Chapter 2

A Modular Approach to Synthesize Enantioenriched Cyclobutane Products[†]

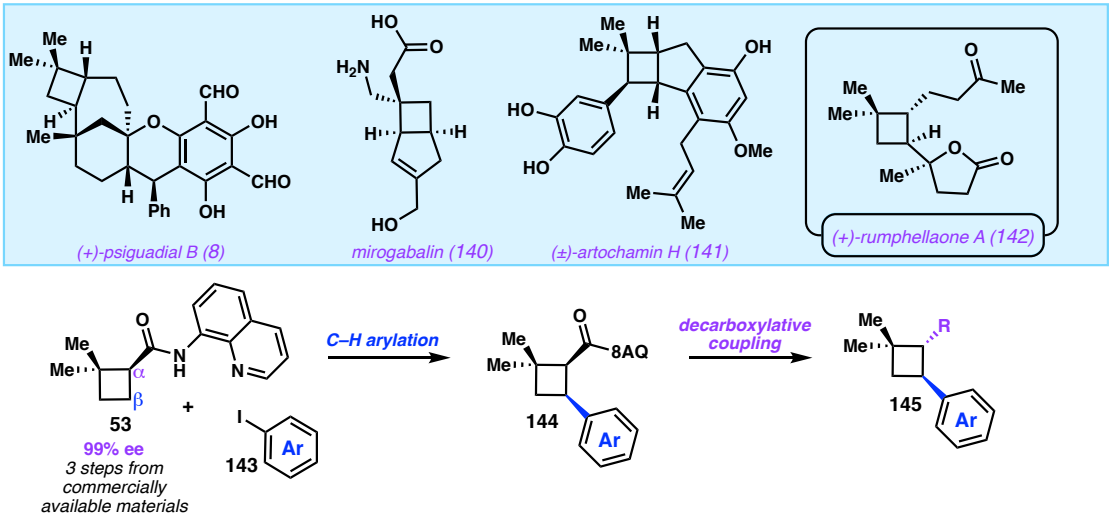
2.1 INTRODUCTION

Having established a novel methodology for the asymmetric synthesis of **55** for application to the synthesis of (+)-psiguadial B (**8**), we wondered if we could potentially leverage this versatile building block to further explore the preparation of *trans*-fused cyclobutane containing products. The cyclobutane structural motif is present in a variety of natural products and pharmaceutical molecules (Scheme **2.1**).[1–7] Cyclobutanes are also versatile synthetic intermediates, as the ring strain inherent to these structures engenders

[†] Portions of this chapter were adapted from the following communication: Beck, J. C.; Lacker, C. R.; Chapman, L. M.; Reisman, S. E. *Chem. Sci.* **2019**, *10*, 2315., DOI: 10.1039/C8SC05444D, copyright 2019 Royal Society of Chemistry. The research discussed in this chapter was completed in collaboration with Caitlin R. Lacker, a graduate student in the Reisman Lab as well as Dr. Lauren M. Chapman, a former graduate student in the Reisman Lab.

them with unique reactivity that can be leveraged in a variety of transformations to build complex frameworks. [8–11] [2+2] cycloaddition reactions represent the most extensively developed approach to construct cyclobutanes, and recent advances have given rise to elegant enantioselective reactions.[12–17] An alternative strategy is to prepare a versatile cyclobutane building block, and then use C–H functionalization or cross-coupling chemistry to elaborate the scaffold in a modular fashion.[18–27] In this latter approach, a single enantioenriched intermediate can quickly be converted to a variety of more functionalized structures.

Scheme 2.1 *Bioactive cyclobutane-containing products and our strategy for cyclobutane vicinal difunctionalization.*



We recently reported the synthesis of **8** which featured a tandem Wolff-rearrangement/asymmetric ketene addition to prepare enantioenriched 8-aminoquinolinamide **53**.[28,29] In the course of our investigation, we became acutely aware of the limitations and difficulties associated with the synthesis of functionalized cyclobutanes as well as the community's interest in more methods for their preparation.

Given the short synthesis of **53** from commercial starting materials, we became interested in further applications of this chiral building block. Specifically, we envisioned that directed C–H arylation could enable diversification at the β-position, while hydrolysis of the 8-aminoquinolinamide followed by decarboxylative radical cross-coupling could enable diversification at the α-position. Herein, we describe the development of this strategy commencing from lynchpin **53** that has enabled the synthesis of a library of vicinal difunctionalized cyclobutanes and our efforts to apply this strategy to the synthesis of **142**.

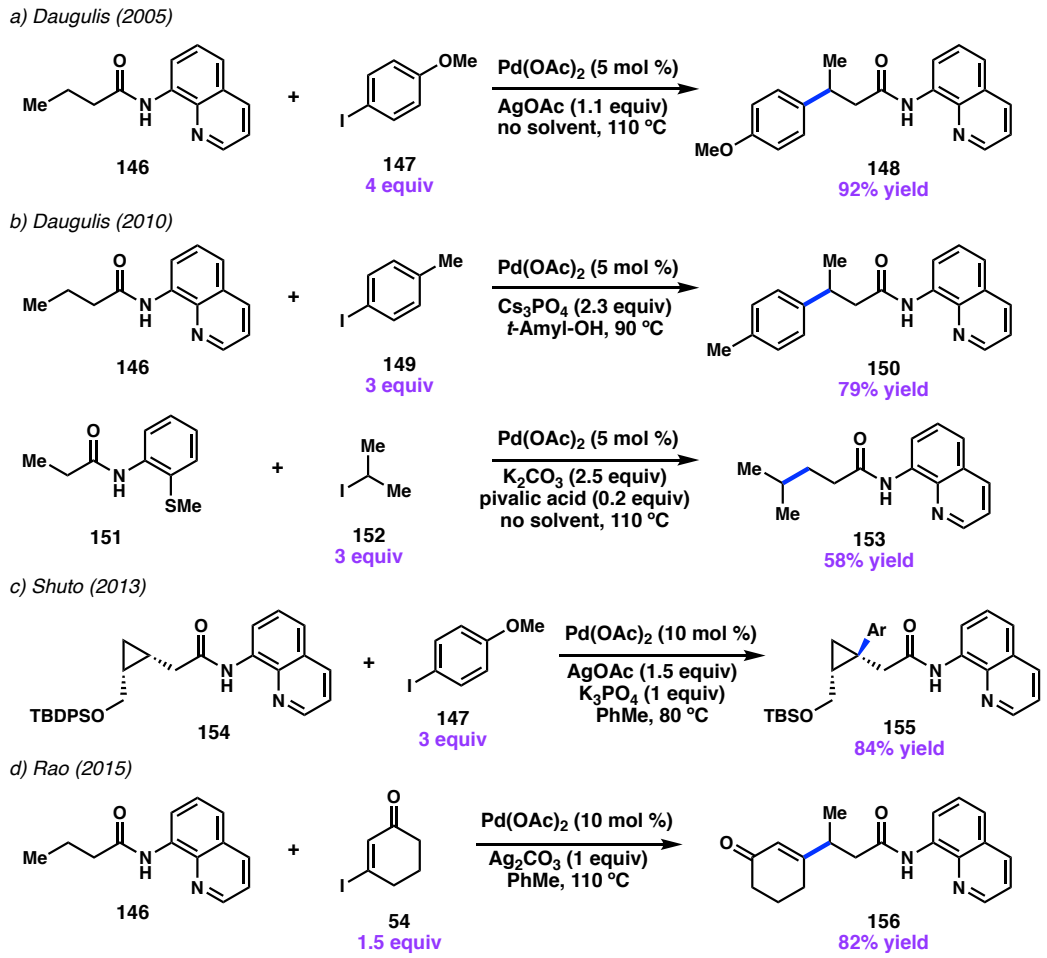
2.2 REVIEW OF AMIDE DIRECTED C(sp^3)–H ACTIVATION TO FORM C–C BONDS

At the outset of our investigation focused on the synthesis of **8**, we were intrigued by reports detailing the use of an aminoquinolinamide directing group to perform palladium-catalyzed C–H functionalization of aliphatic C–H bonds. Having developed a novel Wolff Rearrangement with asymmetric trapping of the ketene to install the quinolinamide and set the first stereocenter in a single step, we hypothesized that we could utilize this quinolinamide-directed methodology to perform functionalization of a cyclobutane.

Notably in 2005, Daugulis and co-workers reported the arylation of a C(sp^3)–H bond under palladium catalysis, utilizing aryl iodides **147** as the cross-coupling partners with silver acetate added to presumably turn over the catalyst (Scheme **2.2a**).[30] This pivotal disclosure was further expanded upon to include additional directing groups enabling C–H functionalization without the addition of stoichiometric silver salts and provided

examples of cross-coupling with additional aryl as well as alkyl iodides **152** (Scheme **2.2b**).[31]

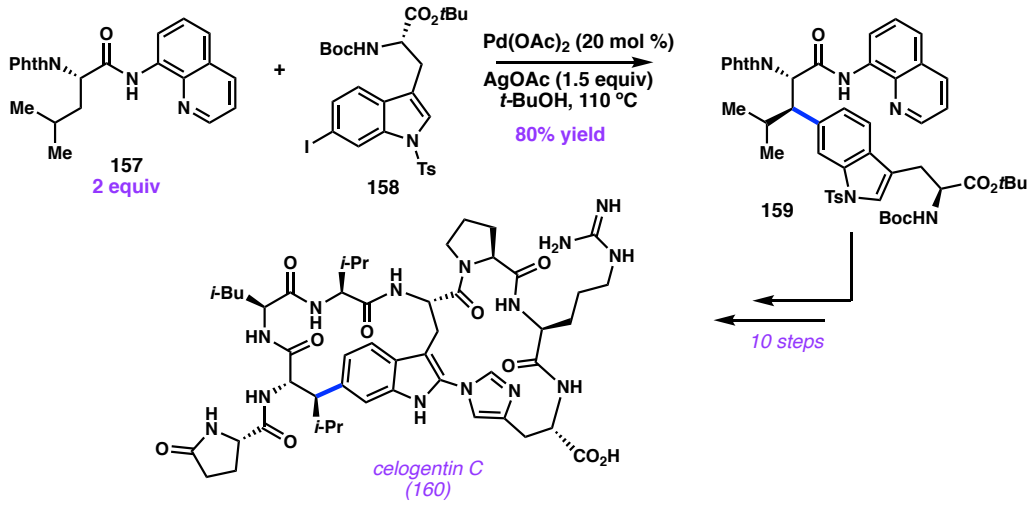
Scheme 2.2 *Precedent for aminoquinolinamide-directed C–H activation.*



We were also intrigued by an early report from the Shuto group in which they were able to activate substituted cyclopropanes utilizing the same quinolinamide directing group, forging all-carbon quaternary centers using a similar Pd(II) catalyst system (Scheme **2.2c**).[32] In their system, they were able to access all-carbon quaternary centers through activation of the tertiary cyclopropyl methine. This example demonstrated the feasibility of building sterically encumbered systems with the quinolinamide auxiliary.

Particularly notable for use in our synthesis was a disclosure from Rao and coworkers in 2015 in which they report functionalization of a methylene group with a variety of alkenyl iodides (Scheme **2.2d**).[33] We were excited to see their use of iodides such as **54** utilized in their system, as these types of unsaturated ketone products mapped on well for our synthesis of **8**.

Scheme 2.3 *Chen synthesis of celogentin C.*

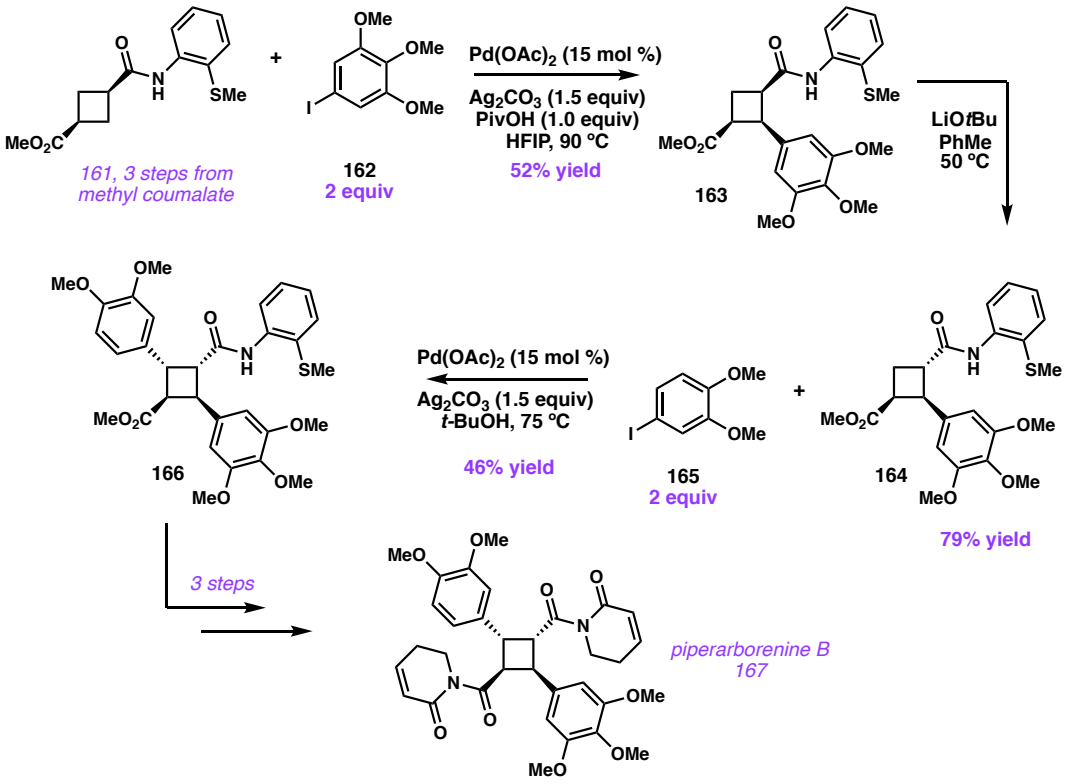


In addition to these key reports of palladium-catalyzed C–H activation methodologies, we were also aware of some examples of total syntheses of complex molecules in which a C–H bond activation strategy was employed to install functionality at an otherwise inert carbon–hydrogen bond. In 2010, the Chen group reported their total synthesis of the bicyclic peptide, celogentin C (**160**) (Scheme **2.3**).[34] Key to their strategy was a C–H activation between leucine derivative **157** bearing an 8-aminoquinolinamide and a modified tryptophan derivative **158**, selectively functionalizing **157** at the β-position. They isolated their product as single diastereomer, presumably due to the coordinating ability of the adjacent imide. It is interesting that in this particular example, the aryl iodide

158 was used as the limiting reagent, as typically the aryl iodide is used in excess. Their key indole intermediate **159** can be advanced an additional 10 steps to access the macrocyclic natural product **160**. Their synthesis elegantly leverages the intrinsic selectivity for β-functionalization of these amino quinolinamides.

A report in 2011 from the Baran lab further demonstrated the utility of C–H activation in the context of natural product total synthesis (Scheme **2.4**).[18] They were able to prepare **161** in three steps from commercially available methyl coumalate as a racemic mixture, at which point they were poised to perform their first C–H activation event.

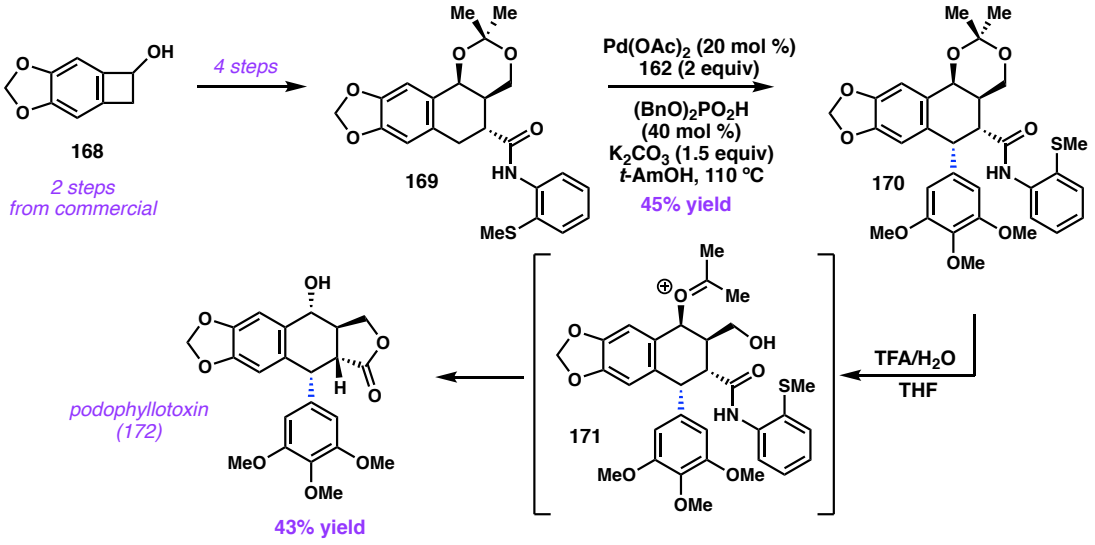
Scheme 2.4 *Baran synthesis of piperarborenine B.*



Treatment of **161** with two equivalents of aryl iodide **162** delivered modest yield of the single arylated product **163**, with all three substituents configured *cis* to one another.

Epimerization of **163** delivered **164**, which underwent a second C–H arylation reaction, this time with aryl iodide **165** as the cross-coupling partner. Arylation directed by the aminothioanisole delivered a single diastereomer of **166**, which was advanced three additional steps to provide piperarborenine B (**167**). This synthesis demonstrated the feasibility of using palladium catalysis to activate cyclobutyl methylenes in a C–H activation event. While their synthesis was limited by their use of racemic starting material, their high levels of diastereoselectivity indicated that we could generate a library of *enantioenriched* cyclobutanes by starting with a chiral cyclobutamide substrate. The Baran lab subsequently published a full paper detailing additional C–H functionalization strategies to access similar natural products.[21]

Scheme 2.5 *Maimone synthesis of podophyllotoxin.*



In 2014, the Maimone group reported a short racemic synthesis of the aryltetralin natural product, podophyllotoxin (**172**), again relying upon a key C–H activation reaction to forge a crucial C–C bond (Scheme **2.5**).[35] Their synthesis commenced with the

preparation of cyclobutanol **168**, which can be made in two steps from commercial material. Four additional steps delivered acetonide **169** containing the key aminothioanisole directing group. This substrate can undergo C–H activation with 2 equivalents of **162**, delivering **170** in modest yield. The arylated was subjected to hydrolysis of the acetonide, during which epimerization of the secondary alcohol and lactonization occured concomitantly to deliver **172**. The utility of the C–H activation is highlighted by the brevity of their synthesis, enabling the synthesis of **172** in just 7 steps from commercial material.

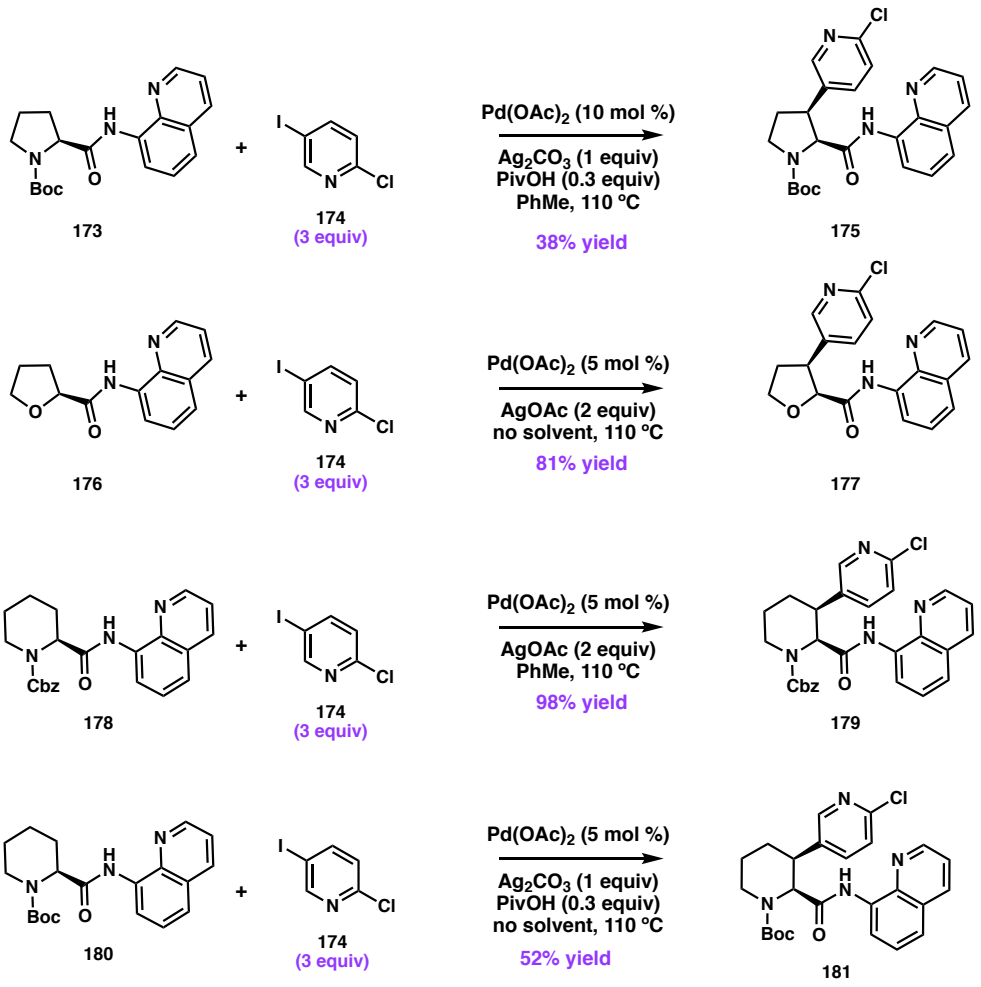
2.3 THE DEVELOPMENT OF A NOVEL C(sp^3)–H HETEROARYLATION REACTION

While C(sp^3)–H bond arylation has been explored by several groups, the corresponding *hetero*arylation reaction remains widely underdeveloped. At the outset of this investigation, we were only aware of one other report in which a heterocycle was used to direct a heteroarylation reaction.[36]

In 2016, the Bull lab published an aminoquinolinamide directed C(sp^3)–H activation reaction (Scheme **2.6**).[36] By utilizing chiral piperidines, pyrrolidines, and tetrahydrofurans, they could perform a site-selective and diastereoselective heteroarylation with 2-chloro-5-iodopyridine (**174**) as the cross-coupling partner. While they were able to achieve excellent yields of the coupled products with a Cbz-protected piperidine **178** or the tetrahydrofuran-containing quinolinamide **176**, their substrates containing Boc-protected piperidines **173** and Boc-protected pyrrolidines **180** were coupled in lower yields (Scheme

2.6). Notably, their reactions enabled the formation of enantioenriched products by starting from the chiral pool.

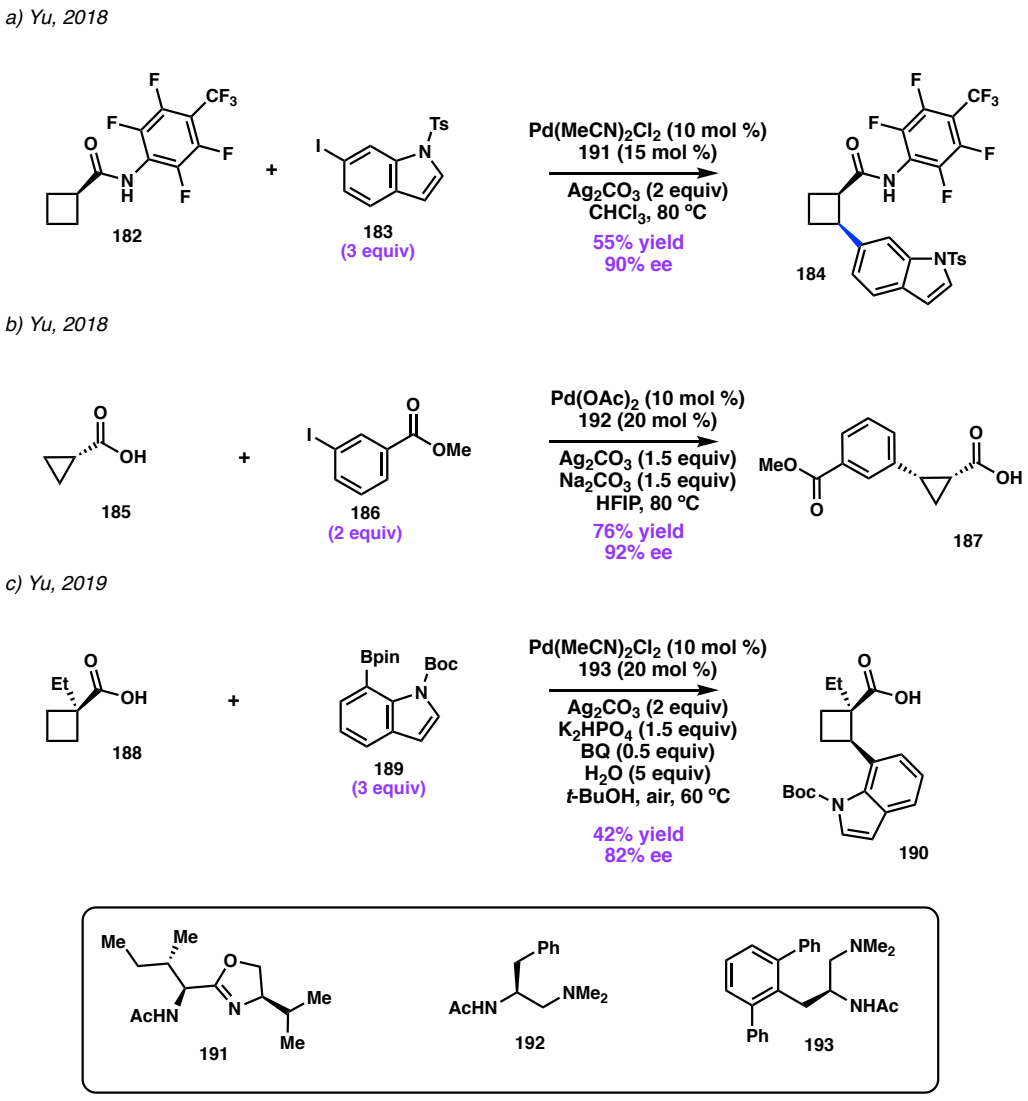
Scheme 2.6 *Bull's heteroarylation of pyrrolidines, tetrahydrofurans, and piperidines.*



During the course of our investigation, the Yu lab reported three elegant C–H activation reactions highlighting both the power of C–H activation as a strategy for the synthesis of chiral cyclic products as well as the difficulties associated with the utilization of heteroaryl moieties in cross-coupling reactions (Scheme **2.7**). In 2018, the Yu group disclosed a palladium-catalyzed C–H activation reaction between cyclobutyl carboxylic

amides **182** and aryl iodides **193** using a chiral mono-*N*-protected aminomethyl oxazoline (MPAO) ligand **191** (Scheme **2.7a**).[27] While they had previously reported the use of the related chiral mono-*N*-protected α-amino-*O*-methylhydroxamic acid (MPAHA) ligands to promote cross-couplings between cyclobutyl carboxylic amides and aryl boron reagents,[22] the development of this reaction utilizing the MPAO ligand class enabled entry into a Pd(II)/Pd(IV) catalytic cycle, improving the scope of substrates tolerated in the reaction.

Scheme 2.7 *Yu's C–H activation of cyclobutanes and cyclopropanes.*



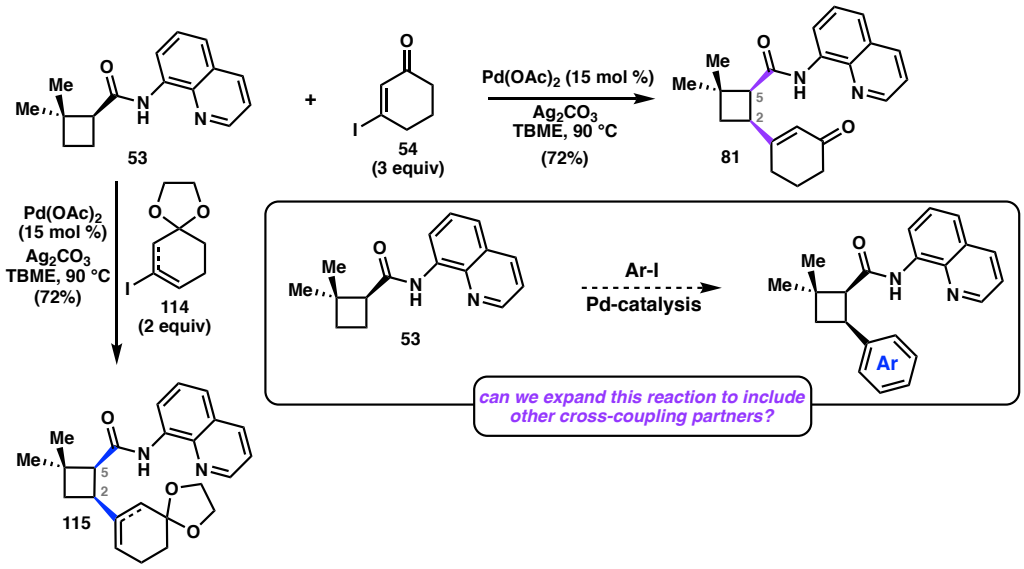
While their reaction notably enables the enantioselective arylation of cyclobutyl carboxylic amides, only two nitrogen-containing aryl iodides are employed in their reaction, both of which proceed in only modest yield.

In 2018, the Yu group reported an additional C–H activation reaction to access chiral carbocycles using carboxylic acid substrates (Scheme **2.7b**).[37] The use of free carboxylic acids in these reactions had previously been limited due to the low reactivity associated with the weak directing ability of the carboxylic acid as well as the conformationally flexibility of the acid in comparison to the rigidified amide substrates. However, this reaction was enabled by the development of the monoprotected aminoethyl amine (MPAAM) ligand class **192**, allowing for enantioselective C(sp^3)–H functionalization of free carboxylic acids **185**. While this report represents an immense achievement in the field of C–H activation, their initial report was limited to cyclopropyl carboxylic acids and did not include the cross-coupling of any nitrogen-containing heterocycles.

In early 2019, the Yu lab reported a subsequent report in which they were able to expand the breadth of their reaction to encompass the direct cross-coupling of cyclobutyl carboxylic acids **188** with aryl boronate esters **189** (Scheme **2.7c**).[38] Key to this reaction was the use of an aryl boronate rather than an aryl iodide coupling partner, presumably changing the mechanism from a Pd(II)/Pd(IV) catalytic cycle to a Pd(0)/Pd(II) catalytic cycle. They report a single cross-coupling with a heteroaryl boronate ester **189**, again highlighting the difficulties associated with using Lewis basic cross-coupling partners in directed C–H functionalization reactions.

After extensive optimization and exploration of a C–H activation for two different substrates *en route* to **8**, we hypothesized that we could expand the scope of this reaction to encompass the cross-coupling of additional electrophiles. With a robust means of preparing **53**, we became interested in identifying cross-coupling conditions that could enable the formation of a library of vicinal disubstituted cyclobutanes from our lynchpin **53** (Scheme **2.8**). We hypothesized that the efficiency with which both **54** and **114** could be coupled with **53** with excellent site- and diastereoselectivity indicated that this particular scaffold was privileged in this type of transformation and warranted further exploration.

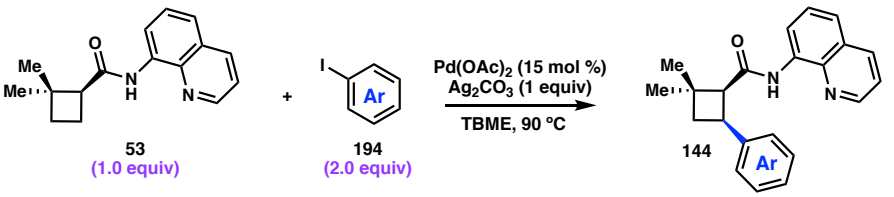
Scheme 2.8 *Our modular approach to prepare chiral disubstituted cyclobutanes.*

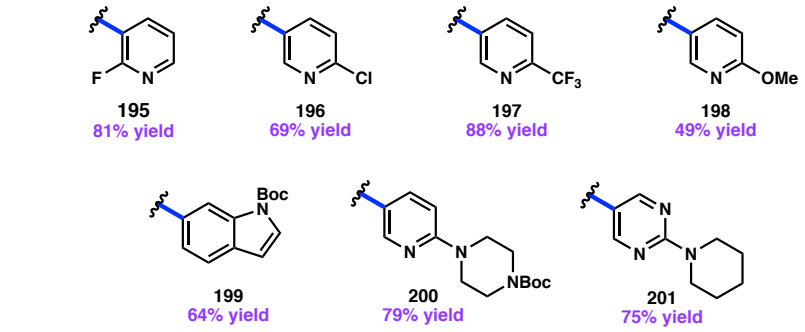


We began by investigating the scope of the directed C–H arylation of 8-aminoquinolinamide **53**, which was prepared in three steps and 99% ee from commercially available 2,2-dimethylcyclopentan-1-one.[28,29] We were pleased to see that by using our previously developed conditions [$Pd(OAc)_2$ (15 mol%), Ag_2CO_3 (1.0 equiv), aryl iodide (2.0 equiv), TBME, 90 °C], a series of heteroaryl iodides could be coupled to generate *cis*-

heteroarylated cyclobutanes (**195**–**201**) in good yields (Table **2.1**). Under these reaction conditions, we could isolate good yields of pyridine-containing cyclobutanes (**195**–**198**) with varying substitution on the arene. We were pleased to see that an indolyl iodide was a competent cross-coupling partner in this reaction (**199**) as was a piperazyl pyridine (**200**) and a piperidyl pyrimidine (**201**). We were particularly excited by products such as **200** and **201**, which contain five nitrogen atoms within the molecule.

Table 2.1. *Cyclobutamide heteroarylation*

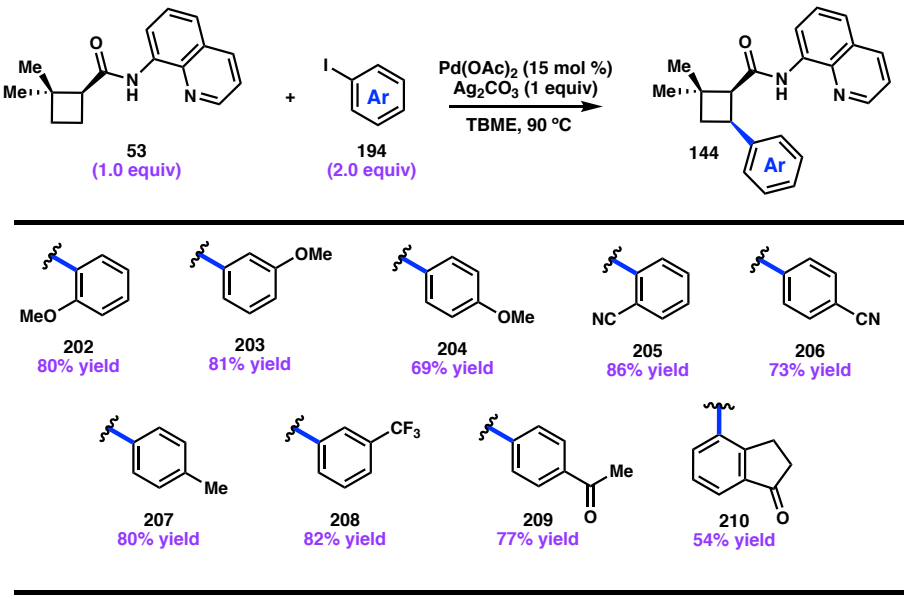




Pleased that we could incorporate heteroaryl moieties through this cross-coupling platform, we became interested in exploring the feasibility of incorporating additional aryl iodides through this reaction. Gratifyingly, we found that installation of a variety of aryl groups proceeded with high levels of yield and selectivity (Table **2.2**). This reaction tolerates aryl substitution at the *ortho*, *meta*, and *para* positions (**202**–**204**) and can tolerate

both electron withdrawing (**205**–**206**, **208**–**210**) as well as electron donating groups (**202**–**204**).

Table 2.2. *Cyclobutamide arylation*

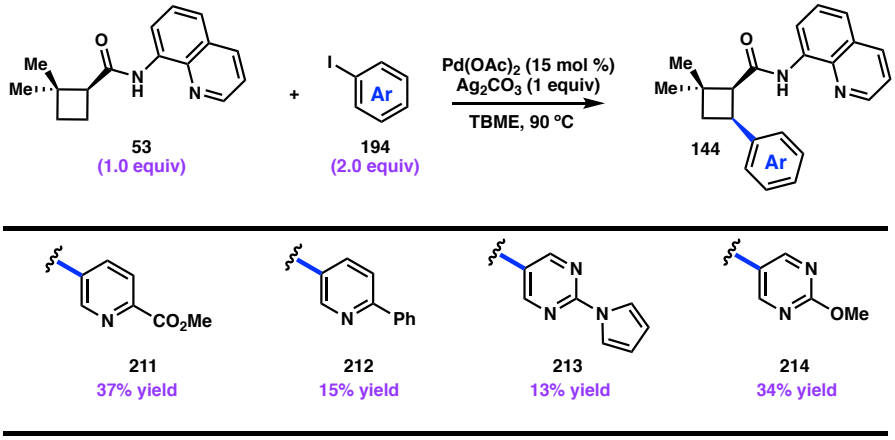


While the reaction worked with excellent efficiency and selectivity for a variety of substrates, we identified key limitations of this transformation. Unfortunately, attempts to lower the catalyst loading (7.5 mol %) or using only 1 equivalent of the aryl iodide decreased the yields by about 30% across the board. While some substrates could be adequately cross-coupled at lower temperatures, we found that 90ºC worked for most of the substrates we explored.

We also found that some substrates did not perform well in the reaction under these general reaction conditions. C–H activation reactions between **53** and pyridyl iodides with an ester at the 2-position or an aromatic ring at the 2-position performed poorly under these conditions (Table **2.3**, **211** and **212**). We also found that pyrimidine substrates with a

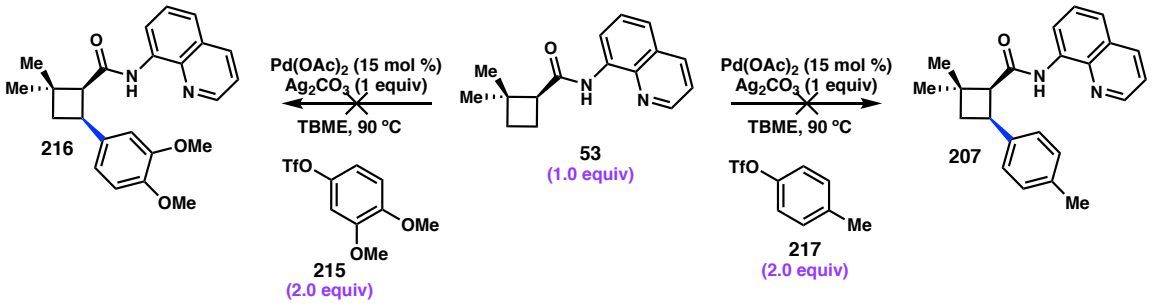
pyrrole (**213**) or a methoxy group at the 2-position (**214**) also did not work well under these reaction conditions.

Table 2.3. *Poorer performing substrates*



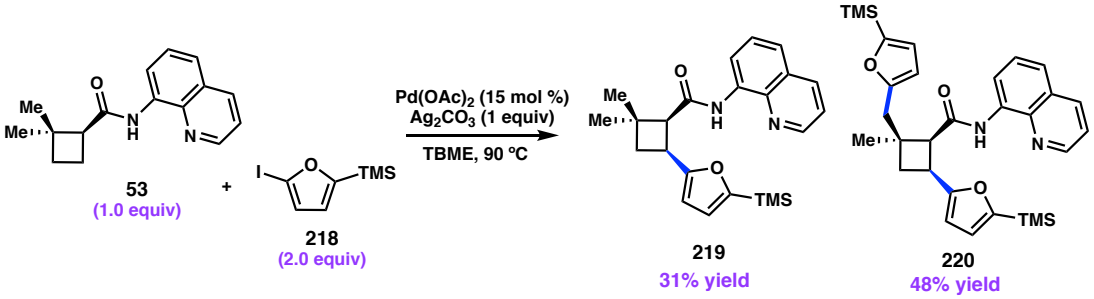
In an attempt to broaden the scope of this reaction, we investigated the feasibility of using aryl triflates as the coupling partners, as we reasoned these might be more appealing due to their ease of handling; however, under the conditions developed for the cross-coupling of aryl and heteroaryl iodides, only starting material was observed (Scheme **2.9**). Expansion of this methodology to encompass the cross-coupling of alternative classes of electrophiles was not further explored, but it would be prudent to look at additional additives as well as alternative solvents and palladium precatalysts.

Scheme 2.9 *Unsuccessful attempts to use aryl triflates in the cross-coupling reaction.*



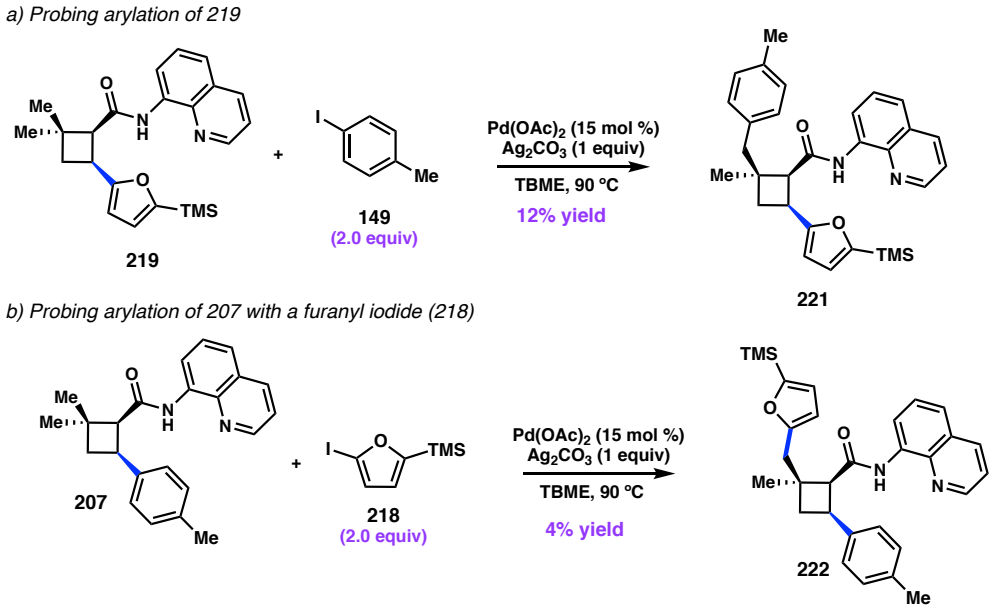
While we almost exclusively observed monofunctionalization of cyclobutane **53**, it is of note that one substrate that we investigated delivered bisarylated product. Treatment of **53** with two equivalents of **218** under the standard reaction conditions delivered significant quantities of bis-arylated product **220** (Scheme **2.10**). 2D NMR experiments indicated that the site of arylation was the beta-disposed methyl group. To the best of our knowledge, this was the only substrate that delivered any quantity of bis-arylated product under our developed reaction conditions.

Scheme 2.10 *Observed bis-arylation.*



We were perplexed by this finding—we had successfully carried out dozens of cross-couplings without observing any appreciable quantity of over-arylation. The reaction profiles were exceedingly clean, and we were often to recover unreacted **53** as well as the additional equivalent of the aryl iodide. In an attempt to better understand the nature of this bis-arylation phenomenon, we conducted a couple of experiments. We first treated **219** with **149** under the standard conditions and observed only trace over-arylation product **221** (Scheme **2.11**). We also attempted to use a different substrate with the iodofuryl cross-coupling partner **218** that had been a competent cross-coupling partner in the over-arylation reaction. Treatment of **207** with **218** under the standard conditions only delivered trace quantities of a bis-arylation product **222**.

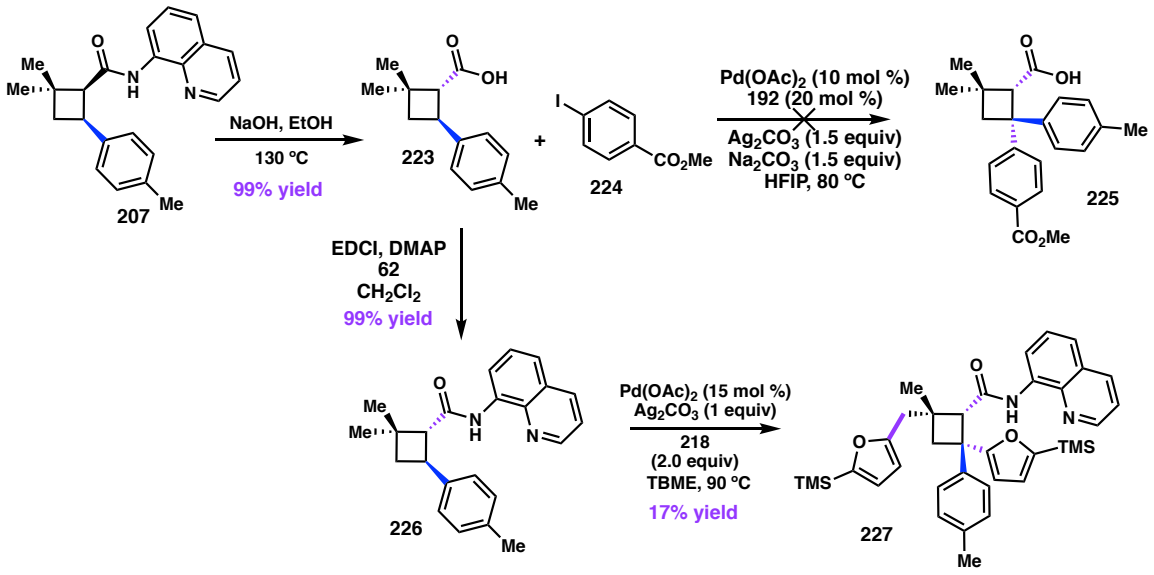
Scheme 2.11 *Probing alternative bisarylation substrates.*



To further explore the feasibility of using C–H activation to derivatize these substrates, we attempted to use Yu's C–H activation of free carboxylic acids, as we felt that the versatility of the carboxylic acid functional group could enable the introduction of additional complexity through an iterative cross-coupling approach (Scheme **2.12**). While hydrolysis of the quinolinamide **207** proceeded smoothly to deliver the *trans*-fused cyclobutanoic acid **223**, we found that this substrate was unreactive under the Yu conditions employing $Pd(OAc)_2$ and the MPAAM ligand **192** (Scheme **2.12**).[39] While the acid was unreactive, the aminoquinolinamide auxiliary could be reinstalled under canonical peptide coupling conditions, delivering **226** as the *trans*-fused cyclobutamide. To our surprise, treatment of **226** with our standard C–H activation conditions delivered a tri-arylated product **227**. While we were unsure of how synthetically useful this particular reaction would be due to the need to cleave and reinstall the auxiliary and our inability to

control or predict the bisarylation event, we were pleased to see that these scaffolds were amenable to further modulation. Satisfied with the excellent yields and diastereoselectivities we were able to observe with a variety of aryl and heteroaryl substrates, we became interested in identifying other means of modulating the cyclobutane scaffold.

Scheme 2.12 *A sequential C–H arylation strategy.*



2.4 DECARBOXYLATIVE CROSS-COUPLINGS FOR CYCLOBUTANE DIVERSIFICATION

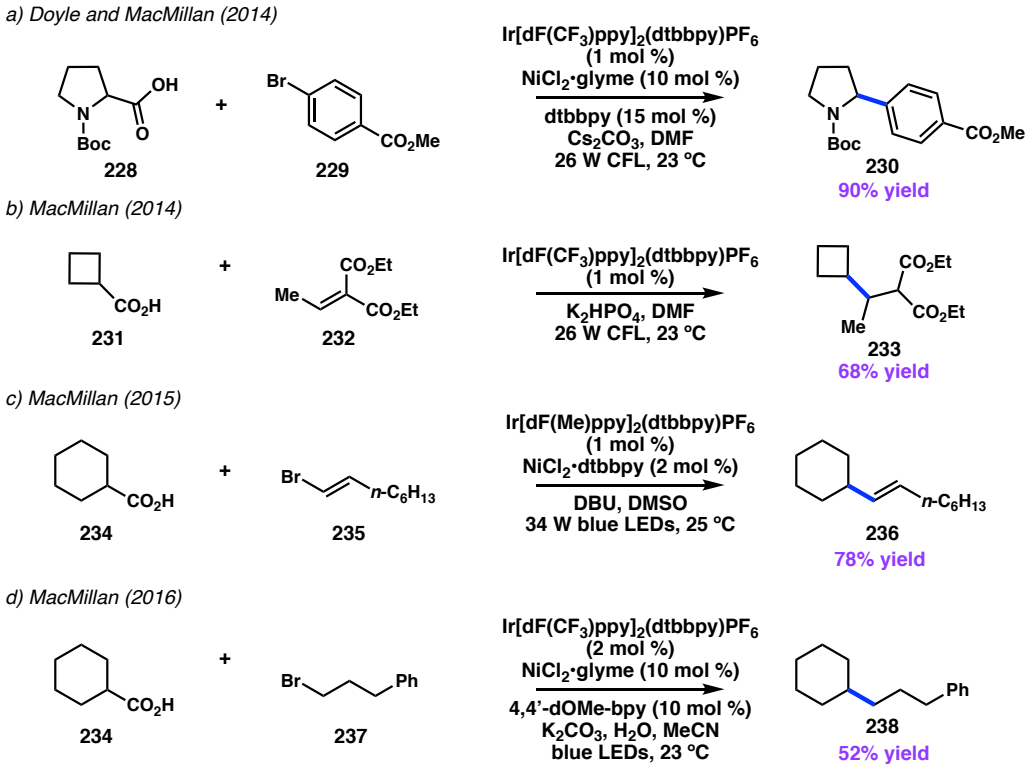
Having established the generality of the C–H arylation step, we turned our attention to diversification at the carbon bearing the 8-aminoquinolinamide. We thought that the carboxylic amide could provide a useful handle that could enable diversification of the α-carbon through either functional group interconversion or decarboxylative cross-coupling

(Scheme **2.1**). During our investigation, the Baran lab disclosed a similar strategy designed to build vicinal difunctionalization using a decarboxylative cross-coupling strategy,[23] indicating the feasibility of a decarboxylative cross-coupling approach to diversify cyclobutane products.

The use of carboxylic acids and redox-active esters in decarboxylative cross-coupling reactions has emerged as a powerful strategy in the construction of carbon-carbon bonds (Scheme **2.13**). In 2014, Doyle and MacMillan reported the decarboxylative cross-coupling between aliphatic carboxylic acids (**228**) and aryl bromides (**229**) under nickel/iridium dual catalysis (Scheme **2.13a**).[40] The iridium photocatalyst is thought to generate an alkyl radical which can be captured by the nickel catalyst and engaged in a nickel-catalyzed cross-coupling reaction. The MacMillan lab also reported a decarboxylative Giese-type addition, using the same iridium catalyst (Scheme **2.13b**).[41]

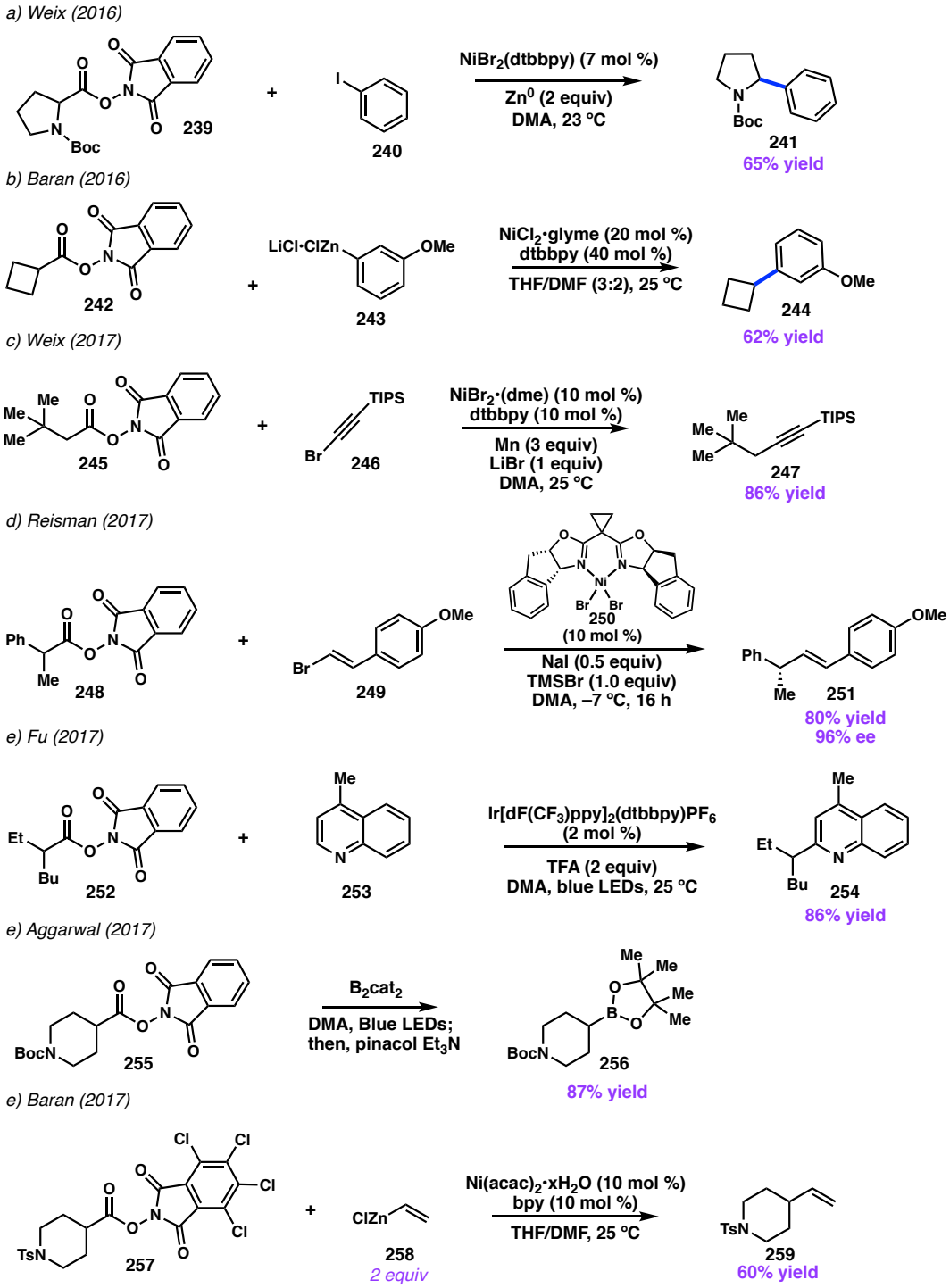
Decarboxylation of acids such as **231** is proposed to generate radical intermediates that can be trapped by a Michael acceptor (**232**) to access adducts such as **233**. The following year, MacMillan and co-workers reported a decarboxylative alkenylation reaction, using the aforementioned iridium/nickel dual-catalysis system (Scheme **2.13c**).[42] They could engage alkyl acids such as **234** in cross-coupling reactions with alkenyl bromides **235** to access cross-coupled products **236**. MacMillan later reported a decarboxylative cross-coupling between carboxylic acids **235** and alkyl bromides **237** to give adducts such as **238**, again using the combination of iridium and nickel catalysis to generate alkylated adducts (Scheme **2.13d**).[43]

Scheme 2.13 *Direct decarboxylative cross-coupling reactions of free acids.*



In addition to using the free carboxylic acids as cross-coupling partners, several groups have recently reported alkyl cross-coupling reactions using redox-active esters as substrates, enabling novel reactivity (Scheme **2.14**). In 2016, the Weix lab reported a reductive decarboxylative arylation reaction between *N*-hydroxyphthalimide (NHP) esters (**239**) and aryl iodides (**240**) to access arylated products (**241**) in good yields (Scheme **2.14a**).[44] The Baran lab has also used these NHP esters to perform a decarboxylative Negishi cross-coupling under nickel catalysis to access similar arylation products (**244**) as well as alkenylation products (**259**) (Scheme **2.14b,e**).[45,46]

Scheme 2.14 *Examples of decarboxylative couplings using NHP esters.*

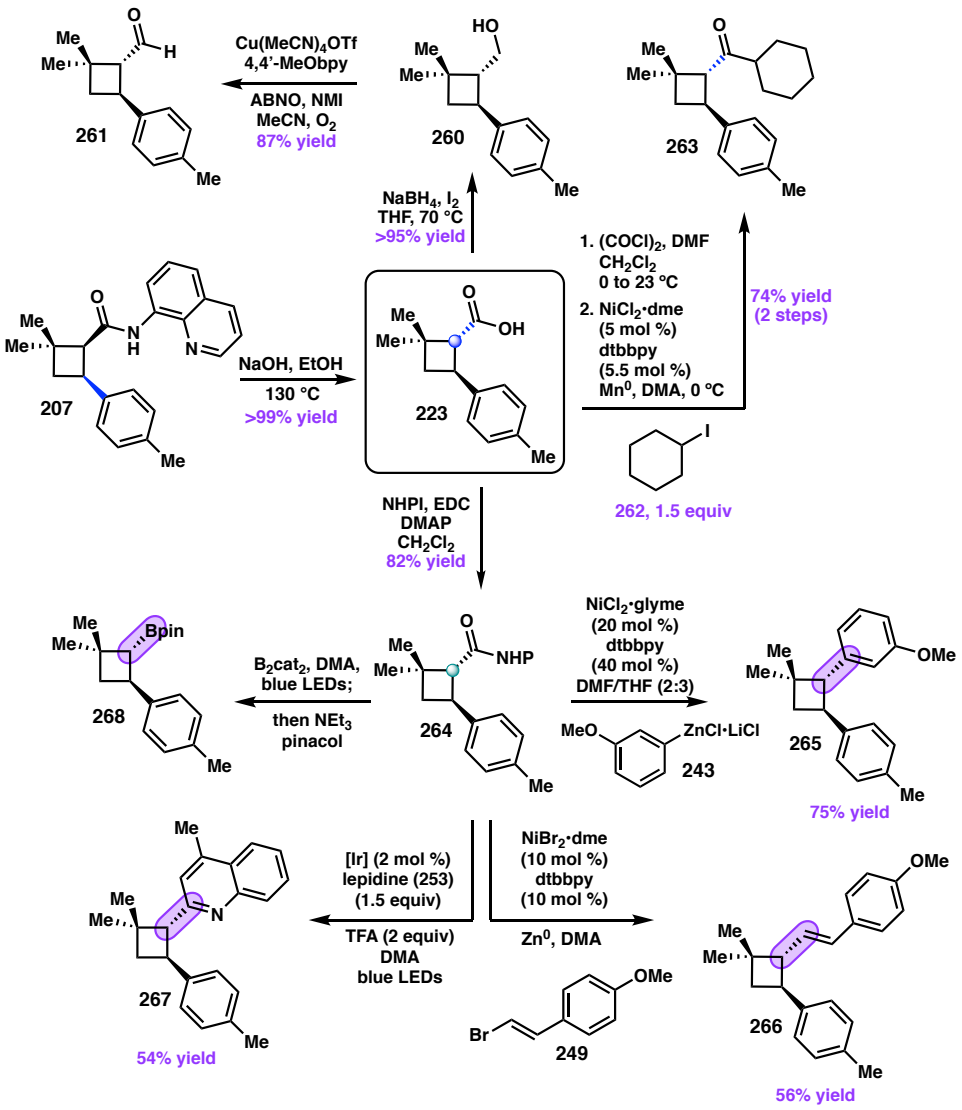


The Weix lab expanded their methodology to include the cross-coupling of alkynyl bromides (**246**), again using the NHP ester (**245**) as a versatile cross-coupling partner (Scheme **2.14c**).[47] Our lab has also explored the asymmetric cross-coupling of these NHP esters (**248**) with styrenyl bromides (**249**) to access enantioenriched benzylic styrenes (**251**) in excellent yield enantioselectivity (Scheme **2.14d**).[48] Groups have also explored activation of NHP esters using irradiation to perform additional cross-coupling reactions, including a decarboxylative Menisci reaction[49] and a decarboxylative borylation (Scheme **2.14e**).[50]

With this precedent in mind, we hypothesized that we could leverage our arylated cyclobutamide products to perform a subsequent cross-coupling reaction, further diversifying these chiral cyclobutane products (Scheme **2.1**). We were excited by the abundance of C–C bond activation strategies that had been reported, and we were eager to explore some of these methodologies with our arylation products. To this end, facile hydrolysis enabled gram-scale synthesis of **223** (Scheme **2.15**). To diversify the products through functional group interconversion, we were pleased to see that reduction of the acid to the primary alcohol **260** could be achieved by generating borane *in situ*, and the corresponding aldehyde **261** could be prepared through a Stahl oxidation.[51] Alternatively, **223** could be converted to the corresponding acid chloride and engaged in a nickel-catalyzed reductive cross-coupling with iodocyclohexane (**262**) to access ketone **263**.[52] In keeping with our goal of quickly building complex, chiral cyclobutane products, we were particularly interested in using the free carboxylic acid as a cross-coupling partner.

Unfortunately, any attempts to engage the free carboxylic acid in direct decarboxylative couplings were unsuccessful.[53]

Scheme 2.15 *Selected transformations of key acid* ***223***.



To further investigate decarboxylative coupling processes, acid **223** was subjected to EDC-mediated coupling with *N*-hydroxyphthalimide to provide NHP ester **264**. Ni-catalyzed coupling of **264** with aryl zinc chloride **243** gave *trans*-diarylcyclobutane **265** in good yield as a single diastereomer.[45] Similarly, NHP ester **264** underwent Ni-catalyzed

reductive alkenylation with styrenyl bromide **249** to furnish cyclobutane **266** in 56% yield.[44,48] Photoinduced decarboxylative Minisci type arylation of **264** under photoredox catalysis delivered quinoline **267**,[49] and borylation of **264** proceeded smoothly to afford boronic ester **268**.[50]

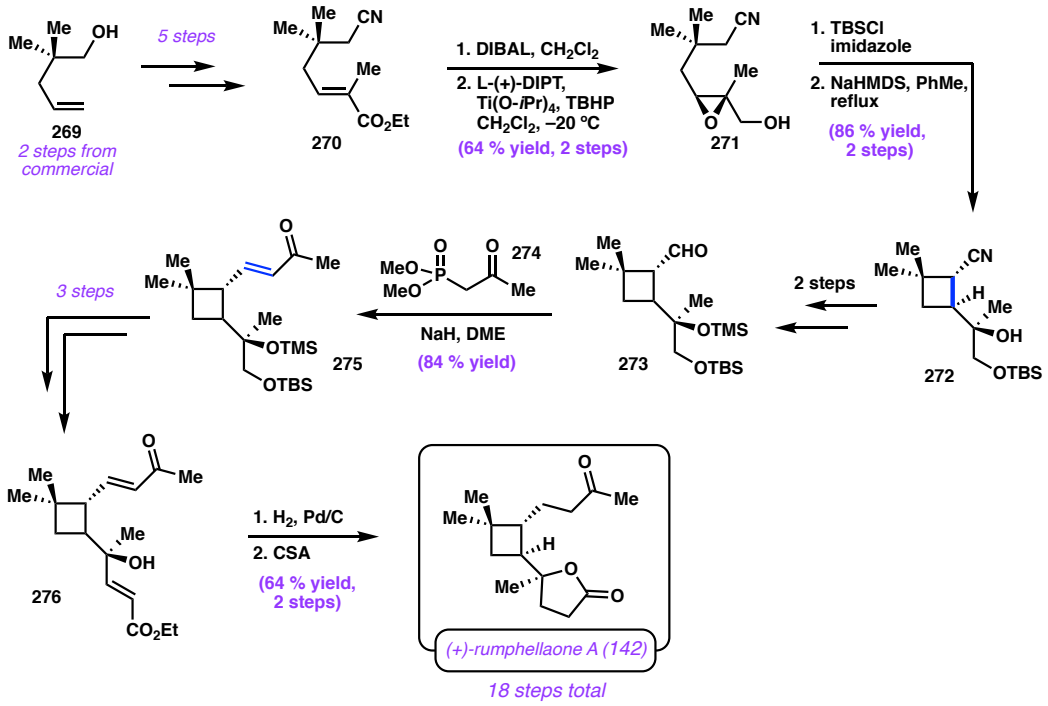
2.5 APPLICATIONS OF CYCLOBUTANE VICINAL DIFUNCTIONALIZATION: TOTAL SYNTHESIS OF (+)-RUMPEHALLONE A

To further demonstrate the utility of this cyclobutane difunctionalization strategy, we designed and executed a synthesis of the natural product (+)-rumphellaone A (**142**). (+)-Rumphellaone A (**142**) was isolated in 2010 from the gorgonian coral, *Rumphella antipathies* and possesses anti-proliferative activity against human T-cell acute lymphoblastic leukemia tumor cells.[7] Having previously targeted the *trans*-fused cyclobutane-containing natural product, (+)-psiguadial B (**8**), we felt that applying our difunctionalization strategy in a total synthesis would elegantly tie together different areas of research within our lab.

(+)-rumphellaone A (**142**) has been the target of a number of total syntheses reported to date. The Kuwahara lab reported an elegant synthesis of (+)-rumphellaone A (**142**) commencing from methyl isobutyrate (Scheme **2.16**).[54,55] Epoxy nitrile **271** can be prepared in short order, using the Sharpless epoxidation protocol to establish the first stereocenter. TBS protection followed by epoxy-nitrile cyclization in the 4-exo-tet manifold provides **272**, which can be elaborated in three

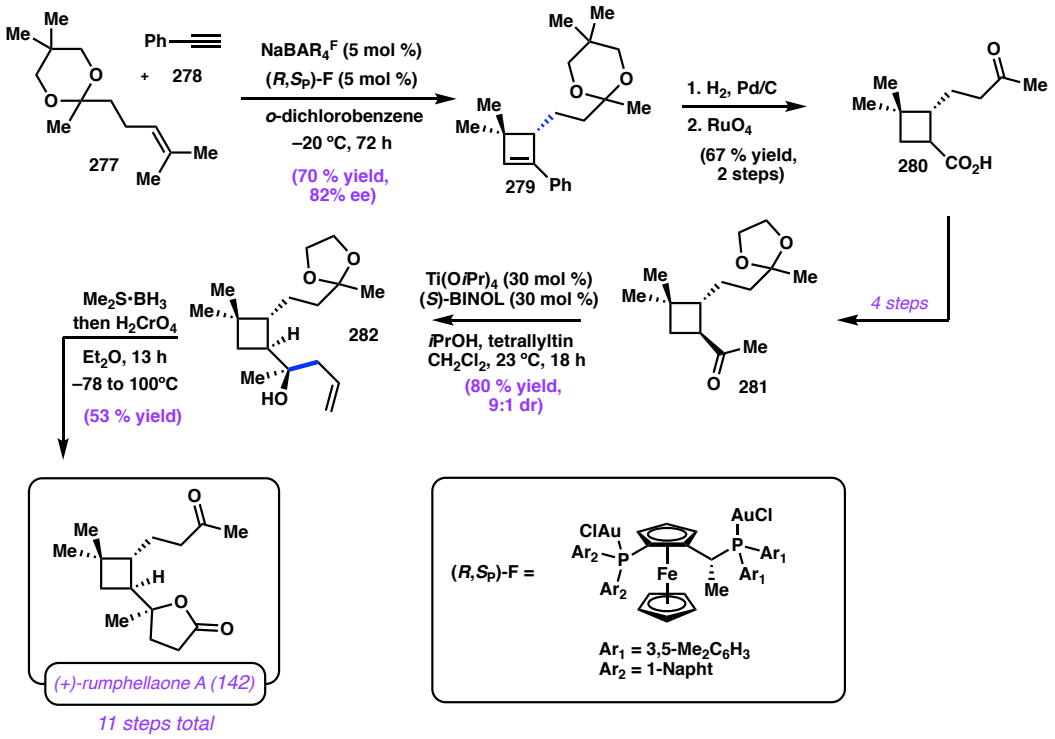
steps to enone **275**. Three additional steps delivers **276**, which can be hydrogenated and lactonized to deliver (+)-rumphellaone A (**142**) in 18 steps total.

Scheme 2.16 *Kuwahara's 2012 synthesis of (+)-rumphellaone A.*



We were also aware of a synthetic campaign from the Echavarren lab in which they were able to carry out a total synthesis of (+)-rumphellaone A (**142**) (Scheme **2.17**).[56] Their synthesis commences with an asymmetric [2+2] cycloaddition between trisubstituted olefin **277** and phenylacetylene **278** using a chiral catalyst. The cycloaddition product **279** can be hydrogenated and then oxidatively cleaved to provide ketone **280**. Four additional steps delivers **281**, which can be subjected to an asymmetric allylation reaction, using (*S*)-BINOL as the chiral controller. Hydroboration followed by an oxidation with chromic acid delivers the natural product **142**.

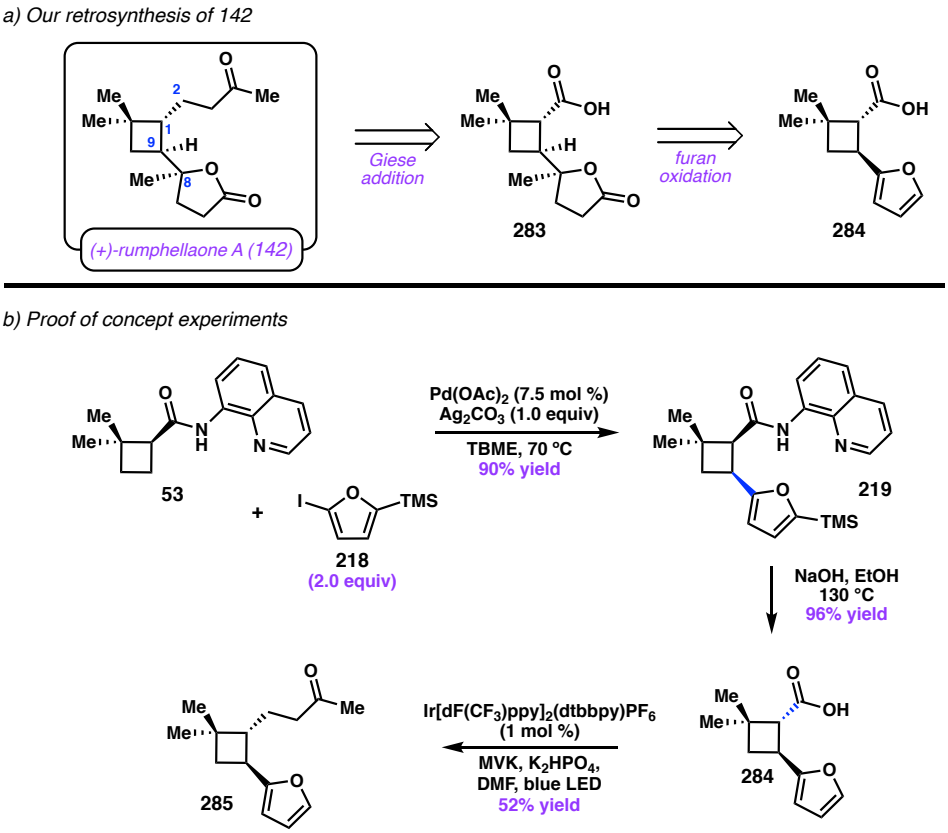
Scheme 2.17 *Echavarren's 2017 synthesis of (+)-rumphellaone A.*



While these syntheses allow for rapid access to **142**, we felt that our cyclobutane difunctionalization strategy could be applied to the synthesis of **142** and shorten the existing route to this compound. Retrosynthetically, we envisioned first disconnecting through C1–C2 bond to give **283** (Scheme **218a**); in the forward sense, the ketone fragment would be incorporated through a decarboxylative Giese addition of **284** to methyl vinyl ketone. The butenolide of **142** could derive from oxidation of furan **284**, which could be prepared from **53** by a directed C–H arylation. As a proof of concept, 8-aminoquinolinamide **53** was subjected to Pd-catalyzed C–H functionalization with furanyl iodide **218** to give *cis*-cyclobutane **219** in 90% yield (Scheme **2.18b**).[57] Hydrolysis and subsequent decarboxylative Giese

reaction with methyl vinyl ketone under photoredox catalysis provided **285** in 50% yield over two steps.

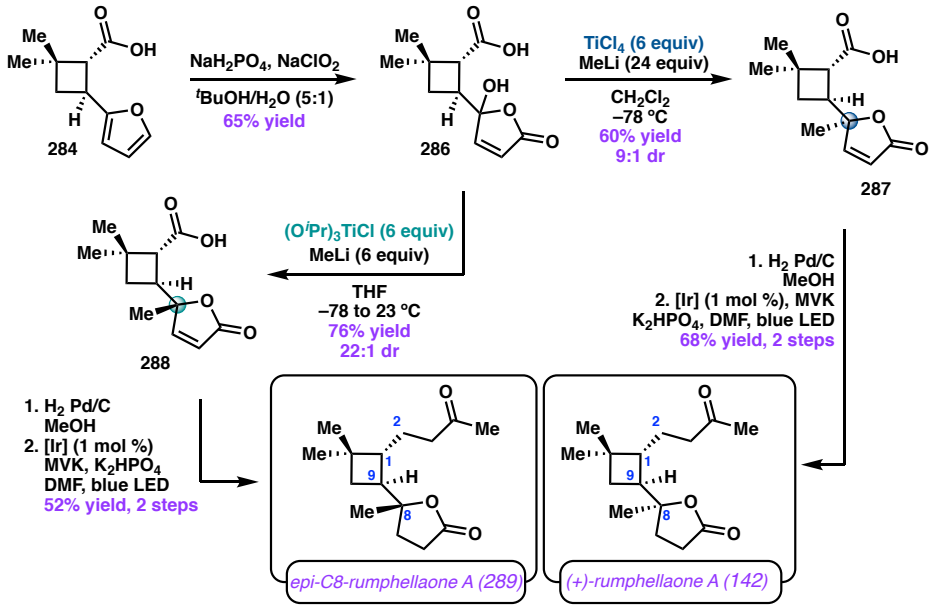
Scheme 2.18 *Our retrosynthesis of (+)-rumphellaone A and proof of concept experiments.*



Having validated the feasibility of the two key cyclobutane functionalization reactions, attention turned to the unmasking of the butenolide functionality prior to the decarboxylative Giese reaction. Treatment of **284** with sodium chlorite under buffered conditions[58] delivered 5-hydroxybutenolide **286** (Scheme **2.19**). The remaining challenge was installation of the C8 methyl substituent with the required *S*-configuration. In prior syntheses of **142**, this stereogenic center was set under the guidance of chiral catalyst

control.[54–56,59] Given that the C8 diastereomers were inseparable by column chromatography, high diastereoselectivity for this methyl addition was important.

Scheme 2.19 *A divergent methylation approach to (+)-rumphellaone A and epi-C8-rumphellaone A.*

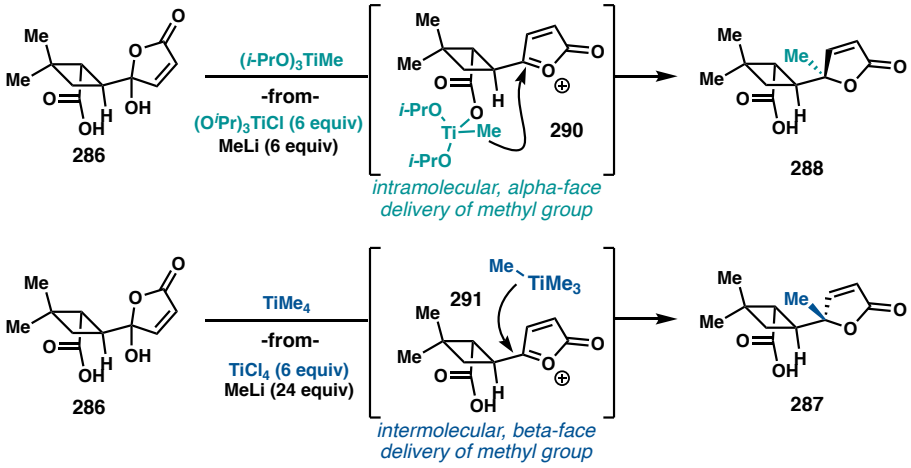


After exploring a range of conditions to effect the methylation, we were pleased to discover that either C8 diastereomer (**287** or **288**) could be prepared using the appropriate methyltitanium reagent (Scheme **2.19**). Thus, addition of **286** to a pre-formed 1:1 mixture of (^{i}PrO)$_3$TiCl and MeLi at –78 °C, with warming to 23 °C, delivered the undesired C8 diastereomer, **288**, in 76% yield and 22:1 dr.[60–62] Alternatively, addition of **286** to a –78 °C solution of Ti(Me)$_4$ in dichloromethane,[60] which was prepared *in situ* by combining MeLi and TiCl$_4$ in a 4:1 ratio, provided the desired diastereomer **287** in 60% yield and 9:1 dr.

We hypothesize that the divergent diastereoselectivity for these two reactions resulted from the different methylating reagents, (^{i}PrO)$_3$TiMe or Ti(Me)$_4$, prepared *in situ*

(Scheme **2.20**). One possible explanation is that **290** is formed by ligand exchange of the carboxylic acid of **286** with (^{i}PrO)$_3$TiMe followed by *intra*molecular delivery of the methyl nucleophile in **290**, providing **288**. Alternatively, we hypothesize that **287** results from intermolecular addition of Ti(Me)$_4$, without the assistance of chelation.

Scheme 2.20 *Stereochemical rationale for divergent methylation of 5-hydroxybutenolides.*



To complete the synthesis, **287** was reduced under standard hydrogenation conditions. Decarboxylative Giese addition to methyl vinyl ketone under the photoredox catalysis conditions we had previously investigated provided (+)-rumphellaone A (**142**) in good yield, completing the synthesis in 9 steps from commercially available material. Epimeric acid **288** could be analogously elaborated to (+)-*epi*-C8-rumphellaone A (**289**).

2.6 CONCLUDING REMARKS

Through a strategy for difunctionalization, we have demonstrated that 8-aminoquinolinamide **53** can serve as a valuable building block for the synthesis of

enantioenriched cyclobutanes. We have prepared a number of heteroarylated and arylated cyclobutane products and demonstrated that we could derivatize them through subsequent C–C bond activation-based cross-coupling reactions. We further illustrated the utility of this method in a 9-step synthesis of (+)-rumphellaone A (**142**). We anticipate that this general strategy could enable the expedient synthesis of additional natural products and other bioactive molecules.

2.7 EXPERIMENTAL SECTION

2.7.1 Materials and Methods

General Procedures. Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Methylene chloride (CH_2Cl_2), diethyl ether (Et_2O), tetrahydrofuran (THF), 1,4-dioxane, *tert*-butyl methyl ether (TBME), and toluene (PhMe) were dried by passing through activated alumina columns. Methanol (MeOH) was distilled over calcium hydride. Acetonitrile (MeCN), *tert*-butanol (*t*-BuOH), anhydrous *N,N*-dimethylformamide (DMF), anhydrous *N,N*-dimethylacetamide (DMA), chloroform ($CHCl_3$), and absolute ethanol (EtOH) were used as received from Fisher Scientific. Methyl vinyl ketone was dried over K_2CO_3 and $CaCl_2$ and then distilled immediately prior to use. K_2HPO_4 was flame-dried under vacuum and dried at 0.200 Torr overnight and stored in a dessicator. Aryl iodides were purchased from Sigma-Aldrich or Combi-Blocks or prepared according to literature procedures. $NiBr_2$•dme and $NiCl_2$•dme were purchased from Strem and stored in a N_2-filled glovebox. Zinc dust and $Pd(OAc)_2$ were purchased from Strem and stored in a dessicator. $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ was purchased from Oakwood chemicals and used as received. $Pd(PPh_3)_4$ and Cs_2CO_3 were

purchased from Sigma-Aldrich and stored in a N_2-filled glovebox. All other commercially obtained reagents were purchased from Sigma-Aldrich and used as received unless specifically indicated. Photochemical reactions were conducted using either Kessil A160WE blue LED lamps positioned 3–6 cm from the reactions using a computer fan to keep the reactions at ambient temperature, or 12W blue LED strips lining a beaker wrapped in aluminum foil . Yields of arylation reactions reported are an average of two runs. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm). Silica gel and basic alumina column chromatography was performed as described by Still et al.[63] using silica gel (particle size 0.032–0.063) purchased from Silicycle and aluminum oxide (activated, basic, Brockmann I, 58 Å pore size, powder) purchased from Sigma-Aldrich. ^{1}H and ^{13}C NMR were recorded on a Varian Inova 500 (at 500 MHz and 125 MHz respectively) or a Bruker Avance III HD with Prodigy cyroprobe (at 400 MHz and 101 MHz respectively). ^{19}F NMR spectra were recorded on a Varian Inova 400 (at 376 MHz). NMR data is reported relative to internal chloroform (^{1}H, $\delta = 7.26$, ^{13}C, $\delta = 77.2$) or to internal methanol (^{1}H, $\delta = 3.31$, ^{13}C, $\delta = 49.0$) and $PhCF_3$ (^{19}F, $\delta = -63.7$). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using either an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode.

Specific optical rotations were recorded on a Jasco P-2000 polarimeter using a 100 mm cell.

2.7.2 Preparative Procedures and Spectroscopic Data

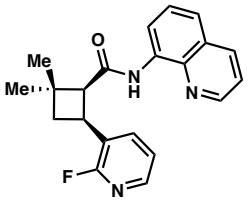
2.7.2.1 C_{sp^3}–H Arylation

General Procedure:

On the bench-top, a 2-dram vial equipped with a stir bar was charged with $Pd(OAc)_2$ (15 mol %, 0.03 mmol), Ag_2CO_3 (1 equiv, 0.2 mmol), cyclobutamide (**4**) (1 equiv, 0.2 mmol), and aryl iodide (2 equiv, 0.4 mmol). TBME (0.2 M, 1 mL) was added to the vial, then the vial was sealed with a Teflon cap and electrical tape and submerged in an oil bath at 90 °C. After approximately 5 minutes for aryl iodide substrates and 30 minutes for heteroaryl iodide substrates, the olive-green mixture became black. The reaction mixture was stirred at 90 °C additional 16 hours, at which point the vial is allowed to cool to room temperature over 15 minutes. The black reaction mixture was diluted with CH_2Cl_2 and filtered over a pad of 20 grams of tightly packed celite. The celite plug was eluted with an additional 100 mL of CH_2Cl_2. Following this, the resultant orange solution was concentrated *in vacuo* and subsequently purified by silica gel column chromatography to give the arylated cyclobutane products. (Note: some substrates required purification with basic alumina as the stationary phase).

Characterization Data for Arylation Products:

195



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 2-fluoro-3-iodopyridine (2 equiv, 89.2 mg, 0.4 mmol). The crude residue was purified by column chromatography using silica gel basified with 4 mL of aqueous ammonium hydroxide (10% EtOAc/2% Et_3N/88% hexanes → 15% EtOAc/2% Et_3N/83% hexanes → 20% EtOAc/2% Et_3N/78% hexanes → 35% EtOAc/2% Et_3N/63% hexanes) to give a white foam.

Run 1: (56.1 mg, 80%), Run 2: (56.4 mg, 81%)

$\mathbf{R_f}$ = 0.22 (silica gel, 20% EtOAc/Hex, UV, p-Anisaldehyde).

$\mathbf{[\alpha]_D^{25}}$ = +60.8° (c = 0.415, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.66 (s, 1H), 8.77 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.54 (dd, *J* = 7.0, 2.1 Hz, 1H), 8.09 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.96 (ddt, *J* = 4.9, 2.0, 1.0 Hz, 1H), 7.72 (ddq, *J* = 9.9, 7.5, 1.2, 0.7 Hz, 1H), 7.45 – 7.34 (m, 3H), 7.15 (ddd, *J* = 7.1, 4.9, 1.9 Hz, 1H), 3.99 (dtd, *J* = 11.0, 8.6, 1.1 Hz, 1H), 3.44 (ddt, *J* = 8.4, 2.5, 1.3 Hz, 1H), 2.76 (t, *J* = 10.7 Hz, 1H), 2.11 (ddd, *J* = 10.4, 8.4, 3.0 Hz, 1H), 1.53 (s, 3H), 1.19 (s, 3H).

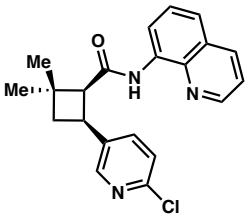
^{13}C NMR (101 MHz, $CDCl_3$): δ 170.2, 161.5 (d, J_{C-F} = 237 Hz), 148.2, 144.6 (d, J_{C-F} = 14.7 Hz), 139.3 (d, J_{C-F} = 6.1 Hz), 138.4, 136.3, 134.4, 127.9, 127.3, 124.2 (d, J_{C-F} = 31.2 Hz), 121.6, 121.4, 121.3 (d, J_{C-F} = 4.0 Hz), 116.4, 57.0, 36.4 (d, J_{C-F} = 14.8 Hz), 30.8, 30.7, 29.8, 25.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ -71.52 (d, *J* = 10.1 Hz).

FTIR (NaCl, thin film, cm^{-1}): 3355, 3058, 2954, 2930, 2866, 1682, 1605, 1577, 1524, 1486, 1431, 1388, 1372, 1324, 1261, 1240, 1162, 1132, 1112, 826, 793, 758.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{21}H_{21}FN_3O$ $[M+H]^+$: 350.1663; found: 350.1659.

196



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 5-iodo-2-chloropyridine (2 equiv, 95.8 mg, 0.4 mmol). The crude residue was purified by column chromatography using basic alumina as the stationary phase (0 → 1% MeOH/CH_2Cl_2) to give a colorless foam.

Run 1: (50.6 mg, 69%), Run 2: (49.7 mg, 68%)

R_f = 0.24 (silica gel, 40% EtOAc/Hex, UV).

$[\alpha]_D^{25}$ = +81.1° (c = 4.3, $CHCl_3$).

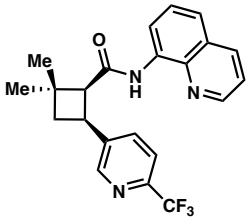
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.64 (s, 1H), 8.76 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.58 (dd, *J* = 6.8, 2.2 Hz, 1H), 8.22 (dt, *J* = 2.6, 0.8 Hz, 1H), 8.11 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1H), 7.46 – 7.38 (m, 3H), 7.17 (d, *J* = 8.2 Hz, 1H), 3.96 (q, *J* = 11.0, 8.5 Hz, 1H), 3.38 (ddd, *J* = 8.5, 3.0, 0.8 Hz, 1H), 2.76 (t, *J* = 10.7 Hz, 1H), 2.15 (ddd, *J* = 10.4, 8.5, 3.0 Hz, 1H), 1.52 (s, 3H), 1.22 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.8, 148.8, 148.5, 148.1, 138.3, 137.7, 136.5, 136.3, 134.2, 127.9, 127.4, 123.5, 121.7, 121.6, 116.5, 57.4, 37.4, 36.3, 33.3, 29.8, 29.8, 25.0.

FTIR (NaCl, thin film, cm^{-1}): 3350, 2954, 1682, 1524, 1485, 1460, 1424, 1386, 1324, 1260, 1162, 1133, 1104, 826, 792, 755, 666.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{21}H_{21}ClN_3O$ $[M+H]^+$: 366.1368; found: 366.1370.

197



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 5-iodo-2-trifluoromethylpyridine (2 equiv, 95.8 mg, 0.4 mmol). The crude residue was purified by column chromatography using silica gel basified with 5 mL of aqueous ammonium hydroxide (5% EtOAc/2% Et_3N/93% hexanes → 10% EtOAc/2% Et_3N/88% hexanes → 15% EtOAc/2% Et_3N/83% hexanes → 20% EtOAc/2% Et_3N/78% hexanes) to give a pale, yellow foam.

Run 1: (71.6 mg, 90%), Run 2: (68.2 mg, 85%)

R_f = 0.19 (silica gel, 20% EtOAc/Hex, UV).

$[\alpha]_D^{25}$ = +67.7° (c = 4.2, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.61 (s, 1H), 8.69 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.52 – 8.41 (m, 2H), 8.04 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.70 – 7.62 (m, 1H), 7.46 (dd, *J* = 8.1, 0.7 Hz, 1H), 7.41 – 7.28 (m, 3H), 3.95 (q, *J* = 11.0, 8.5 Hz, 1H), 3.37 (ddd, *J* = 8.4, 2.9, 0.9 Hz, 1H), 2.73 (t, *J* = 10.7 Hz, 1H), 2.12 (ddd, *J* = 10.4, 8.5, 3.0 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.7, 148.8, 148.2, 145.5 (q, J_{C-F} = 35 Hz), 141.2, 138.3, 136.5, 135.7, 134.1, 128.0, 127.4, 123.2, 121.7, 120.5, 119.9, 119.9, 119.8, 119.8, 116.5, 57.4, 37.3, 36.5, 33.7, 29.8, 25.0.

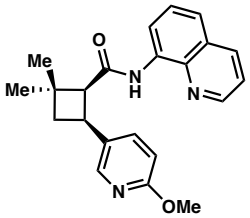
^{19}F NMR (282 MHz, $CDCl_3$): δ –68.6.

FTIR (NaCl, thin film, cm^{-1}): 3351, 2957, 1682, 1524, 1486, 1425, 1387, 1340, 1261, 1164, 1134, 1088, 1030, 826, 792, 756, 667.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{22}H_{21}F_3N_3O$ $[M+H]^+$: 400.1631; found: 400.1621.

198

Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 5-iodo-2-methoxypyridine (2 equiv, 94.0 mg, 0.4 mmol). The crude residue was purified by column chromatography using silica gel basified with 4 mL of aqueous ammonium hydroxide (10% EtOAc/2% Et_3N/88% hexanes → 15% EtOAc/2% Et_3N/83% hexanes → 20% EtOAc/2% Et_3N/78% hexanes → 30% EtOAc/2% Et_3N/68% hexanes) to give a white solid.



Run 1: (34.9 mg, 48%), Run 2: (36.1 mg, 50%)

R_f = 0.14 (silica gel, 20% EtOAc/Hex, UV, *p*-anisaldehyde).

$[\alpha]_D^{25}$ = +61.1° (c = 0.415, $CHCl_3$).

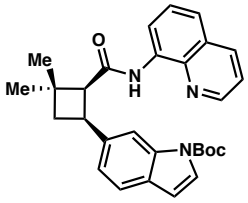
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.60 (s, 1H), 8.76 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.62 (dd, *J* = 5.3, 3.7 Hz, 1H), 8.12 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.01 (dt, *J* = 2.5, 0.9 Hz, 1H), 7.54 (ddd, *J* = 8.6, 2.5, 0.7 Hz, 1H), 7.46 – 7.39 (m, 3H), 6.61 (dd, *J* = 8.6, 0.7 Hz, 1H), 3.96 (qd, *J* = 11.0, 8.6, 1.1 Hz, 1H), 3.84 (s, 3H), 3.33 (ddd, *J* = 8.7, 2.9, 0.8 Hz, 1H), 2.76 (t, *J* = 10.8 Hz, 1H), 2.14 (ddd, *J* = 10.4, 8.6, 3.0 Hz, 1H), 1.51 (s, 3H), 1.23 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.3, 162.7, 148.1, 145.3, 138.4, 138.0, 136.4, 134.5, 129.6, 128.0, 127.5, 121.6, 121.4, 116.5, 110.1, 57.6, 53.4, 37.7, 36.1, 33.4, 30.1, 25.1.

FTIR (NaCl, thin film, cm^{-1}): 3352, 2922, 2850, 2351, 1682, 1606, 1574, 1523, 1494, 1486, 1424, 1385, 1324, 1285, 1259, 1160, 1132, 1032, 826, 792, 756.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{22}H_{24}N_3O_2$ $[M+H]^+$: 362.1863; found: 362.1856

199



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 6-iodo-N-Boc-indole (2 equiv, 137 mg, 0.4 mmol). The crude residue was purified by column chromatography (10% → 15% EtOAc/hexanes) to give a colorless foam.

Run 1: (56.1 mg, 60%), Run 2: (62.8 mg, 67%)

R_f = 0.36 (silica gel, 20% EtOAc/Hex, UV, *p*-anisaldehyde).

$[\alpha]_D^{25}$ = +114.7° (c = 5.7, $CHCl_3$).

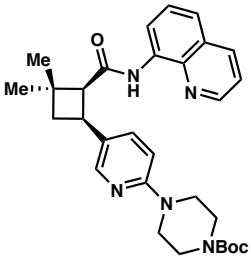
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (s, 1H), 8.65 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.60 (dd, *J* = 6.3, 2.8 Hz, 1H), 8.08 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.03 (s, 1H), 7.47 (d, *J* = 3.7 Hz, 1H), 7.43 – 7.32 (m, 4H), 7.09 (dt, *J* = 8.1, 1.1 Hz, 1H), 6.44 (dd, *J* = 3.7, 0.8 Hz, 1H), 4.19 (dt, *J* = 10.9, 8.6 Hz, 1H), 3.44 (dd, *J* = 8.7, 2.9 Hz, 1H), 2.85 (t, *J* = 10.7 Hz, 1H), 2.25 (ddd, *J* = 10.3, 8.6, 3.0 Hz, 1H), 1.61 (s, 9H), 1.54 (s, 3H), 1.23 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.6, 150.0, 147.9, 138.6, 138.4, 136.3, 135.5, 134.7, 128.7, 127.9, 127.5, 125.3, 121.6, 121.5, 121.1, 120.5, 116.5, 113.4, 107.4, 83.4, 57.9, 38.2, 36.4, 35.9, 30.2, 28.3, 25.3.

FTIR (NaCl, thin film, cm^{-1}): 3358, 3008, 2954, 2929, 2866, 1730, 1686, 1618, 1578, 1523, 1485, 1424, 1386, 1370, 1338, 1253, 1214, 1151, 117, 1077, 1022, 826, 816, 756.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{29}H_{32}N_3O_3$ $[M+H]^+$: 470.2438; found: 470.2449.

200



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 4-(5-iodopyrin-2-yl)piperazine-1-carboxylic acid *tert*-butyl ester (2 equiv, 156 mg, 0.4 mmol). The crude residue was purified by column chromatography using silica gel basified with 5 mL of aqueous ammonium hydroxide (20% EtOAc/2% Et_3N/78% hexanes → 30% EtOAc/2% Et_3N/68% hexanes → 40% EtOAc/2% Et_3N/58% hexanes) to give a pale, yellow foam.

Run 1: (79.9 mg, 77%), Run 2: (84.6 mg, 82%)

R_f = 0.27 (silica gel, 40% EtOAc/Hex, UV, *p*-anisaldehyde). $[\alpha]_D^{25}$ = +69.2° (c = 5.1, $CHCl_3$).

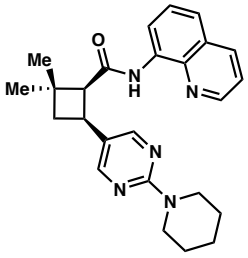
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.58 (s, 1H), 8.74 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.62 (p, *J* = 4.4 Hz, 1H), 8.10 (dd, *J* = 8.2, 1.7 Hz, 1H), 8.06 (dt, *J* = 2.5, 0.8 Hz, 1H), 7.50 (ddd, *J* = 8.7, 2.5, 0.7 Hz, 1H), 7.46 – 7.37 (m, 3H), 6.53 (dd, *J* = 8.8, 0.8 Hz, 1H), 3.93 (dt, *J* = 11.0, 8.6 Hz, 1H), 3.45 (dd, *J* = 6.6, 3.5 Hz, 4H), 3.39 (dd, *J* = 6.3, 3.6 Hz, 4H), 3.30 (dd, *J* = 8.4, 2.9 Hz, 1H), 2.74 (t, *J* = 10.8 Hz, 1H), 2.10 (ddd, *J* = 10.4, 8.5, 2.9 Hz, 1H), 1.51 (s, 4H), 1.47 (s, 9H), 1.24 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.4, 158.0, 154.9, 148.0, 146.8, 138.4, 137.0, 136.4, 134.5, 127.9, 127.4, 126.4, 121.6, 121.2, 116.4, 106.9, 79.9, 57.7, 45.5, 37.6, 35.9, 33.5, 30.1, 28.5, 25.1.

FTIR (NaCl, thin film, cm^{-1}): 3357, 3007, 2973, 2928, 2864, 2360, 1686, 1605, 1560, 1524, 1486, 1424, 1391, 1324, 1241, 1166, 1129, 1084, 1000, 934, 864, 826, 792, 756, 686, 666.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{30}H_{38}N_5O_3$ $[M+H]^+$: 516.2969; found: 516.2955.

201



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 5-iodo-2-(1-piperidinyl)pyrimidine (2 equiv, 116 mg, 0.4 mmol). The crude residue was purified by column chromatography using silica gel basified with 5 mL of aqueous ammonium hydroxide (10% EtOAc/2% Et_3N/88% hexanes → 20% EtOAc/2% Et_3N/78% hexanes → 30% EtOAc/2% Et_3N/68% hexanes) to give a pale yellow foam.

Run 1: (63.0 mg, 76%), Run 2: (60.6 mg, 73%)

R_f = 0.44 (silica gel, 40% EtOAc/Hex, UV).

$[\alpha]_D^{25}$ = +83.3° (c = 3.1, $CHCl_3$).

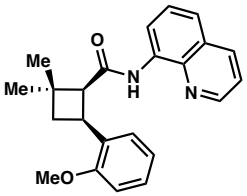
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.59 (s, 1H), 8.74 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.67 (dd, *J* = 6.6, 2.4 Hz, 1H), 8.25 (s, 2H), 8.10 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.47 – 7.42 (m, 2H), 7.40 (dd, *J* = 8.2, 4.2 Hz, 2H), 3.81 (dt, *J* = 11.0, 8.6 Hz, 1H), 3.67 (dd, *J* = 6.2, 4.9 Hz, 4H), 3.27 (dd, *J* = 8.6, 2.9 Hz, 1H), 2.74 (t, *J* = 10.8 Hz, 1H), 2.07 (ddd, *J* = 10.6, 8.5, 2.9 Hz, 1H), 1.60 (p, *J* = 5.5 Hz, 2H), 1.52 (qd, *J* = 5.6, 5.1, 2.3 Hz, 4H), 1.49 (s, 3H), 1.24 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.2, 160.8, 157.1, 148.1, 138.4, 136.4, 134.5, 127.9, 127.5, 121.6, 121.3, 120.8, 116.5, 57.4, 45.0, 37.3, 36.1, 31.8, 30.0, 25.8, 25.1, 25.0.

FTIR (NaCl, thin film, cm^{-1}): 3355, 2031, 2853, 1682, 1603, 1524, 1485, 1462, 1447, 1366, 1324, 1274, 1256, 1160, 1025, 946, 826, 792, 754.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{25}H_{30}N_5O$ $[M+H]^+$: 416.2445; found: 416.2440.

202



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 2-iodoanisole (2 equiv, 93.6 mg, 0.4 mmol). The crude residue was purified by column chromatography (10 → 15 → 20% EtOAc/Hexanes) to give a colorless foam.

Run 1: (54.4 mg, 75%), Run 2: (61.2 mg, 84%)

R_f = 0.48 (silica gel, 30% EtOAc/Hex, UV, *p*-anisaldehyde).

$[\alpha]_D^{25}$ = +84.8° (c = 3.3, $CHCl_3$).

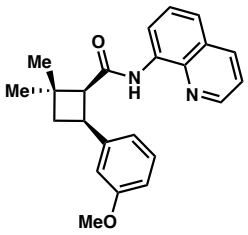
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.57 (s, 1H), 8.77 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.60 (dd, *J* = 4.9, 4.2 Hz, 1H), 8.10 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.44 – 7.36 (m, 3H), 7.24 (dt, *J* = 7.4, 1.5 Hz, 1H), 7.09 (dddd, *J* = 8.2, 7.4, 1.8, 0.8 Hz, 1H), 6.96 (tdd, *J* = 7.5, 1.1, 0.4 Hz, 1H), 6.61 (dd, *J* = 8.1, 1.1 Hz, 1H), 4.09 – 3.95 (m, 1H), 3.62 (s, 3H), 3.46 (ddd, *J* = 8.6, 2.9, 0.8 Hz, 1H), 2.74 (t, *J* = 10.8 Hz, 1H), 2.13 (ddd, *J* = 10.4, 8.4, 2.9 Hz, 1H), 1.53 (s, 3H), 1.22 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.13, 157.19, 147.90, 138.41, 136.31, 134.88, 130.18, 127.92, 127.66, 127.54, 127.00, 121.45, 120.75, 120.43, 116.27, 109.43, 58.05, 55.05, 37.10, 35.89, 32.81, 30.33, 25.14.

FTIR (NaCl, thin film, cm^{-1}): 3366, 2952, 5927, 2863, 2361, 1685, 1523, 1485, 1464, 1424, 1324, 1241, 1161, 1132, 1161, 1029, 826, 792, 751.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{23}H_{25}N_2O_2$ $[M+H]^+$: 361.1911; found: 361.1925.

203



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 3-iodoanisole (2 equiv, 93.6 mg, 0.4 mmol). The crude residue was purified by column chromatography (10 → 15 → 20% EtOAc/Hexanes) to give a white solid.

Run 1: (59.0 mg, 82%), Run 2: (58.3 mg, 81%)

$\mathbf{R_f}$ = 0.36 (silica gel, 20% EtOAc/Hex, UV, *p*-anisaldehyde).

$\mathbf{[\alpha]_D^{25}}$ = +61.6° (c = 0.4, $CHCl_3$).

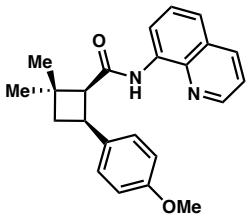
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.62 (s, 1H), 8.75 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.64 (p, *J* = 4.3 Hz, 1H), 8.11 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.45 – 7.38 (m, 3H), 7.13 (t, *J* = 7.9 Hz, 1H), 6.82 (ddt, *J* = 7.6, 1.8, 1.0 Hz, 1H), 6.77 (dt, *J* = 2.7, 1.3 Hz, 1H), 6.63 (ddt, *J* = 8.2, 2.6, 0.9 Hz, 1H), 4.03 (dtd, *J* = 11.0, 8.6, 1.1 Hz, 1H), 3.67 (s, 3H), 3.39 (ddd, *J* = 8.7, 2.9, 0.8 Hz, 1H), 2.76 (t, *J* = 10.7 Hz, 1H), 2.16 (ddd, *J* = 10.4, 8.5, 3.0 Hz, 1H), 1.51 (s, 3H), 1.22 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.5, 159.5, 148.0, 143.7, 138.4, 136.4, 134.6, 129.1, 127.9, 127.5, 121.5, 121.2, 119.1, 116.5, 112.3, 111.3, 57.7, 55.1, 37.8, 36.0, 35.8, 30.2, 25.1.

FTIR (NaCl, thin film, cm^{-1}): 3357, 2952, 2925, 1684, 1600, 1582, 1521, 1485, 1424, 1386, 1323, 1259, 1160, 1049, 878, 826, 790, 756, 694.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{23}H_{25}N_2O_2$ $[M+H]^+$: 361.1911; found: 361.1915.

204



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 4-iodoanisole (2 equiv, 93.6 mg, 0.4 mmol). The crude residue was purified by column chromatography (10 → 15% EtOAc/Hexanes) to give a white, amorphous solid.

Run 1: (47.7 mg, 66%), Run 2: (51.2 mg, 71%)

R_f = 0.23 (silica gel, 20% EtOAc/Hex, UV, *p*-anisaldehyde).

$[\alpha]_D^{25}$ = +59.8° (c = 1.3, $CHCl_3$).

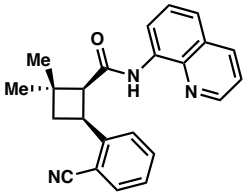
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.58 (s, 1H), 8.75 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.63 (p, *J* = 4.4 Hz, 1H), 8.10 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.45 – 7.38 (m, 3H), 7.20 – 7.13 (m, 2H), 6.80 – 6.73 (m, 2H), 4.00 (q, *J* = 11.1, 8.6 Hz, 1H), 3.70 (s, 3H), 3.34 (ddd, *J* = 8.7, 3.0, 0.8 Hz, 1H), 2.75 (t, *J* = 10.8 Hz, 1H), 2.13 (ddd, *J* = 10.4, 8.6, 3.0 Hz, 1H), 1.51 (s, 3H), 1.23 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.6, 157.7, 148.0, 138.4, 136.4, 134.6, 133.7, 127.9, 127.5, 121.5, 121.1, 116.5, 113.6, 57.7, 55.3, 37.9, 35.7, 35.5, 30.2, 25.2.

FTIR (NaCl, thin film, cm^{-1}): 2926, 2361, 1685, 1523, 1485, 1288, 1324, 1247, 1160, 1038, 826, 772.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{23}H_{25}N_2O_2$ $[M+H]^+$: 361.1911; found: 361.1921.

205



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 2-iodobenzonitrile (2 equiv, 91.8 mg, 0.4 mmol). The crude residue was purified by column chromatography (10 → 15% EtOAc/Hexanes) to give a pale, yellow foam.

Run 1: (57.6 mg, 81%), Run 2: (64.7 mg, 91%)

$\mathbf{R}_f$ = 0.55 (silica gel, 30% EtOAc/Hex, UV, *p*-anisaldehyde).

$\mathbf{[\alpha]_D^{25}}$ = –24.4° (c = 5.4, $CHCl_3$).

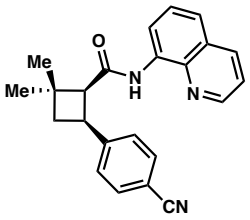
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.76 (s, 1H), 8.81 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.53 (dd, *J* = 7.4, 1.7 Hz, 1H), 8.10 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 (td, *J* = 8.0, 7.6, 1.2 Hz, 1H), 7.51 – 7.35 (m, 5H), 7.21 (tdd, *J* = 7.6, 1.3, 0.7 Hz, 1H), 4.21 (dt, *J* = 11.1, 8.3, 7.8 Hz, 1H), 3.74 (ddd, *J* = 8.3, 3.0, 0.8 Hz, 1H), 2.87 (t, *J* = 10.7 Hz, 1H), 2.16 (ddd, *J* = 10.4, 8.3, 3.1 Hz, 1H), 1.57 (s, 3H), 1.20 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.0, 148.3, 146.9, 138.5, 136.3, 134.5, 132.6, 128.1, 127.9, 127.2, 126.3, 121.7, 121.4, 118.8, 116.3, 110.6, 57.7, 36.6, 36.1, 35.2, 29.8, 25.1.

FTIR (NaCl, thin film, cm^{-1}): 3353, 2954, 2361, 2222, 1683, 1523, 1485, 1424, 1388, 1323, 1260, 1161, 826, 791, 755, 668.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{23}H_{21}N_3O$ $[M+H]^+$: 356.1757; found: 356.1773.

206



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 4-iodobenzonitrile (2 equiv, 91.8 mg, 0.4 mmol). The crude residue was purified by column chromatography (10 → 15 → 20 →25 % EtOAc/Hexanes) to give a pale, yellow foam.

Run 1: (50.5 mg, 71%), Run 2: (53.3 mg, 75%)

$\mathbf{R}_f$ = 0.32 (silica gel, 30% EtOAc/Hex, UV, *p*-anisaldehyde).

$\mathbf{[\alpha]_D^{25}}$ = +102.7° (c = 5.1, $CHCl_3$).

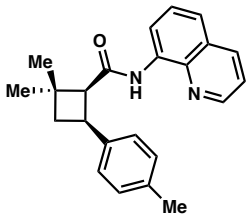
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.66 (s, 1H), 8.79 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.56 (dd, *J* = 7.2, 1.8 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.50 (dt, *J* = 8.3, 1.8 Hz, 2H), 7.49 – 7.37 (m, 3H), 7.33 – 7.24 (m, 2H), 4.02 (dt, *J* = 10.8, 8.3 Hz, 1H), 3.43 (ddd, *J* = 8.5, 3.0, 0.8 Hz, 1H), 2.77 (t, *J* = 10.7 Hz, 1H), 2.18 (ddd, *J* = 10.4, 8.5, 3.0 Hz, 1H), 1.53 (s, 3H), 1.20 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 148.4, 148.2, 138.3, 136.5, 134.2, 131.9, 128.0, 127.5, 127.3, 121.7, 121.6, 119.5, 116.5, 109.3, 57.7, 37.5, 36.1, 36.0, 29.9, 25.0.

FTIR (NaCl, thin film, cm^{-1}): 3353, 2954, 2930, 2361, 2226, 1684, 1608, 1524, 1486, 1424, 1288, 1323, 1161, 826, 792, 755, 668.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{23}H_{22}N_3O$ $[M+H]^+$: 356.1757; found: 356.1752.

207



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 4-iodotoluene (2 equiv, 87.2 mg, 0.4 mmol). The crude residue was purified by column chromatography (10 → 15 → 20% EtOAc/Hexanes) to give a white, amorphous solid.

Run 1: (54.1 mg, 79%), Run 2: (55.9 mg, 81%)

R_f = 0.29 (silica gel, 20% EtOAc/Hex, UV, *p*-anisaldehyde).

$[\alpha]_D^{25}$ = +54.2° (c = 2.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.60 (s, 1H), 8.76 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.65 (h, *J* = 4.2 Hz, 1H), 8.11 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.50 – 7.36 (m, 3H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.02 (d, *J* = 7.4 Hz, 2H), 4.01 (td, *J* = 10.8, 8.1 Hz, 1H), 3.37 (ddd, *J* = 8.7, 2.9, 0.8 Hz,

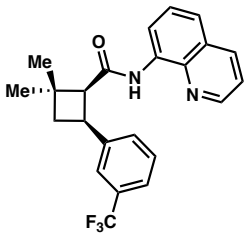
1H), 2.76 (t, *J* = 10.8 Hz, 1H), 2.24 (s, 3H), 2.14 (ddd, *J* = 10.4, 8.6, 2.9 Hz, 1H), 1.51 (s, 3H), 1.22 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.6, 148.0, 138.7, 138.4, 136.4, 135.0, 134.7, 128.9, 127.9, 127.5, 126.7, 121.5, 121.1, 116.5, 57.7, 37.8, 35.8, 35.7, 30.2, 25.2, 21.2.

FTIR (NaCl, thin film, cm^{-1}): 3360, 2924, 2359, 1686, 1522 1485, 1424, 1386, 1324, 1160, 826, 792.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{23}H_{25}N_2O$ $[M+H]^+$: 345.1961; found: 345.1971.

208



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 3-iodotrifluorotoluene (2 equiv, 109.1 mg, 0.4 mmol). The crude residue was purified by column chromatography (10% EtOAc/Hexanes) to give a colorless oil.

Run 1: (67.7 mg, 85%), Run 2: (62.9 mg, 79%)

R_f = 0.23 (silica gel, 20% EtOAc/Hex, UV, *p*-anisaldehyde).

$[\alpha]_D^{25}$ = +47.3° (c = 3.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.63 (s, 1H), 8.77 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.57 (dd, *J* = 6.6, 2.4 Hz, 1H), 8.12 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.50 – 7.36 (m, 5H), 7.39 – 7.26 (m, 2H), 4.05 (dt, *J* = 11.0, 8.7 Hz, 1H), 3.42 (ddd, *J* = 8.6, 3.0, 0.8 Hz, 1H), 2.80 (t, *J* = 10.8 Hz, 1H), 2.20 (ddd, *J* = 10.4, 8.5, 3.0 Hz, 1H), 1.53 (s, 3H), 1.23 (s, 3H).

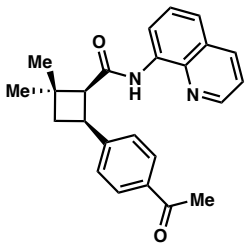
^{13}C NMR (101 MHz, $CDCl_3$): δ 170.2, 148.2, 143.2, 138.5, 136.6, 134.5, 130.4 (q, J_{C-F} = 32 Hz), 130.3, 128.5, 128.1, 127.6, 125.9, 123.7 (q, J_{C-F} = 3.7 Hz), 123.2, 122.8 (q, J_{C-F} = 3.8 Hz), 121.7, 121.5, 116.6, 57.8, 37.8, 36.1, 36.0, 30.2, 30.0, 25.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ -63.50.

FTIR (NaCl, thin film, cm^{-1}): 3355, 2931, 2360, 1684, 1523, 1486, 1425, 1388, 1324, 1162, 1122, 1072, 901, 826, 793, 756, 701, 659.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{23}H_{22}F_3N_2O$ $[M+H]^+$: 399.1679; found: 399.1679.

209



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 4-iodoacetophenone (2 equiv, 98.7 mg, 0.4 mmol). The crude residue was purified by column chromatography (20% EtOAc/Hexanes) to give a white, amorphous solid.

Run 1: (57.3 mg, 77%), Run 2: (56.6 mg, 76%)

R_f = 0.41 (silica gel, 40% EtOAc/Hex, UV, *p*-anisaldehyde).

$[\alpha]_D^{25}$ = +95.0° (c = 3.0, $CHCl_3$).

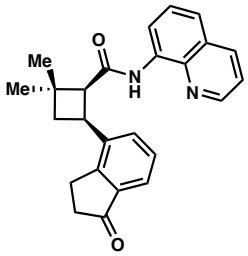
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (s, 1H), 8.85 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.66 (dd, *J* = 7.1, 1.8 Hz, 1H), 8.20 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.94 – 7.87 (m, 2H), 7.51 (dd, *J* = 8.5, 4.1 Hz, 2H), 7.48 (q, *J* = 9.2, 8.2, 8.2 Hz, 1H), 7.39 – 7.33 (m, 2H), 4.12 (td, *J* = 11.3, 9.7, 8.4 Hz, 1H), 3.51 (ddd, *J* = 8.6, 2.9, 0.8 Hz, 1H), 2.88 (t, *J* = 10.7 Hz, 1H), 2.58 (s, 3H), 2.26 (ddd, *J* = 10.3, 8.5, 3.0 Hz, 1H), 1.61 (s, 3H), 1.29 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.1, 170.1, 148.5, 148.1, 138.4, 136.5, 134.8, 134.4, 128.4, 128.0, 127.5, 126.7, 121.6, 121.4, 116.5, 57.8, 37.7, 36.1, 36.0, 30.0, 26.7, 25.1.

FTIR (NaCl, thin film, cm^{-1}): 3354, 2954, 2928, 2866, 1678, 1606, 1523, 1485, 1424, 1387, 1323, 1267, 1161, 956, 826, 792, 754, 657.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{24}H_{25}N_2O_2$ $[M+H]^+$: 373.1911; found: 373.1900.

210



Prepared from cyclobutamide **53** (1 equiv, 50.8 mg, 0.2 mmol) and 4-iodo-1-indanone (2 equiv, 103.5 mg, 0.4 mmol). The crude residue was purified by column chromatography (30% EtOAc/Hexanes) to give a pale, yellow foam.

Run 1: (43.4 mg, 56%), Run 2: (39.7 mg, 52%)

R_f = 0.32 (silica gel, 40% EtOAc/Hex, UV, *p*-anisaldehyde).

$[\alpha]_D^{25}$ = +2.0° (c = 5.0, $CHCl_3$).

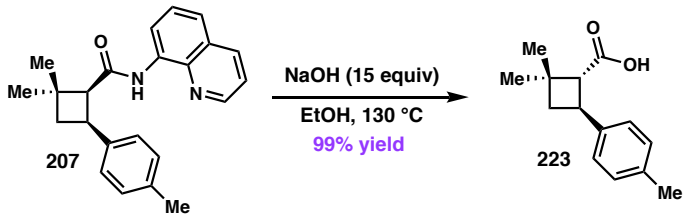
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.57 (s, 1H), 8.74 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.54 (dd, *J* = 7.1, 2.0 Hz, 1H), 8.10 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 (ddt, *J* = 17.3, 7.6, 1.1 Hz, 2H), 7.46 – 7.33 (m, 4H), 4.07 (dt, *J* = 11.2, 8.4 Hz, 1H), 3.47 (ddd, *J* = 8.4, 3.0, 0.9 Hz, 1H), 3.10 (ddd, *J* = 17.1, 7.8, 3.8 Hz, 1H), 2.98 (ddd, *J* = 17.1, 7.6, 3.9 Hz, 1H), 2.92 (t, *J* = 10.8 Hz, 1H), 2.57 (dddd, *J* = 32.0, 19.4, 7.8, 3.7 Hz, 2H), 2.18 (ddd, *J* = 10.5, 8.4, 3.1 Hz, 1H), 1.58 (s, 3H), 1.23 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.3, 170.1, 153.3, 148.1, 139.5, 138.3, 136.8, 136.5, 134.2, 132.9, 127.9, 127.5, 127.4, 121.6, 121.5, 121.4, 116.6, 57.2, 37.0, 36.5, 36.2, 34.1, 30.1, 25.2, 25.1.

FTIR (NaCl, thin film, cm^{-1}): 3353, 3012, 2954, 2927, 2866, 2359, 1709, 1587, 1523, 1485, 1425, 1386, 1324, 1265, 1162, 1055, 827, 790, 754, 666.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{25}H_{25}N_2O_2$ $[M+H]^+$: 385.1911; found: 385.1921.

2.7.2.2 Cyclobutane Derivatization



A 48 mL pressure flask was charged with *cis*-cyclobutamide **207** (693 mg, 2.01 mmol, 1.00 equiv), sodium hydroxide (1.21 g, 30.2 mmol, 15 equiv), and absolute ethanol (8.5 mL, 0.24 M). The flask was sealed and placed in a pre-heated oil bath (130 ºC) and stirred for 18 h. The reaction mixture was cooled to room temperature, and the solvent was removed *in vacuo*. The crude residue was diluted with 1 M aq HCl (38 mL) and EtOAc (38 mL). The organic and aqueous layers were separated, and the organic layer was washed with 1 M HCl (2 x 38 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reddish solid was purified by silica gel flash chromatography (15 → 20% EtOAc/hexanes) to afford **223** as an off-white solid (443 mg, 99% yield).

R_f = 0.31 (silica gel, 20% EtOAc/Hexanes, *p*-anisaldehyde)

$[\alpha]_D^{25}$ = +123.6° (c = 0.28, $CHCl_3$).

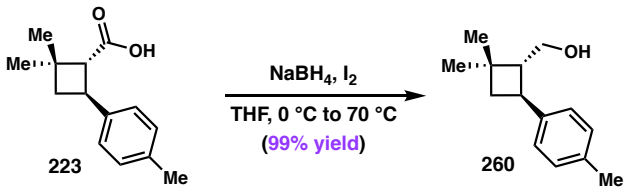
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, *J* = 1.1 Hz, 4H), 3.74 (q, *J* = 9.8 Hz, 1H), 2.91 (dd, *J* = 10.0, 0.8 Hz, 1H), 2.32 (s, 3H), 2.11 (ddd, *J* = 10.9, 8.9, 0.9 Hz, 1H), 1.95 (t, *J* = 10.5 Hz, 1H), 1.29 (s, 3H), 1.25 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.8, 140.7, 135.9, 129.2, 126.6, 55.2, 39.4, 36.6, 35.1, 30.6, 23.6, 21.2.

FTIR (NaCl, thin film, cm^{-1}): 3021, 2957, 2927, 2867, 2731, 2647,1699, 1516, 1464, 1421 1370, 1281, 1238, 1162 1118, 937, 806, 716.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{14}H_{22}NO_2$ $[M+NH_4]^+$: 236.1645; found: 236.1645.

Acid reduction to provide **260**.



A 2-dram vial containing a stir bar was charged with **223** (87 mg, 0.400 mmol, 1.00 equiv) and $NaBH_4$ (37.8 mg, 1.00 mmol, 2.5 equiv). The vial was then evacuated and backfilled with N_2 three times. THF (3.0 mL) was added and the reaction mixture was cooled to 0 °C. I_2 (121.8 mg, 0.480 mmol, 1.2 equiv) was then added as a solution in THF (1 mL) dropwise. The vial was then sealed with a Teflon-lined cap, placed in a pre-heated oil bath (70 ºC), and allowed to stir overnight. Once the reaction was complete, the reaction was cooled to room temperature and quenched with MeOH until bubbling stopped and the reaction mixture turned clear. The reaction mixture was concentrated, then treated with 20% KOH (4 mL) and allowed to stir for 5 h at room temperature. The aqueous layer was then extracted with EtOAc (6 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford **260** (82.2 mg, quant yield) as a white solid which was carried forward without further purification.

R_f = 0.38 (silica gel, 20% EtOAc/Hexanes, UV, *p*-anisaldehyde)

$[\alpha]_D^{25}$ = +57.0° (c = 0.42, $CHCl_3$).

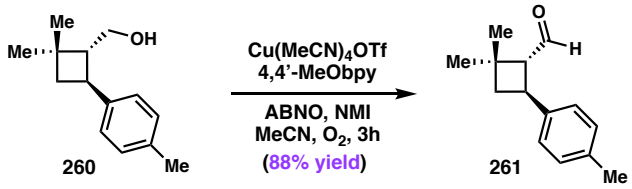
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 – 7.08 (m, 4H), 3.75 (qd, *J* = 11.0, 7.2 Hz, 2H), 3.06 (q, *J* = 9.5 Hz, 1H), 2.34 (s, 3H), 2.28 (dddd, *J* = 9.4, 8.3, 6.1, 0.7 Hz, 1H), 2.05 (ddd, *J* = 10.8, 8.7, 0.8 Hz, 1H), 1.82 (t, *J* = 10.3 Hz, 1H), 1.21 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 141.9, 135.6, 129.1, 126.7, 63.6, 53.9, 40.6, 37.6, 33.7, 31.4, 22.5, 21.1.

FTIR (NaCl, thin film, cm^{-1}): 3248, 2954, 2926, 2896, 2864, 1896, 1514, 1453, 1413, 1379, 1368, 1326, 1260, 1218, 1190, 1110, 1092, 1033, 1013, 812, 772.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{14}H_{24}NO$ $[M+NH_4]^+$: 222.1852; found: 222.1846.

Oxidation of **260** to prepare aldehyde **261**



260 (0.400 mmol, 1.00 equiv) was dissolved in 1.2 mL MeCN in a 20 mL scintillation vial. In a separate vial, $Cu(MeCN)_4OTf$ (7.5 mg, 0.02 mmol, 0.05 equiv) and 4,4'-MeObpy (4.3 mg, 0.02 mmol, 0.05 equiv)) were dissolved in 0.4 mL MeCN and allowed to stir until the solution turned an opaque blue. To this vial was added a solution of ABNO (0.6 mg, 0.004 mmol, 0.01 equiv) and *N*-methylimidazole (3.3 mg, 0.04 mmol, 0.10 equiv) in 0.4 mL MeCN. Once the catalyst solution turned green, it was added to the reaction mixuture and allowed to stir open to air. After 3 h and 6 h, additional portions of catalyst ($Cu(MeCN)_4OTf$ (7.5 mg, 0.02 mmol, 0.05 equiv), 4,4'-MeObpy (4.3 mg, 0.02 mmol, 0.05 equiv) ABNO (0.6 mg, 0.004 mmol, 0.01 equiv), and *N*-methylimidazole (3.3

mg, 0.04 mmol, 0.10 equiv) dissolved in 0.8 mL MeCN) were added. After the addition at 6 h, the reaction vessel was sealed with a rubber septum and the reaction mixture was sparged with $O_{2(g)}$ and allowed to stir under an O_2 atmosphere for an additional 15.5 h. When the reaction was judged to be done by TLC, the reaction mixture was filtered over a short silica plug, eluting with 20% EtOAc/hexanes, and the resulting solution was concentrated *in vacuo* to give **261** as a brown oil (71.1 mg, 87% yield).

R_f = 0.69 (silica gel, 20% EtOAc/Hexanes, UV, *p*-anisaldehyde)

$[\alpha]_D^{25}$ = +62.9° (c = 1.66, $CHCl_3$).

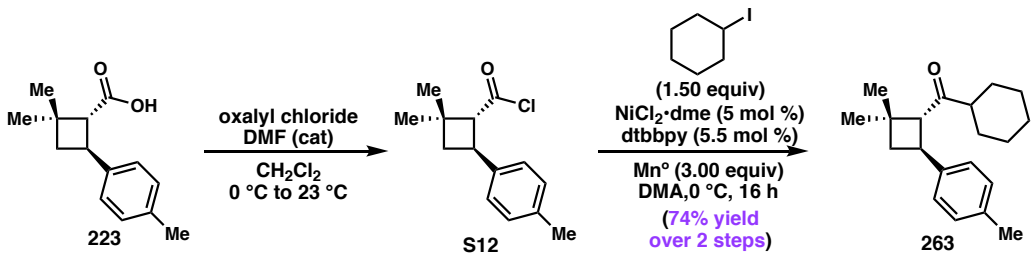
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (d, *J* = 1.6 Hz, 1H), 7.21 – 7.01 (m, 5H), 3.88 (q, *J* = 9.6 Hz, 1H), 2.97 (ddd, *J* = 9.7, 1.7, 0.9 Hz, 1H), 2.34 (s, 3H), 2.12 (ddt, *J* = 10.5, 8.9, 0.8 Hz, 1H), 2.02 (t, *J* = 10.5 Hz, 1H), 1.36 (s, 3H), 1.26 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.0, 140.8, 135.8, 129.1, 129.1, 126.5, 126.5, 62.5, 39.9, 37.5, 33.0, 31.3, 24.0, 23.6, 21.1, 21.1.

FTIR (NaCl, thin film, cm^{-1}): 3248, 2954, 2926, 2896, 2864, 1896, 1514, 1453, 1413, 1379, 1368, 1326, 1260, 1218, 1190, 1110, 1092, 1033, 1013, 812, 772.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{14}H_{22}NO$ $[M+NH_4]^+$: 220.1696; found: 220.1691.

Cross-coupling to prepare cyclohexyl ketone **263**.



A 1-dram vial containing a stir bar was charged with carboxylic acid **223** (87.3 mg, 0.400 mmol, 1 equiv). The vial was sealed with a septum vial cap and tape and was evacuated and backfilled with N_2 three times. CH_2Cl_2 (0.8 mL, 0.5 M) and 2 drops DMF were added, and the reaction mixture was cooled to 0 °C. Oxalyl chloride (0.050 mL, 0.560 mmol, 1.4 equiv) was then added dropwise. Once the addition was complete, the reaction was allowed to stir at room temperature for 1 h, at which point the solvent was removed *in vacuo* to afford acid chloride **S12** as a crude oil. **S12** was taken forward without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 – 7.06 (m, 4H), 3.79 (q, *J* = 9.7 Hz, 1H), 3.29 (dd, *J* = 9.8, 0.9 Hz, 1H), 2.33 (s, 3H), 2.11 (ddd, *J* = 10.9, 9.1, 1.0 Hz, 1H), 2.01 – 1.88 (m, 1H), 1.41 (s, 3H), 1.31 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.3, 139.2, 136.5, 129.4, 126.5, 66.1, 39.0, 37.0, 30.0, 23.2, 21.2.

A flame-dried 1-dram vial containing a 2-dram stir bar (tested before to ensure it would stir) was charged with $NiCl_2$•dme (4.4 mg, 0.020 mmol, 0.05 equiv), dtbbpy (5.9 mg, 0.022 mmol, 0.055 equiv), and Mn° powder (65.9 mg, 1.20 mmol, 3.00 equiv). The vial was sealed with a septa and tape and evacuated and backfilled with N_2 three times. 0.6 mL DMA was then added, and the reaction mixture was stirred vigorously (~1300 rpm) for about 30 min. The mixture became a dark black color. The reaction mixture was then cooled to 0 °C in an ice bath. Iodocyclohexane (0.078 mL, 0.600 mmol, 1.50 equiv) was then added, followed by freshly prepared acid chloride **S12** (94.7 mg, 0.400 mmol, 1.0 equiv) dissolved in 0.8 mL DMA. The sealed vial was then placed in a cryocool set to 0 °C

and allowed to stir for 16 h. The reaction mixture was then quenched with 1.0 mL H_2O and extracted with CH_2Cl_2 (4 x 2.0 mL). The combined organic layers were filtered through a Na_2SO_4 plug and concentrated *in vacuo*. The resulting crude oil was purified by silica gel flash chromatography (0 → 5% EtOAc/hexanes) to afford **263** as a pale yellow, clear oil (84.6 mg, 74% yield over 2 steps).

R_f = 0.76 (silica gel, 20% EtOAc/Hexanes, UV, *p*-anisaldehyde)

$[\alpha]_D^{25}$ = +17.1° (c = 2.247, $CHCl_3$).

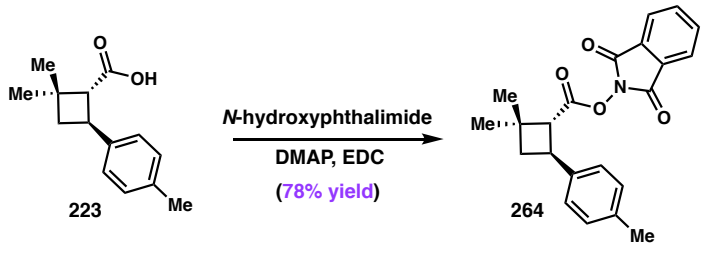
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 – 7.05 (m, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 3.85 (q, *J* = 9.6 Hz, 1H), 3.13 (dd, *J* = 9.6, 0.8 Hz, 1H), 2.31 (s, 3H), 2.21 (tt, *J* = 11.3, 3.3 Hz, 1H), 2.02 (ddd, *J* = 10.6, 8.8, 0.8 Hz, 1H), 1.92 (t, *J* = 10.5 Hz, 1H), 1.88 – 1.62 (m, 3H), 1.44 (tdd, *J* = 13.0, 11.4, 3.6 Hz, 1H), 1.34 (s, 3H), 1.31 – 1.11 (m, 4H), 1.06 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 212.7, 141.7, 135.5, 129.1, 126.5, 60.9, 50.8, 39.1, 37.4, 33.2, 31.3, 29.6, 26.9, 26.3, 26.0, 25.5, 24.0, 21.1.

FTIR (NaCl, thin film, cm^{-1}): 3380, 3048, 3020, 2929, 2855, 1894, 1698, 1515, 1449, 1370, 1331, 1288, 1244, 1183, 1145, 1066, 1021m 994, 952, 892, 829, 805, 759.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{20}H_{32}NO$ $[M+NH_4]^+$: 302.2478; found: 302.2470.

Synthesis of NHP-ester **264**



A 20 mL vial was charged with carboxylic acid **223** (208.9 mg, 0.957 mmol, 1.00 equiv), *N*-hydroxyphthalimide (156.1 mg, 0.957 mmol, 1.00 equiv), and 4-dimethylaminopyridine (11.7 mg, 0.096 mmol, 0.10 equiv). The vial was sealed with a rubber septum and evacuated and backfilled with N_2 three times. The solids were dissolved in CH_2Cl_2 (4 mL), and then EDC (201.8 mg, 1.05 mmol, 1.10 equiv) was added as a slurry in CH_2Cl_2 (1.3 mL). The reaction mixture was allowed to stir for 23 hours at room temperature. The reaction mixture was then transferred to a flask containing EtOAc (50 mL), and the resulting solids were removed by filtration. The filtrate was concentrated *in vacuo* and the crude oil was purified by silica gel flash chromatography (15 → 40% EtOAc/hexanes) to afford **264** as a white solid (272.8 mg, 78% yield).

R_f = 0.46 (silica gel, 20% EtOAc/Hexanes, UV, *p*-anisaldehyde)

$[\alpha]_D^{25}$ = +100.5° (c = 0.42, $CHCl_3$).

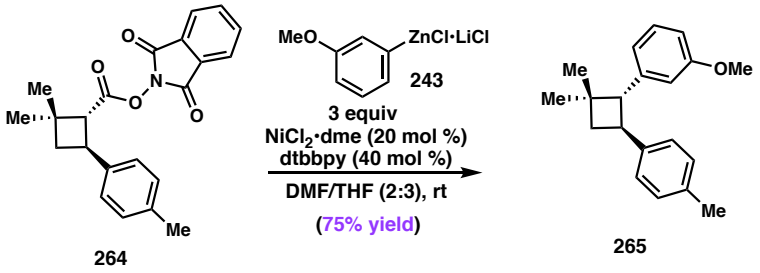
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 – 7.83 (m, 2H), 7.83 – 7.73 (m, 2H), 7.14 (s, 4H), 3.87 (q, *J* = 9.8 Hz, 1H), 3.21 (dd, *J* = 9.9, 0.9 Hz, 1H), 2.33 (s, 3H), 2.20 (ddd, *J* = 10.8, 8.9, 0.9 Hz, 1H), 2.08 (t, *J* = 10.5 Hz, 1H), 1.42 (s, 3H), 1.39 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.9, 162.2, 139.7, 136.3, 134.8, 129.3, 129.1, 126.5, 124.0, 52.5, 39.6, 37.5, 35.3, 30.5, 23.7, 21.2.

FTIR (NaCl, thin film, cm^{-1}): 3520, 3022, 2959, 2927, 2868, 1808, 1794, 1745, 1615, 1516, 1467, 1368, 1274, 1186, 1132, 1081, 1016, 972, 878, 811, 786, 696.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{22}H_{21}NO_4$ $[M+NH_4]^+$: 381.1809; found: 381.1814.

Nickel-catalyzed arylation of **264**.



A 25 mL round bottom flask was charged with **264** (109 mg, 0.300 mmol, 1.00 equiv), $NiCl_2$•dme (13.2 mg, 0.060 mmol, 0.20 equiv), and dtbbpy (32.2 mg, 0.120 mmol, 0.40 equiv). The flask was sealed with a septum and then evacuated and backfilled with argon three times. DMF was then added (3.2 mL), forming a green solution. Freshly prepared aryl zinc reagent **243** (4.8 mL, 0.90 mmol, 3.0 equiv, 0.19 M in THF) was then added and the solution turned red. The reaction was allowed to stir for 18 h, at which point the reaction was quenched with 1 M HCl (10 mL) and diluted with EtOAc (10 mL). The organic and aqueous layers were separated, and the organic layer was washed with water (10 mL) and brine (10 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to afford a red oil. The crude material was then purified by silica gel flash chromatography (2.5 → 25% PhMe/hexanes) to afford **265** as a clear oil (63 mg, 75% yield).

R_f = 0.77 (silica gel, 20% EtOAc/Hexanes, UV, *p*-anisaldehyde)

$[\alpha]_D^{25}$ = +195° (c = 0.42, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 – 7.17 (m, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 6.81 (ddt, *J* = 7.6, 1.7, 0.9 Hz, 1H), 6.80 – 6.71 (m, 2H), 3.79 (s, 3H), 3.32

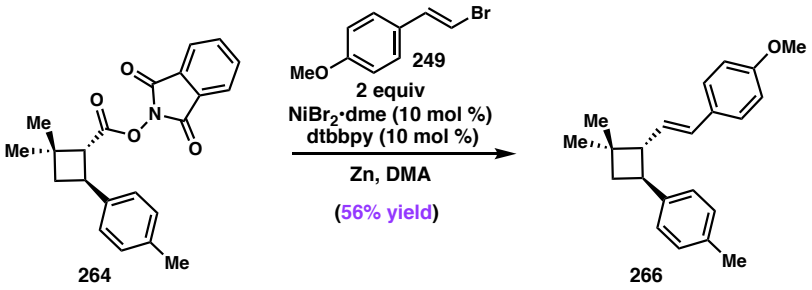
(d, J = 10.4 Hz, 1H), 2.30 (s, 3H), 2.16 (ddd, J = 10.3, 8.5, 0.7 Hz, 1H), 1.90 (t, J = 10.1 Hz, 1H), 1.28 (s, 3H), 0.88 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.6, 142.8, 142.1, 135.5, 129.1, 129.0, 126.6, 120.0, 113.6, 111.0, 56.7, 55.2, 40.2, 37.4, 37.2, 30.9, 23.3, 21.1.

FTIR (NaCl, thin film, cm^{-1}): 3014, 2947, 2859, 1596, 1514, 1490, 1458, 1428, 1371, 1318, 1292, 1252, 1166, 1040, 832, 808, 797, 694.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{15}H_{25}O_3$ $[M+H]^+$: 281.1900; found: 281.1899.

Reductive alkenylation of **264**



A 1-dram vial containing a 2-dram stir bar was charged with NHP ester **264** (75.7 mg, 0.208 mmol, 1.00 equiv) and vinyl bromide **249** (63.9 mg, 0.300 mmol, 1.50 equiv). A separate ½-dram vial containing a stir bar was charged with dtbbpy (5.4 mg, 0.020 mmol, 0.10 equiv). Both vials were brought into a N_2 filled glovebox. The vial containing dtbbpy was charged with $NiBr_2$•dme (6.2 mg, 0.020 mmol, 0.10 equiv) and DMA (0.200 mL, 1.0 M) and allowed to stir for 10 minutes. The vial containing **264** and **249** was charged with Zn powder (25.4 mg, 0.400 mmol, 2.00 equiv). Once the catalyst solution prestir was complete, the catalyst solution was added to the reaction vial via pipette. The vial was then

sealed with a Teflon-lined cap, removed from the glovebox, placed in a pre-heated oil bath (28 °C), and allowed to stir for 15 h. Once the reaction was complete, the reaction mixture was diluted with Et_2O and passed through a short silica plug, eluting with Et_2O. The material was concentrated onto celite *in vacuo*, and the resulting powder was purified by silica gel flash chromatography (0 → 30% PhMe/hexanes) to afford **266** as a white solid (34.1 mg, 56% yield).

R_f = 0.71 (silica gel, 20% EtOAc/Hexanes, UV, *p*-anisaldehyde)

$[\alpha]_D^{25}$ = +238° (c = 1.66, $CHCl_3$).

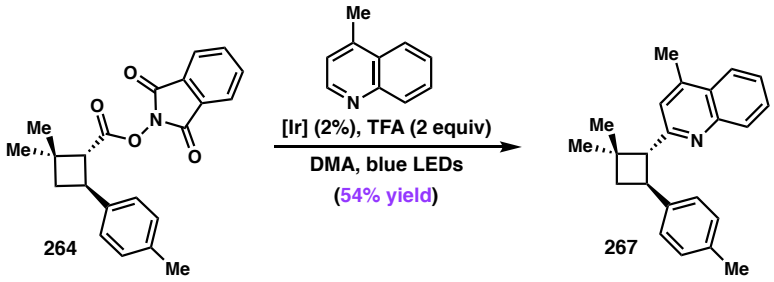
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.28 (m, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.89 – 6.83 (m, 2H), 6.34 (d, *J* = 15.8 Hz, 1H), 6.22 (dd, *J* = 15.8, 7.8 Hz, 1H), 3.81 (s, 3H), 3.41 (q, J = 9.5 Hz, 1H), 2.73 (ddt, *J* = 9.5, 7.7, 0.9 Hz, 1H), 2.33 (s, 3H), 2.11 (ddd, *J* = 10.7, 8.5, 0.8 Hz, 1H), 1.87 (t, *J* = 10.3 Hz, 1H), 1.18 (s, 3H), 1.16 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.9, 142.3, 135.3, 130.7, 130.0, 129.0, 128.1, 127.3, 126.6, 114.0, 55.9, 55.4, 40.0, 39.6, 36.9, 30.4, 23.6, 21.2.

FTIR (NaCl, thin film, cm^{-1}): 2999, 2951, 2921, 2860, 1607, 1511, 1462, 1370, 1249, 1174, 1106, 1036, 966, 806.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{22}H_{27}O$ $[M+H]^+$: 307.2056; found: 307.2062.

Decarboxylative heteroarylation of **264**



A flame-dried 2-dram vial was charged with NHP ester **264** (72.7, mg, 0.200 mmol, 1.00 equiv) and Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (4.5 mg, 0.004 mmol, 0.02 equiv). The vial was evacuated and backfilled with Ar three times. DMA (2.0 mL, 0.1 M) and lepidine (43.0 mg, 0.300 mmol, 1.50 equiv) were then added, and the reaction mixture was cooled to 0 °C and sparged with Ar for 10 minutes. The reaction vial was removed from the ice bath, trifluoroacetic acid (30.6 μL, 0.400 mmol, 2.00 equiv) was added, and the reaction mixture was allowed to stir in front of a 34W blue LED lamp (~3 cm from the lamp). The reaction was monitored by TLC (20% EtOAc/hexanes). Once the reaction was complete (~4 h), the reaction was quenched with 1 mL NEt_3 and 2 mL H_2O. The aqueous layer was extracted with EtOAc (3 mL x 4), and the combined organics were washed with 1 M LiCl. The organic layer was then dried with Na_2SO_4, filtered, and concentrated onto celite *in vacuo*, and the resulting powder was purified by silica gel flash chromatography (0 → 5% EtOAc/hexanes) to afford **267** as a yellow solid (34.1 mg, 54% yield).

$\mathbf{R_f}$ = 0.76 (silica gel, 20% EtOAc/Hexanes, UV, *p*-anisaldehyde)

$\mathbf{[\alpha]_D^{25}}$ = +305° (c = 1.47, $CHCl_3$).

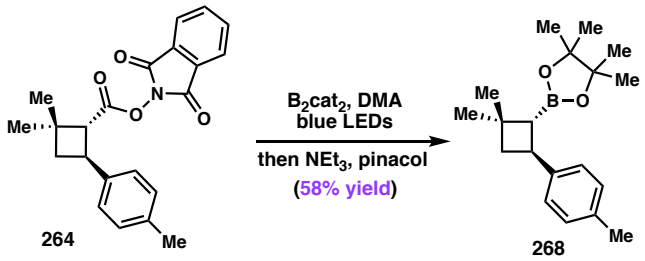
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.4 Hz, 1H), 7.95 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.67 (ddd, *J* = 8.3, 6.7, 1.4 Hz, 1H), 7.50 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 7.21 (d, *J* = 7.9 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 3H), 4.39 (q, *J* = 9.7 Hz, 1H), 3.52 (d, *J* = 10.1 Hz, 1H), 2.67 (s, 3H), 2.30 (s, 3H), 2.20 (dd, *J* = 10.4, 8.8 Hz, 1H), 2.04 (t, *J* = 10.3 Hz, 1H), 1.39 (s, 3H), 0.89 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6, 148.0, 143.4, 142.6, 135.2, 130.2, 129.0, 128.9, 128.8, 128.7, 127.1, 126.9, 126.8, 125.4, 123.7, 121.7, 59.1, 39.7, 37.9, 35.4, 31.2, 23.7, 21.1, 18.9.

FTIR (NaCl, thin film, cm^{-1}): 3428, 3950, 2925, 2360, 1603, 1558, 1514, 1446, 1379, 1260, 1176, 1162, 1034, 809, 756.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{23}H_{26}N$ $[M+H]^+$: 316.2060; found: 316.2063.

Decarboxylative borylation of **264**



A flame-dried 2-dram vial was charged with NHP ester **264** (72.7, mg, 0.200 mmol, 1.00 equiv) and B_2cat_2 (59.5 mg, 0.250 mmol, 1.25 equiv). The vial was evacuated and backfilled with Ar three times. DMA (2.0 mL, 0.1 M) was then added, and the reaction mixture was cooled to 0 °C and sparged with Ar for 10 minutes. The reaction vial was removed from the ice bath and suspended inside a large beaker lined with 12W blue LED

strips and covered with foil. After 21 h, pinacol (94.5 mg, 0.800 mmol, 4.00 equiv) was added as a solution in NEt_3 (700 μL, 5.04 mmol, 25.2 equiv). After 2 h, the reaction was quenched with H_2O, saturated aqueous NH_4Cl, and EtOAc. The organic and aqueous layers were separated, and the aqueous layer was extracted with EtOAc (2 mL x 3). The combined organics were then dried with Na_2SO_4, filtered, and concentrated onto celite *in vacuo*, and the resulting powder was purified by silica gel flash chromatography (0 → 5% EtOAc/hexanes) to afford **268** as a white solid (35.1 mg, 58% yield).

R_f = 0.81 (silica gel, 20% EtOAc/Hexanes, UV, *p*-anisaldehyde)

$[\alpha]_D^{25}$ = +77.5° (c = 1.47, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (s, 4H), 3.53 (td, *J* = 10.2, 8.2 Hz, 1H), 2.31 (s, 3H), 2.13 (ddd, *J* = 10.6, 8.2, 0.8 Hz, 1H), 2.02 (t, *J* = 10.3 Hz, 1H), 1.68 (d, *J* = 10.5 Hz, 1H), 1.26 (s, 6H), 1.24 (d, *J* = 1.1 Hz, 9H), 1.16 (s, 3H).

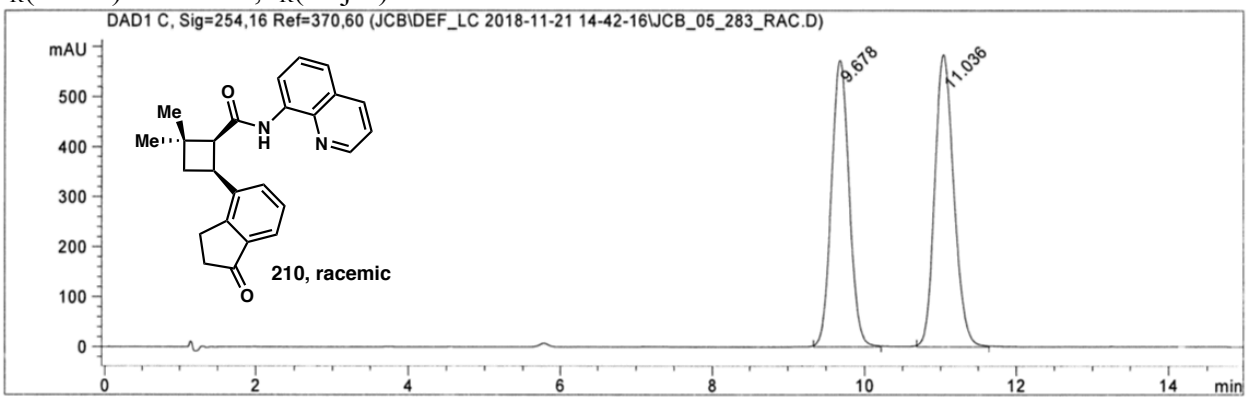
^{13}C NMR (101 MHz, $CDCl_3$): δ 144.1, 134.9, 128.9, 126.3, 83.2, 42.9, 34.3, 34.0, 32.4, 26.6, 25.3, 24.9, 21.1. (Note: the resonance from the carbon attached to the boron was not visible).

FTIR (NaCl, thin film, cm^{-1}): 3444, 2980, 2922, 2946, 2862, 2728, 1898, 1652, 1514, 1462, 1414, 1380, 1363, 1345, 1329, 1275, 1237, 1143, 1112, 1080, 1020, 967, 854, 809, 730.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{19}H_{29}BO_2Na$ $[M+Na]^+$: 323.2158; found: 323.2174.

2.7.2.3 Proof of Enantiopurity

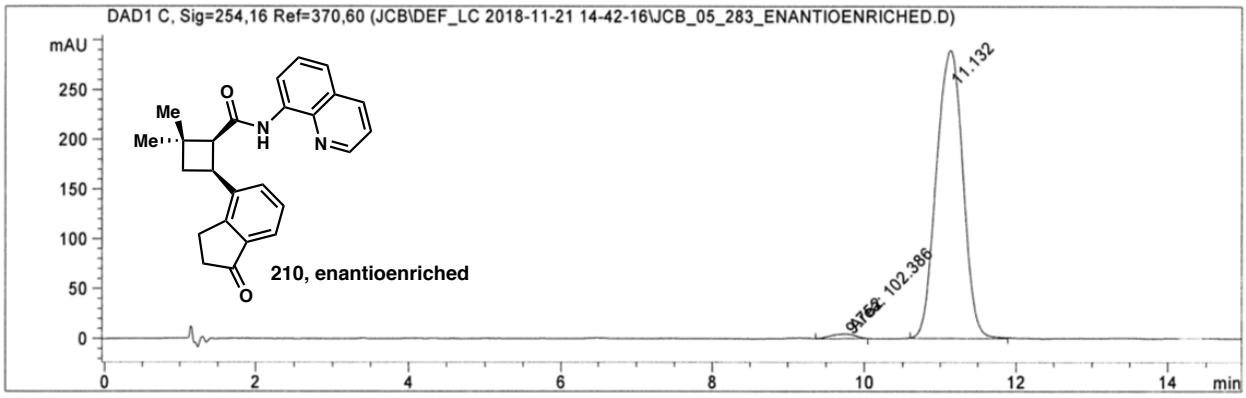
210, racemic sample. Chiral SFC: (OD-H, 2.5 mL/min, 20% IPA in CO_2, λ = 254 nm): t_R(minor) = 9.7 min, t_R(major) = 11.1 min.



Signal 1: DAD1 C, Sig=254,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.678	BB	0.2468	9170.02637	572.63605	47.0183
2	11.036	BB	0.2746	1.03331e4	583.59204	52.9817
Totals :				1.95031e4	1156.22809	

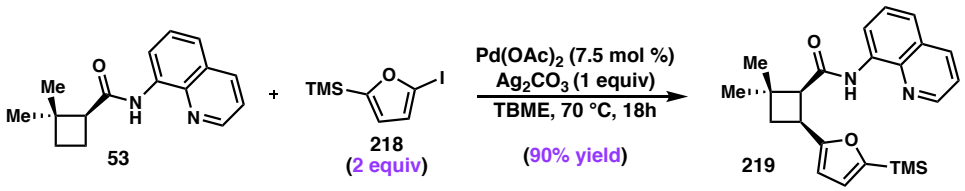
210, enantioenriched sample. Chiral SFC: (OD-H, 2.5 mL/min, 20% IPA in CO_2, λ = 254 nm): t_R(minor) = 9.7 min, t_R(major) = 11.1 min.



Signal 1: DAD1 C, Sig=254,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.752	MM	0.3621	102.38605	4.71307	1.4187
2	11.132	BB	0.3991	7114.58105	289.14011	98.5813
Totals :				7216.96710	293.85318	

2.7.2.4 *Total Synthesis of (+)-rumphellaone A*



A 48 mL pressure flask was charged with cyclobutamide **53** (400 mg, 1.57 mmol, 1.00 equiv), Ag_2CO_3 (434 mg, 1.57 mmol, 1.00 equiv), and $Pd(OAc)_2$ (26.5 mg, 0.118 mmol, 7.5 mol %) followed by TMS-iodofuran **218** (834 mg, 3.15 mmol, 2.00 equiv). The mixture was then suspended in TBME (8.0 mL, 0.2 M). The vessel was sealed under ambient conditions and placed in a pre-heated oil bath (70 ºC). After about 10 minutes, the olive-green mixture becomes black, and the reaction mixture is stirred for an additional 18 hours. The reaction mixture was then concentrated, diluted with toluene (3 mL), and loaded directly onto a silica gel column (0 → 20% EtOAc/hexanes) to afford **219** as a clear yellow oil (556 mg, 90% yield).

R_f = 0.56 (silica gel, 20% EtOAc/Hex, UV, *p*-anisaldehyde).

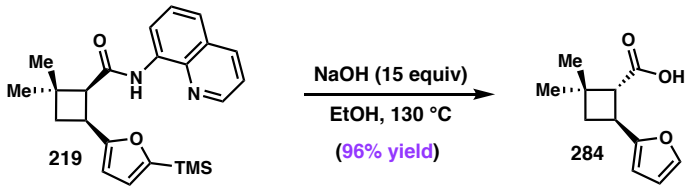
$[\alpha]_D^{25}$ = –57.2° (c = 1.22, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.61 (s, 1H), 8.77 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.68 (dd, *J* = 6.7, 2.3 Hz, 1H), 8.11 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.48 – 7.39 (m, 3H), 6.48 (d, *J* = 3.1 Hz, 1H), 6.23 (dd, *J* = 3.2, 1.1 Hz, 1H), 4.07 – 3.94 (m, 1H), 3.34 (ddd, *J* = 9.0, 2.2, 0.8 Hz, 1H), 2.61 – 2.50 (m, 1H), 2.19 (ddd, *J* = 11.0, 8.9, 2.3 Hz, 1H), 1.45 (s, 3H), 1.32 (s, 3H), -0.08 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.1, 160.1, 158.7, 148.0, 138.5, 136.3, 134.8, 127.9, 127.6, 127.5, 121.5, 121.2, 121.1, 120.5, 120.5, 116.5, 106.8, 55.8, 38.1, 36.6, 32.3, 30.9, 30.7, 30.7, 24.9, –1.8.

FTIR (NaCl, thin film, cm^{-1}): 3360, 3109, 3049, 2954, 2866, 2613, 1944, 1878, 1687, 1595, 1578, 1522, 1485, 1424, 1385, 1324, 1249, 1161, 1131, 1009, 924, 842, 791, 757.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{23}H_{29}N_2O_2Si$ $[M+H]^+$: 392.1993; found: 393.1990.



A 15 mL pressure flask was charged with *cis*-cyclobutamide **219** (532 mg, 1.36 mmol, 1.00 equiv), sodium hydroxide (813 mg, 20.33 mmol, 15 equiv), and absolute ethanol (5.7 mL, 0.24 M). The flask was sealed and placed in a pre-heated oil bath (130 ºC) and stirred for 18 h. The solvent was then concentrated *in vacuo*, and the crude residue was diluted with 1 M HCl (20 mL) and EtOAc (20 mL). The organic layer was separated and washed with 1 M HCl (2 x 20 mL). At this point, the aqueous layers should be yellow, and the organic layer should be faint brown. The combined aqueous layers were extracted with EtOAc (25 mL), and the second organic layer was washed with 1 M HCl (25 mL) until it was free of 8-aminoquinoline as indicated by TLC (usually 1-2 times). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reddish solid was purified by silica gel flash chromatography (20 → 40 % EtOAc/hexanes) to afford **284** as an off-white solid (250 mg, 96 % yield).

R_f = 0.5 (silica gel, 30% EtOAc/Hex, *p*-anisaldehyde).

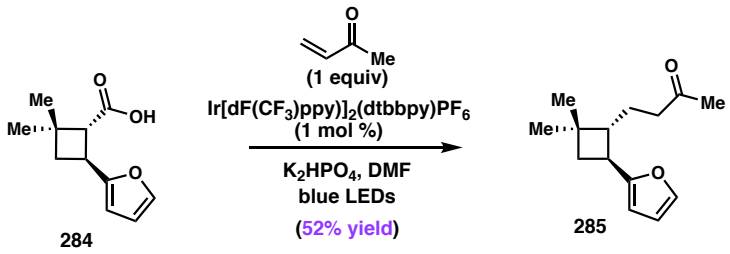
$[\alpha]_D^{25}$ = +133.0° (c = 0.85, $CHCl_3$).

^{1}H NMR (400 MHz, $CHCl_3$): δ 7.32 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.28 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.05 (dt, *J* = 3.2, 0.8 Hz, 1H), 3.72 (q, *J* = 9.5 Hz, 1H), 3.11 – 3.02 (m, 1H), 2.12 – 1.95 (m, 2H), 1.30 (s, 3H), 1.19 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.3, 156.6, 141.5, 110.3, 105.0, 53.2, 38.3, 36.8, 30.4, 29.2, 23.4.

FTIR (NaCl, thin film, cm^{-1}): 3119, 2993, 2956, 2869, 1722, 1682, 1604, 1506, 1461, 1411, 1390, 1371, 1276, 1224, 1208, 1175, 1161, 1104, 1067, 1008, 946, 918, 884, 850, 804, 743, 730, 695.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{11}H_{15}O_3$ $[M+H]^+$: 195.1016; found: 195.1019.



A 100 mL flame-dried, round-bottom flask was charged with carboxylic acid **284** (342 mg, 1.76 mmol, 1.00 equiv), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (19.7 mg, 0.0176 mmol, 0.01 equiv), and K_2HPO_4 (368 mg, 1.76 mmol, 1.00 equiv). The flask was evacuated and backfilled with N_2 three times. DMF (17.6 mL, 0.1 M) and freshly distilled methyl vinyl ketone (144 μL, 1.76 mmol, 1.0 equiv) were then added, and the reaction mixture was sparged with Ar for 5 minutes. The reaction flask was placed about 5 cm from a 34W blue

LED lamp and was allowed to stir at room temperature under N_2. After 42 h, the reaction was quenched with sat aq $NaHCO_3$ and extracted with EtOAc (75 mL x 3). The combined organics were then dried with $MgSO_4$, filtered, and concentrated *in vacuo* to afford the product as a crude oil, which was then purified by silica gel flash chromatography (3 → 10% EtOAc/hexanes) to afford **285** as a white solid (201 mg, 52% yield).

R_f = 0.79 (silica gel, 20% EtOAc/Hexanes, UV, *p*-anisaldehyde)

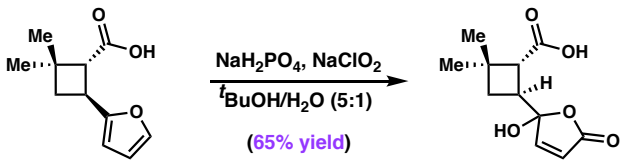
$[\alpha]_D^{25}$ = +57.8° (c = 1.07, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.27 (dd, *J* = 3.1, 1.9 Hz, 1H), 5.97 (dt, *J* = 3.2, 0.7 Hz, 1H), 2.97 (td, *J* = 9.6, 8.5 Hz, 1H), 2.41 – 2.21 (m, 2H), 2.09 – 1.97 (m, 4H), 1.93 (ddd, *J* = 10.7, 8.5, 0.7 Hz, 1H), 1.88 – 1.79 (m, 1H), 1.74 – 1.59 (m, 2H), 1.11 (s, 3H), 1.08 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 209.1, 158.9, 140.9, 110.3, 104.0, 50.4, 41.5, 39.0, 34.6, 34.3, 30.6, 30.1, 24.2, 22.3.

FTIR (NaCl, thin film, cm^{-1}): 3114, 2953, 2933, 2863, 1717, 1593, 1506, 1451, 1411, 1368, 1360, 1235, 1159, 1150, 1009, 799, 729.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{14}H_{20}O_2Na$ $[M+Na]^+$: 243.1356; found: 243.1359.



A 50 mL round bottom flask was charged with carboxylic acid **284 (**200 mg, 1.03 mmol, 1.00 equiv) and was evacuated and backfilled with N_2 three times. 5:1 ^{t}BuOH/H_2O (5.2 mL, 0.2 M) was added. Once the starting material was fully dissolved, NaH_2PO_4•H_2O

(213 mg, 1.54 mmol, 1.50 equiv) was added in one portion, followed by $NaClO_2$ (349 mg, 3.09 mmol, 3.00 equiv, 80%). The suspension turned bright yellow within the first 10-15 minutes. The reaction mixture was allowed to stir 2–3 hours, at which point the yellow color dissipated and no more starting material was observed by TLC. The reaction mixture was concentrated *in vacuo*, and the resulting solids were solubilized with a mixture of EtOAc and minimal H_2O. This crude mixture was concentrated onto 4 g SiO_2. The powder was applied to a silica gel column and purified by flash silica gel chromatography (0 → 5% MeOH/CH_2Cl_2, followed by flushing with 50% MeOH/CH_2Cl_2) to afford **286** as a white solid (151 mg, 65% yield, 93% pure by qNMR).

R_f = 0.20 (silica gel, 10% MeOH/CH_2Cl_2, UV, *p*-anisaldehyde)

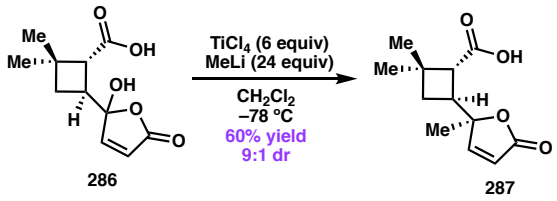
$[\alpha]_D^{25}$ +62.6° (c = 0.22, MeOH).

^{1}H NMR (400 MHz, MeOD-*d*$_4$): δ 7.27 (d, *J* = 5.9 Hz, 1H), 6.12 (d, *J* = 5.8 Hz, 1H), 2.92 (q, *J* = 9.4 Hz, 1H), 2.72 (d, *J* = 9.6 Hz, 1H), 1.80 (t, *J* = 10.3 Hz, 1H), 1.70 (dd, *J* = 11.0, 9.0 Hz, 1H), 1.20 (s, 3H), 1.10 (s, 3H).

^{13}C NMR (101 MHz, MeOD-*d*$_4$): δ 175.7, 172.9, 155.7, 123.6, 51.5, 49.5, 37.8, 37.1, 36.9, 36.2, 33.7, 30.4, 30.3, 24.1, 23.7.

FTIR (NaCl, thin film, cm^{-1}): 3098, 2960, 2871, 1726, 1416, 1373, 1280, 1255, 1187, 1160, 1114, 1032, 1007, 935, 852, 829, 713.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{11}H_{16}O_5$ $[M+H]^+$: 227.0919; found: 227.0922.



A 50 mL round bottom flask was flame-dried under vacuum and then back-filled with N_2. The flask was charged with CH_2Cl_2 (5 mL) and cooled to –78 ºC, at which point, $TiCl_4$ (142 µL, 1.33 mmol, 6.00 equiv) was added. The flask was then charged with MeLi (1.5 M in Et_2O; 4.00 mL, 5.30 mmol, ~24 equiv) dropwise via syringe, until the color of the solution changed from dark brown, to bright orange, and finally to dark green. The resulting solution was stirred for 1h at –78 ºC. A flame-dried 50 mL pear-shaped (pointed) flask was charged with **286** (49.0 mg, 0.217 mmol, 1.00 equiv) and then evacuated and backfilled with N_2 three times. The substrate was dissolved in CH_2Cl_2 (23 mL) and sonicated to dissolve any particulates. The solution was cooled to –78 ºC, then added to the reaction flask via a slow cannula transfer. If the addition proceeds too quickly or the solution of starting material is not sufficiently cooled, the reaction will favor the undesired diastereomer. The flask containing **286** was rinsed with 2 mL CH_2Cl_2 to complete the transfer. The resulting mixture was allowed to stir at –78 ºC. After 4 h the reaction was quenched with 1 M HCl (20 mL), allowed to warm to 23 °C, and stirred for 30 minutes during which time the aqueous layer became blue/green. The organic and aqueous layers were separated, and the aqueous layer was extracted with EtOAc (20 mL x 4), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (0 → 10% MeOH/CH_2Cl_2) to afford **287** as a white solid (29 mg, 9:1 dr, 60% yield).

R_f = 0.43 (silica gel, 10% MeOH/CH_2Cl_2, UV, *p*-anisaldehyde)

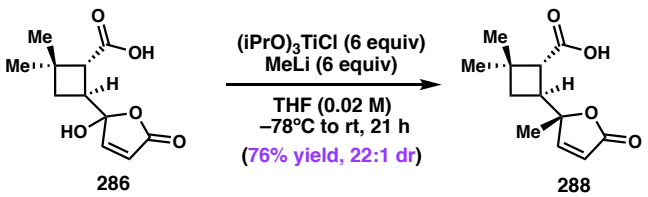
$[\alpha]_D^{25}$ = +43.0° (c = 0.46, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): 7.23 (d, *J* = 5.6 Hz, 1H), 6.01 (d, *J* = 5.6 Hz, 1H), 3.48 (s, 1H), 2.99 (dd, *J* = 9.4, 0.8 Hz, 1H), 2.92 – 2.78 (m, 1H), 1.46 – 1.41 (m, 1H), 1.39 (s, 3H), 1.35 (dd, *J* = 11.1, 9.9 Hz, 1H), 1.20 (s, 3H), 1.10 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.3, 172.9, 172.8, 158.8, 121.1, 88.5, 49.1, 47.1, 36.4, 35.6, 35.5, 32.1, 29.9, 23.8, 21.7.

FTIR (NaCl, thin film, cm^{-1}): 3087, 2958, 2869, 1737, 1600, 1463, 1453, 1403, 1380, 1372, 1305, 1280, 1266, 1218, 1183, 1163, 1136, 1093, 1037, 961, 924, 880, 852, 824, 728, 711, 658.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{12}H_{20}NO_4$ $[M+NH_4]^+$: 242.1387; found: 242.1394.



A flame-dried 50 mL round bottom flask was backfilled with N_2 and charged with THF (5 mL). The flask was cooled to –78 °C and (*i*-PrO)$_3$TiCl (1 M solution in hexanes; 1.33 mL, 1.33 mmol, 6.00 equiv) was added. MeLi (1.6 M solution in ether; 0.83 mL, 1.33 mmol, 6.00 equiv) was then added dropwise. This mixture was allowed to stir at –78 °C for 1 h. **286** (50 mg, 0.221 mmol, 1.00 equiv) was then added as a solution in THF (5.5 mL). The reaction mixture was slowly warmed to 23 °C over 21h. The reaction was then carefully quenched with 1 M HCl (11 mL) and stirred vigorously for 30 min. The organic

and aqueous layers were then separated, and the aqueous layer was extracted with EtOAc (12 mL x 4). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel flash chromatography (0 → 4% MeOH/CH_2Cl_2) to afford **288** (37.5 mg, 76% yield, 22:1 dr)

R_f = 0.43 (silica gel, 10% MeOH/CH_2Cl_2, UV, *p*-anisaldehyde)

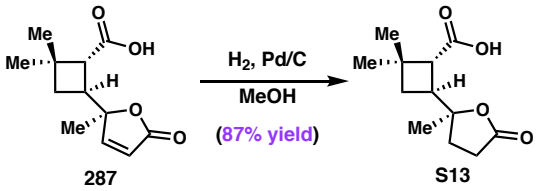
$[\alpha]_D^{25}$ = +120.4° (c = 1.20, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (d, *J* = 5.6 Hz, 1H), 5.97 (d, *J* = 5.6 Hz, 1H), 2.79 (td, *J* = 9.9, 8.9 Hz, 1H), 2.39 (dd, *J* = 9.8, 0.8 Hz, 1H), 1.93 (t, *J* = 10.4 Hz, 1H), 1.78 (ddd, *J* = 10.8, 8.9, 1.0 Hz, 1H), 1.39 (s, 3H), 1.21 (s, 3H), 1.11 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 177.4, 172.9, 159.5, 120.5, 88.4, 46.9, 36.8, 35.5, 33.5, 29.9, 23.6, 21.6.

FTIR (NaCl, thin film, cm^{-1}): 3091, 2936, 2958, 1869, 1741, 1702, 1464, 1454, 1417, 1371, 1282, 1247, 1208, 1166, 1119, 1090, 1051, 956, 912, 820, 727, 661.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{12}H_{20}NO_4$ $[M+NH_4]^+$: 242.1387; found: 242.1390.



A 2-dram vial was charged with lactone **287** (29 mg, 0.129 mmol, 1.00 equiv) and Pd/C (10% by weight, 47 mg, 0.044 mmol, 0.34 equiv). The vial was then evacuated and backfilled with N_2 three times. The solids were suspended in MeOH (1.4 mL, 0.095 M), and the reaction mixture was sparged with a balloon of H_2 for 20 minutes at 0°C, at which

point the balloon was replaced with a fresh balloon, and the reaction was allowed to warm to room temperature. The reaction mixture was then stirred for 7 h under an atmosphere of H_2. Once the reaction was complete, the reaction mixture was sparged with argon for 20 minutes, diluted with EtOAc (15 mL), and filtered through celite, and concentrated *in vacuo*. The crude residue was then purified by silica gel flash chromatography (5% MeOH/CH_2Cl_2) to afford **S13** (25 mg, 88% yield) as a white solid.

R_f = 0.44 (silica gel, 10% MeOH/CH_2Cl_2, *p*-anisaldehyde)

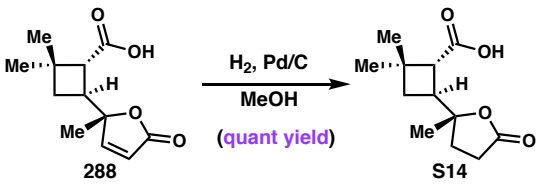
$[\alpha]_D^{25}$ = +76.3° (c = 0.72, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.91 (d, *J* = 9.7 Hz, 1H), 2.72 (t, *J* = 9.5 Hz, 1H), 2.70 – 2.59 (m, 1H), 2.53 (ddd, *J* = 18.2, 9.6, 5.0 Hz, 1H), 2.04 – 1.86 (m, 2H), 1.67 (s, 1H), 1.65 (s, 1H), 1.30 (s, 3H), 1.22 (s, 3H), 1.11 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.4, 177.1, 86.3, 86.3, 48.7, 39.1, 35.3, 32.6, 30.9, 29.9, 29.3, 24.0, 23.7.

FTIR (NaCl, thin film, cm^{-1}): 2958, 2934, 2869, 1773, 1736, 1702, 1459, 1420, 1382, 1369, 1283, 1248, 1166, 1142, 1077, 940, 914, 802, 646.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{12}H_{22}NO_4$ $[M+NH_4]^+$: 244.1543; found: 244.1541.



288 (31.0 mg, 0.138 mmol, 1.00 equiv) was subjected to analogous conditions to afford **S14** (32.2 mg, quant yield), which was taken forward without further purification.

R_f = 0.44 (silica gel, 10% MeOH/CH_2Cl_2, *p*-Anisaldehyde)

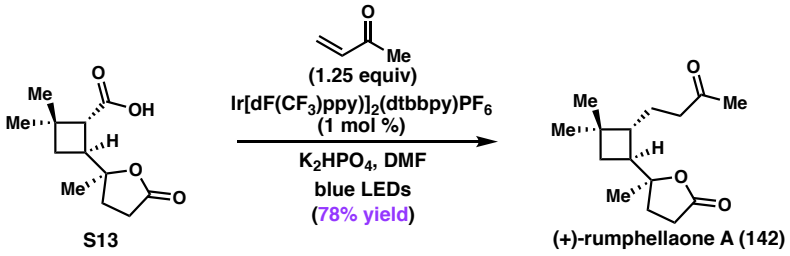
$[\alpha]_D^{25}$ = +51.2° (c = 0.53, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.78 – 2.56 (m, 3H), 2.50 (ddd, *J* = 18.1, 9.9, 4.9 Hz, 1H), 2.17 – 2.06 (m, 1H), 1.91 (ddd, *J* = 13.1, 10.0, 4.9 Hz, 1H), 1.81 (td, *J* = 9.8, 1.2 Hz, 1H), 1.71 (dd, *J* = 10.8, 8.0 Hz, 1H), 1.29 (s, 3H), 1.21 (s, 3H), 1.11 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.4, 177.2, 86.5, 48.1, 39.2, 35.5, 33.6, 30.9, 29.9, 29.3, 23.9, 23.7.

FTIR (NaCl, thin film, cm^{-1}): 2958, 2869, 1770, 1738, 1732, 1704, 1699, 1463, 1422, 1383, 1369, 1283, 1245, 1222, 1165, 1138, 1075, 1002, 965, 941, 914, 802, 757, 711, 648.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{12}H_{22}NO_4$ $[M+NH_4]^+$: 244.1543; found: 244.1537.



To a 2 dram vial charged with saturated lactone **S13** (16 mg, 0.0707 mmol, 1.00 equiv) was added $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.8 mg, 0.0007 mmol, 0.01 equiv) and K_2HPO_4 (14.8 mg, 0.0849 mmol, 1.20 equiv). The reaction vessel was evacuated and backfilled with N_2 three times. DMF (0.71 mL, 0.1 M) was then added, and the reaction mixture was cooled to 0 °C and sparged with argon for 15 minutes. Freshly distilled methyl vinyl ketone (7.2 μL, 0.0884 mmol, 1.25 equiv) was then added, and the reaction vessel was placed between two 34W blue LEDs (~5-6 cm away from each lamp) and stirred for 24 h with a small fan to keep the reactions at 23 ºC. Once complete, the reaction was diluted

with sat. aq. $NaHCO_3$ (0.8 mL) and EtOAc (0.8 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (4 x 1 mL). The combined organic layers were washed with 1 M LiCl (5 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated *in vacuo.* The crude material was purified by silica gel flash chromatography (20 → 40% EtOAc/hexanes) to afford pure (+)-rumphellaone A (**142**) (15 mg, 78% yield) as a yellow solid.

R_f = 0.27 (silica gel, 40% EtOAc/Hexanes, UV, *p*-anisaldehyde)

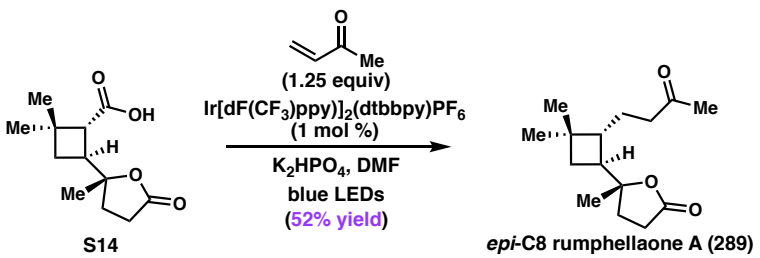
$[\alpha]_D^{25}$ = +43.4° (c = 0.35, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 (ddd, *J* =18.1, 10.0, 8.9 Hz, 1H), 2.53 (ddd, *J* = 18.1, 10.0, 5.0 Hz, 1H), 2.36 (t, *J* = 7.9 Hz, 2H), 2.12 (s, 3H), 2.09 – 2.02 (m, 2H), 2.03 – 1.97 (m, 1H), 1.90 (ddd, *J* = 10.2, 9.6, 5.3 Hz, 2H), 1.88 – 1.81 (m, 1H), 1.69 – 1.61 (m, 2H), 1.57 (ddd, *J* = 10.8, 8.6, 0.8 Hz, 1H), 1.42 (t, *J* = 10.3 Hz, 1H), 1.31 (s, 3H), 1.06 (s, 3H), 1.03 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 208.8, 177.1, 87.4, 44.6, 44.4, 42.1, 33.7, 33.1, 31.1, 30.8, 30.1, 29.3, 25.2, 25.0, 22.6.

FTIR (NaCl, thin film, cm^{-1}): 2953, 2929, 2865, 1770, 1715, 1455, 1366, 1250, 1162, 1124, 1077, 938, 803, 645.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{15}H_{25}O_3$ $[M+H]^+$: 253.1798; found: 253.1799.



S14 (15.0 mg, 0.066 mmol, 1.00 equiv) was subjected to an analogous procedure to afford *epi*-C8-rumphellaone A (**289**) (8.1 mg, 52% yield) as a white solid.

R_f = 0.33 (silica gel, 40% EtOAc/Hexanes, UV, *p*-anisaldehyde)

$[\alpha]_D^{25}$ = +38.5° (c = 0.41, $CHCl_3$).

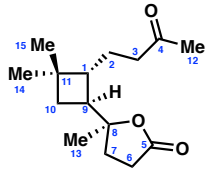
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 – 2.56 (m, 2H), 2.39 (dd, *J* = 8.6, 6.6 Hz, 2H), 2.13 (s, 3H), 2.10 – 1.96 (m, 2H), 1.90 (ddd, *J* = 13.0, 8.8, 7.2 Hz, 1H), 1.78 (tdd, *J* = 9.2, 6.6, 0.8 Hz, 1H), 1.71 – 1.57 (m, 3H), 1.51 (t, *J* = 10.4 Hz, 1H), 1.29 (s, 3H), 1.06 (s, 3H), 1.03 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 208.7, 177.1, 87.3, 44.6, 44.1, 41.9, 34.5, 33.4, 31.6, 31.1, 30.2, 29.3, 25.0, 24.0, 22.6.

FTIR (NaCl, thin film, cm^{-1}): 2952, 2932, 2865, 1769, 1715, 1455, 1422, 1365, 1234, 1169, 1155, 1075, 963, 939, 801, 647.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{15}H_{25}O_3$ $[M+H]^+$: 253.1798; found: 253.1799.

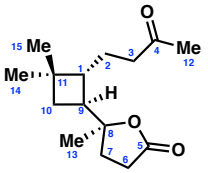
Comparison of ^{1}H NMR spectroscopic data for natural and synthetic (+)-rumphellaone A (142)



(+)-rumphellaone A (142)

Carbon Number	**Natural (+)-rumphellaone A** ^{1}H 400 MHz, $CDCl_3$	**Synthetic (+)-rumphellaone A** ^{1}H 400 MHz, $CDCl_3$
1	1.91 (ddd, *J* = 10.0, 9.2, 5.6 Hz, 2H)	1.90 (ddd, *J* = 10.2, 9.6, 5.3 Hz, 2H)
2	1.67 (m, 2H)	1.65 (m, 2H)
3	2.37 (t, *J* = 8.0 Hz, 2H)	2.36 (t, *J* = 7.9 Hz, 2H)
6α	2.63 (ddd, *J* = 18.0, 9.6, 8.8 Hz, 1H)	2.63 (ddd, *J* =18.1, 10.0, 8.9 Hz, 1H)
6β	2.54 (ddd, *J* = 18.0, 10.0, 4.8 Hz, 1H)	2.53 (ddd, *J* = 18.1, 10.0, 5.0 Hz, 1H)
7α	1.84 (m, 1H)	1.84 (m, 1H)
7β	2.01 (m, 1H)	2.01 (m, 1H)
9	2.06 (ddd, 10.4, 10.0, 10.0 Hz, 2H)	2.06 (m, 2H)
10α	1.57 (dd, *J* = 10.0, 10.0 Hz, 1H)	1.57 (ddd, *J* = 10.8, 8.6, 0.8 Hz, 1H)
10β	1.42 (dd, *J* = 10.4, 10.0 Hz, 1H))	1.42 (t, *J* = 10.3 Hz, 1H)
12	2.13 (s, 3H)	2.12 (s, 3H)
13	1.31 (s, 3H)	1.31 (s, 3H)
14	1.03 (s, 3H)	1.03 (s, 3H)
15	1.07 (s, 3H)	1.06 (s, 3H)

Comparison of ^{13}C NMR spectroscopic data for natural and synthetic (+)-rumphellaone A (142).



(+)-rumphellaone A (142)

Carbon Number	**Natural (+)-rumphellaone A** ^{13}C 100 MHz, $CDCl_3$	**Synthetic (+)-rumphellaone A** ^{13}C 101 MHz, $CDCl_3$	**Δ**
1	44.5	44.6	0.1
2	25.1	25.2	0.1
3	42.0	42.1	0.1
4	208.6	208.8	0.2
5	177.0	177.1	0.1
6	29.2	29.3	0.1
7	30.6	30.8	0.2
8	87.2	87.4	0.2
9	44.3	44.4	0.1
10	33.6	33.7	0.1
11	33.0	33.1	0.1
12	29.9	30.1	0.2
13	24.9	25.0	0.1
14	22.5	22.6	0.1
15	30.9	31.1	0.2

2.8 NOTES AND REFERENCES

(1) Dembitsky, V. M. *J. Nat. Med.* **2007**, *62*, 1.
(2) Hong, Y. J.; Tantillo, D. J. *Chem. Soc. Rev.* **2014**, *43*, 5042.
(3) Ortuno, R.; Moglioni, A.; Moltrasio, G. *Curr. Org. Chem.* **2005**, *9*, 237.
(4) Shao, M.; Wang, Y.; Liu, Z.; Zhang, D.-M.; Cao, H.-H.; Jiang, R.-W.; Fan, C.-L.; Zhang, X.-Q.; Chen, H.-R.; Yao, X.-S.; et al. *Org. Lett.* **2010**, *12*, 5040.
(5) Vinik, A.; Rosenstock, J.; Sharma, U.; Feins, K.; Hsu, C.; Merante, D. *Diabetes Care* **2014**, *37*, 3253.
(6) Wang, Y.-H.; Hou, A.-J.; Chen, D.-F.; Weiller, M.; Wendel, A.; Staples, R. J. *Eur. J. Org. Chem.* **2006**, *2006*, 3457.
(7) Chung, H.-M.; Chen, Y.-H.; Lin, M.-R.; Su, J.-H.; Wang, W.-H.; Sung, P.-J. *Tetrahedron Lett.* **2010**, *51*, 6025.

(8) Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. *Angew. Chem. Int. Ed.* **2011**, *50*, 7740.
(9) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485.
(10) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449.
(11) Wang, M.; Lu, P. *Org. Chem. Front.* **2018**, *5*, 254.
(12) Xu, Y.; Conner, M. L.; Brown, M. K. *Angew. Chem. Int. Ed.* **2015**, *54*, 11918.
(13) Bach, T.; Hehn, J. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 1000.
(14) Brimioulle, R.; Bach, T. *Science* **2013**, *342*, 840.
(15) Du, J.; Skubi, K. L.; Schultz, D. M.; Yoon, T. P. *Science* **2014**, *344*, 392.
(16) Vallavoju, N.; Selvakumar, S.; Jockusch, S.; Sibi, M. P.; Sivaguru, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 5604.
(17) Pagar, V. V.; RajanBabu, T. V. *Science* **2018**, *361*, 68.
(18) Gutekunst, W. R.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 19076.
(19) Gutekunst, W. R.; Gianatassio, R.; Baran, P. S. *Angew. Chem. Int. Ed.* **2012**, *51*, 7507.
(20) Parella, R.; Gopalakrishnan, B.; Babu, S. A. *J. Org. Chem.* **2013**, *78*, 11911.
(21) Gutekunst, W. R.; Baran, P. S. *J. Org. Chem.* **2014**, *79*, 2430.
(22) Xiao, K.-J.; Lin, D. W.; Miura, M.; Zhu, R.-Y.; Gong, W.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 8138.
(23) Chen, T.; Barton, L. M.; Lin, Y.; Tsien, J.; Kossler, D.; Bastida, I.; Asai, S.; Bi, C.; Chen, J. S.; Shan, M.; et al. *Nature* **2018**, *560*, 350.
(24) Zhuang, Z.; Yu, C.-B.; Chen, G.; Wu, Q.-F.; Hsiao, Y.; Joe, C. L.; Qiao, J. X.; Poss, M. A.; Yu, J.-Q. *J. Am. Chem. Soc.* **2018**, *140*, 10363.
(25) Shi, H.; Herron, A. N.; Shao, Y.; Shao, Q.; Yu, J.-Q. *Nature* **2018**, *558*, 581.
(26) Park, H.; Verma, P.; Hong, K.; Yu, J.-Q. *Nat. Chem.* **2018**, *10*, 755.
(27) Wu, Q.-F.; Wang, X.-B.; Shen, P.-X.; Yu, J.-Q. *ACS Catal.* **2018**, *8*, 2577.
(28) Chapman, L. M.; Beck, J. C.; Wu, L.; Reisman, S. E. *J. Am. Chem. Soc.* **2016**, *138*, 9803.
(29) Chapman, L. M.; Beck, J. C.; Lacker, C. R.; Wu, L.; Reisman, S. E. *J. Org. Chem.* **2018**, *83*, 6066.
(30) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154.
(31) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965.
(32) Hoshiya, N.; Kobayashi, T.; Arisawa, M.; Shuto, S. *Org. Lett.* **2013**, *15*, 6202.
(33) Shan, G.; Huang, G.; Rao, Y. *Org. Biomol. Chem.* **2014**, *13*, 697.
(34) Feng, Y.; Chen, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 958.
(35) Ting, C. P.; Maimone, T. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 3115.
(36) Affron, D. P.; Bull, J. A. *Eur. J. Org. Chem.* **2016**, No. 1, 139.
(37) Shen, P.-X.; Hu, L.; Shao, Q.; Hong, K.; Yu, J.-Q. *J. Am. Chem. Soc.* **2018**, *140*, 6545.
(38) Hu, L.; Shen, P.-X.; Shao, Q.; Hong, K.; Qiao, J. X.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2019**, *58*, 2134.
(39) Unfortunately, our efforts to derivatize the 8-aminoquinolinamide without epimerization to the trans-cyclobutane proved unfruitful.
(40) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, *345*, 437.
(41) Chu, L.; Ohta, C.; Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 10886.
(42) Noble, A.; McCarver, S. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 624.

(43) Johnston, C. P.; Smith, R. T.; Allmendinger, S.; MacMillan, D. W. C. *Nature* **2016**, *536*, 322.
(44) Huihui, K. M. M.; Caputo, J. A.; Melchor, Z.; Olivares, A. M.; Spiewak, A. M.; Johnson, K. A.; DiBenedetto, T. A.; Kim, S.; Ackerman, L. K. G.; Weix, D. J. *J. Am. Chem. Soc.* **2016**, *138*, 5016.
(45) Cornella, J.; Edwards, J. T.; Qin, T.; Kawamura, S.; Wang, J.; Pan, C.-M.; Gianatassio, R.; Schmidt, M.; Eastgate, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 2174.
(46) Edwards, J. T.; Merchant, R. R.; McClymont, K. S.; Knouse, K. W.; Qin, T.; Malins, L. R.; Vokits, B.; Shaw, S. A.; Bao, D.-H.; Wei, F.-L.; et al. *Nature* **2017**, *545*, 213.
(47) Huang, L.; Olivares, A. M.; Weix, D. J. *Angew. Chem. Int. Ed.* **2017**, *56*, 11901.
(48) Suzuki, N.; Hofstra, J. L.; Poremba, K. E.; Reisman, S. E. *Org. Lett.* **2017**, *19*, 2150.
(49) Cheng, W.-M.; Shang, R.; Fu, M.-C.; Fu, Y. *Chem. – Eur. J.* **2017**, *23*, 2537.
(50) Fawcett, A.; Pradeilles, J.; Wang, Y.; Mutsuga, T.; Myers, E. L.; Aggarwal, V. K. *Science* **2017**, *357*, 283.
(51) Steves, J. E.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 15742.
(52) Wotal, A. C.; Weix, D. J. *Org. Lett.* **2012**, *14*, 1476.
(53) Several direct decarboxylative coupling reactions using [Ir]/[Ni] catalyst systems performed poorly on this substrate. For example, cross-coupling of **223** with 3-phenyl-1-bromopropane under [Ir]/[Ni] (see ref. 40) resulted in formation of the corresponding ester.
(54) Hirokawa, T.; Kuwahara, S. *Tetrahedron* **2012**, *68*, 4581.
(55) Hirokawa, T.; Nagasawa, T.; Kuwahara, S. *Tetrahedron Lett.* **2012**, *53*, 705.
(56) García-Morales, C.; Ranieri, B.; Escofet, I.; López-Suarez, L.; Obradors, C.; Konovalov, A. I.; Echavarren, A. M. *J. Am. Chem. Soc.* **2017**, *139*, 13628.
(57) Under the conditions reported in Table **2.1**, significant amounts of the bis-arylated product (**220**) was formed (Scheme **2.9**). Use of 2-iodofuran instead of **218** resulted in lower yields.
(58) Annangudi, S. P.; Sun, M.; Salomon, R. G. *Synlett* **2005**, *2005*, 1468.
(59) Ranieri, B.; Obradors, C.; Mato, M.; Echavarren, A. M. *Org. Lett.* **2016**, *18*, 1614.
(60) Reetz, M. T.; Westermann, J.; Kyung, S.-H. *Chem. Ber.* **1985**, *118*, 1050.
(61) Miles, W. H.; Duca, D. G.; Freedman, J. T.; Goodzeit, E. O.; Hamman, K. B.; De, S. C. A. P.; Selfridge, B. R. *Heterocycl. Commun.* **2011**, *13*, 195.
(62) Zúñiga, A.; Pazos, G.; Besada, P.; Fall, Y. *Tetrahedron Lett.* **2012**, *53*, 4293.
(63) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.