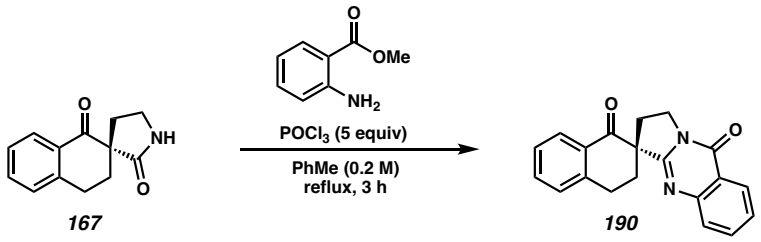
^{13}C NMR (100 MHz, $CDCl_3$): 182.4, 135.4, 134.5, 129.7, 129.0, 126.1, 126.0, 42.7, 39.0, 36.2, 31.7, 29.2, 25.8.

IR (Neat Film, NaCl): 3224, 3012, 2926, 2352, 1694, 1455, 1297 cm^{-1}.

HRMS (MM: ESI+): m/z calc'd for $C_{13}H_{15}NO$ $[M+H]^+$: 202.1226, found 202.1217.

Optical Rotation: $[\alpha]_D^{21}$ –9.2 (c 0.53, $CHCl_3$).

*Preparation of pyrimidone **190***



(*R*)-1',2',3,4-tetrahydro-1*H*,9'*H*-spiro[naphthalene-2,3'-pyrrolo[2,1-*b*]quinazoline]-1,9'-dione (190)

To a vial containing **167** (21.5 mg, 0.1 mmol) in toluene (0.5 mL, 0.2 M) added methyl anthranilate (13 uL, 0.1 mmol, 1.0 equiv) and $POCl_3$ (47 uL, 0.5 mmol, 5.0 equiv). The vial was capped and heated to 110 °C for 3 h, at which point the reaction had reached completion by TLC analysis. The reaction mixture was cooled and poured over a cold solution of saturated $NaHCO_3$. The crude mixture was extracted three times with ethyl acetate, and the combined organics were dried over Na_2SO_4, filtered, concentrated, and dried under reduced pressure. The crude material was purified on column chromatography (0–50% ethyl acetate/hexanes) to afford **190** (23.7 mg, 0.075 mmol, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (dd, J = 8.0, 1.5 Hz, 1H), 8.06 (dd, J = 7.9, 1.4 Hz, 1H), 7.69 (ddd, J = 8.5, 7.0, 1.6 Hz, 1H), 7.65 – 7.59 (m, 1H), 7.55 (td, J = 7.5, 1.5 Hz, 1H), 7.45 (ddd, J = 8.2, 7.0, 1.3 Hz, 1H), 7.40 – 7.29 (m, 2H), 4.37 (ddd, J = 11.8, 8.7, 2.8 Hz, 1H), 4.16 (ddd, J = 12.1, 9.0, 7.5 Hz, 1H), 3.36 (dt, J = 16.6, 4.8 Hz, 1H), 3.11 (ddd, J = 16.3, 10.8, 4.3 Hz, 1H), 2.98 (ddd, J = 13.5, 10.8, 4.5 Hz, 1H), 2.69 (ddd, J = 13.1, 7.6, 2.8 Hz, 1H), 2.34 – 2.22 (m, 2H).

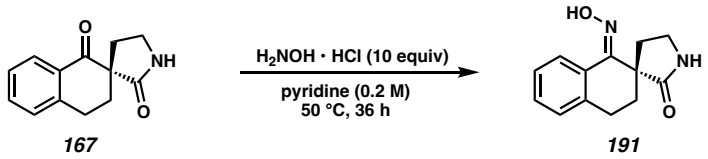
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.8, 161.0, 159.9, 149.4, 143.8, 134.4, 134.1, 130.5, 128.9, 128.6, 127.6, 127.3, 126.7, 126.5, 121.3, 58.1, 44.0, 32.4, 30.9, 25.7.

IR (neat film, NaCl): 2928, 1673, 1614, 1468, 1320, 1221, 774, 683 cm^{-1}.

HMRS (ESI+): m/z calc'd for $C_{20}H_{17}N_2O_2$ $[M+H]^+$: 317,1285, found 317.1275.

Optical Rotation: $[\alpha]_D^{24}$ = 14.21 (c 1.0, $CHCl_3$).

*Preparation of oxime **191***



167 ***191***

(*S*,*E*)-1-(hydroxyimino)-3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidin]-2'-one (191)

To a vial containing **167** (21.5 mg, 0.1 mmol) in pyridine (0.5 mL, 0.2 M) added hydroxylamine HCl (70 mg, 1.0 mmol, 10 equiv). The vial was capped and heated to 50 °C for 36 h, at which point the reaction had reached completion by TLC analysis. The reaction mixture was cooled, concentrated under reduced pressure, and then partitioned between water and ethyl acetate. The crude mixture was extracted three times with ethyl acetate, and the combined organics were dried over Na_2SO_4, filtered, concentrated, and dried under reduced pressure to afford **191** (22.9 mg, 0.10 mmol, 99% yield).

^{1}H NMR (400 MHz, CD_3OD): δ 7.94 (dd, J = 8.3, 1.4 Hz, 1H), 7.30 – 7.19 (m, 1H), 7.19 – 6.95 (m, 2H), 4.60 (s, 2H), 3.62 – 3.41 (m, 2H), 2.95 – 2.77 (m, 2H), 2.65 (dddd, J = 12.7, 10.0, 7.5, 1.2 Hz, 1H), 2.22 (ddd, J = 12.7, 8.4, 3.2 Hz, 1H), 2.03 (dddd, J = 13.0, 10.3, 5.9, 1.2 Hz, 1H), 1.93 (t, J = 4.1 Hz, 1H), 1.90 (t, J = 4.1 Hz, 1H).

^{13}C NMR (100 MHz, CD_3OD): δ 182.6, 154.3, 139.7, 132.5, 129.8, 129.1, 127.4, 125.7, 40.6, 33.4, 30.9, 27.1.

IR (neat film, NaCl): 3265, 2913, 2512, 2070, 1669, 1163, 978, 830, 773, 687 cm^{-1}.

HMRS (ESI+): m/z calc'd for $C_{13}H_{15}N_2O_2$ $[M+H]^+$: 231.1128, found 231.1126.

Optical Rotation: $[\alpha]_D^{24} = 50.32$ (c 1.0, $CHCl_3$).

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(14) We briefly explored phenolic carbamates as alternative electrophiles to isocyanates with the hypothesis that an electron deficient variant might be sufficiently electrophilic to outcompete allylic alkylation, or that these carbamates could act as blocked isocyanates under tailored reaction conditions; ultimately, this approach yielded limited success, generating product **167** in both diminished yields and enantioselectivities.

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(16) Substoichiometric use of additive **174** (less than 0.5 equiv) delivers oligomeric byproducts arising from condensation of the unprotonated product with the isocyanate starting material.

(17) Attempts to improve the ee of substrates **176** or **184** by using (*S*)-$(CF_3)_3$-*t*-Bu-PHOX failed.

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