CHAPTER 2

Orthogonal Synthesis of Indolines and Isoquinolines via Aryne Annulation

2.1 INTRODUCTION

The challenge of incorporating nitrogen into organic molecules has confronted researchers since the emergence of organic synthesis as an independent field of study.[1] As synthetic chemistry has advanced, the target structures for synthesis have grown increasingly complex, requiring constant evolution in the methods available to make them. Consequently, there has been a sustained focus on the synthesis of nitrogen-containing benzannulated heterocycles that spans more than 120 years.[2] The justification for this persistent synthetic effort is due to the prevalence of these heterocycle motifs in molecules that have interesting structures[3] or unique biological activity.[4] In the chapter that follows, the efforts to construct two such benzannulated moieties—indoles and isoquinolines—will be discussed in the context of both historical and contemporary reports devoted to the synthesis of these exceptionally valuable molecules.[5] This survey of indole and isoquinoline syntheses will focus on well-cited techniques used to make

these heterocycles, and consider their impact from a strategic perspecitive. Methods that incorporate the base structural motif into a larger, polycyclic system have been omitted.

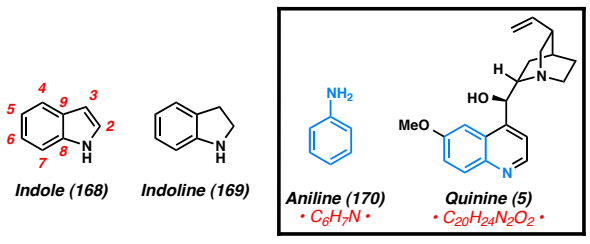
2.2 A SURVEY OF INDOLE AND ISOQUINOLINE SYNTHETIC METHODS

2.2.1 Indole Synthesis

2.2.1.1 Indole Background

As organic synthesis began to coalesce as an established scientific field during the late 19th century, the rational design of methodical approaches to specific structures was superseded in importance by efforts to understand basic chemical reactivity. The contemporary synthetic approach to the important alkaloids of the day centered on aniline motifs (**170**), which were widely believed to be synthetic precursors to many natural products, such as quinine (**5**, Figure 2.1).[6] This assumption, while naive in hindsight, was based on the limited structural data available to pioneering synthetic chemists; all such information was based on the empirical formula of a molecule. As such, many early indole syntheses used aniline-like starting materials, and were serendipitous in nature. They did, however, predominantly rely upon closure of the heterocycle by terminal C(3)–C(9) bond forming reactions.

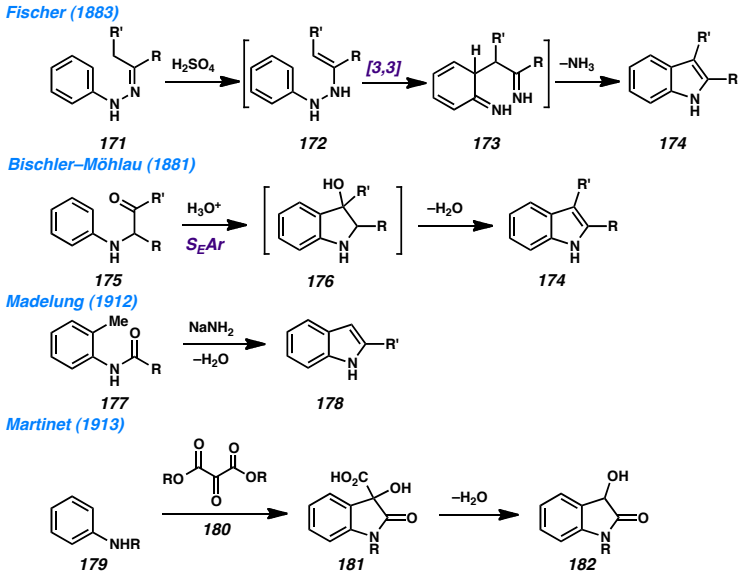
Figure 2.1. *The indole heterocycle and the aniline component in quinine (**5**)*



2.2.1.2 Indole Synthesis by Terminal C–C Bond Formation

In their efforts to understand the properties of aryl hydrazones (**171**),[7] Fischer and Jourdan discovered that treatment with acid led to the formation of indole derivatives (**174**, Scheme 2.1). Later examination of the reaction mechanism indicated that it proceeds through an ene-hydrazine intermediate (**172**) and *[3,3]*-sigmatropic rearrangement (**173**) before forming the indole (**174**).[8]

Scheme 2.1. *Early developments in indole synthesis with terminal C–C bond formation*

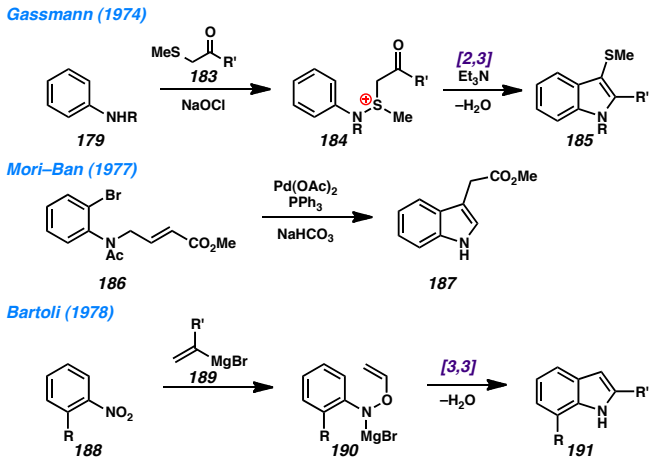


Concomitant with this work, Bischler and Möhlau independently reported that aryl ketones α-substituted with anilines (**175**) undergo electrophilic aromatic substitution (**176**) and dehydration when treated with acid, to produce indole derivatives (**174**).[9] Later, Madelung discovered that *ortho*-alkyl acetanilides (**177**), when treated with amide bases, provide alkyl indoles (**178**).[10] Soon afterward, Martinet used an intermolecular approach that condenses an *N*-alkyl aniline with an equivalent of mesoxalic acid diester

180 to form β-keto acid **181**. Subsequent decarboxylation of this intermediate furnishes 3-hydroxy-2-oxindole **182**.[11]

As synthesis advanced, the understanding of structure and reactivity significantly improved. Consequently, the synthetic approaches to indoles became much less serendipitous and far more calculated in the modern era, expanding to include additional intermolecular processes. Gassman reported that alkyl anilines (**179**), when mixed with α-sulfidoketones (**183**) in the presence of an oxidant, yield 3-thioindoles (**185**) after a [2,3] sigmatropic rearrangement of sulfonium intermediate **184** (Scheme 2.2).[12] Mori and Ban reported that *N*-allyl, *o*-bromo anilines (**186**), in the presence of a catalytic amount of palladium, undergo a Heck-type C–C bond formation to construct derivatives of 3-indoleacetic acid (**187**).[13] In another organometallic approach, Bartoli disclosed the synthesis of indoles (**191**) by successive reduction of *o*-functionalized nitrobenzenes (**188**) with excess vinyl Grignard reagents (e.g., **189**).[14] The intermediate alkoxyaniline (**190**) then undergoes a [3,3]-sigmatropic rearrangement and subsequent condensation to form the product (**191**).

Scheme 2.2. *Modern indole syntheses terminating in C–C bond formation*

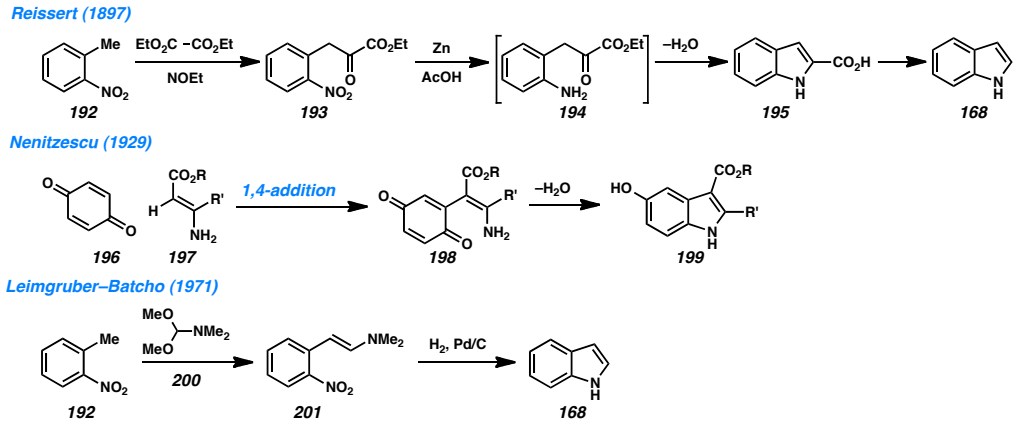


The roots of indole synthesis lie with aniline precursors, making closure of the heterocycle via C–C bond formation a natural direction to take these endeavors. Simultaneously with all of this work, however, many efforts were underway to employ a complementary strategic approach.

2.2.1.3 Indole Synthesis by Terminal C–N Bond Formation

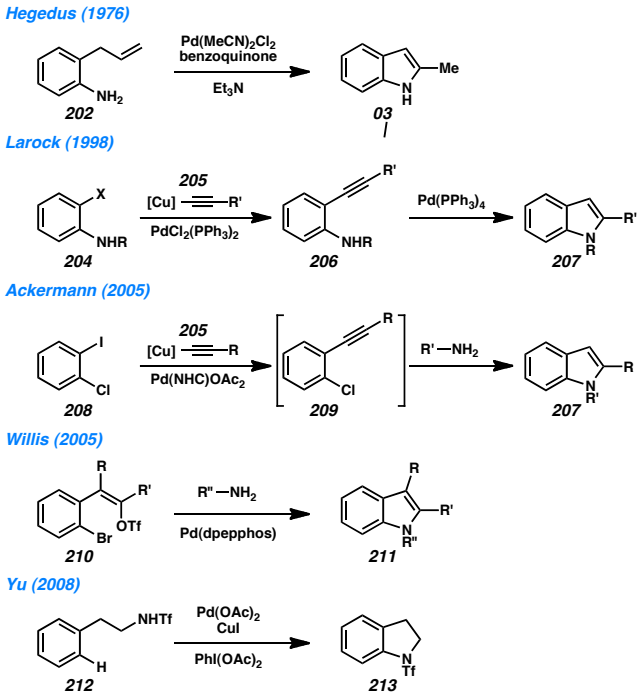
The development of nitroaromatic explosives in the 1800s gave the synthetic community a practical understanding of these compounds. Largely as a result of this knowledge base, Reissert was able to complete the first rational, de novo indole synthesis (Scheme 2.3).[15] Beginning with *o*-nitrotoluene (**192**), reaction with diethyloxalate under basic conditions installs the α-ketoester at the benzylic position (**193**). In the next step, reduction of the nitro group reveals aniline intermediate **194** that cyclizes upon the pendant ketone to furnish indole-2-carboxylic acid (**195**). Finally, thermal decarboxylation of **195** produces indole (**168**). Nenitzescu reported a unique approach to indole synthesis by coupling benzoquinone (**196**) with β-aminocrotonic esters (**197**), and cyclizing the product (**198**) to furnish 5-hydroxy indoles (**199**).[16] The Leimgruber–Batcho synthesis was developed in analogy to the Reissert synthesis, beginning with *o*-nitrotoluene (**192**) and performing a benzylic condensation with an orthoamide (**200**), and reducing the nitro-enamine product with catalytic palladium to furnish indole (**201**).[17]

Scheme 2.3. *Indole syntheses employing terminal C–N bond formation*



More recently, a number of transition metal-catalyzed transformations have exploited this late-stage C–N bond formation to close the indole heterocycle (Scheme 2.4). Hegedus has developed an alternative approach mediatated by a Pd(II) catalyst, where the amine of *o*-allyl anilines (**202**) performs a Wacker-type oxidative cyclization onto the alkene to generate the 2-methylindole structure (**203**).[18] Larock disclosed an alternative, two-step palladium-catalyzed approach.[19] An *o*-halogenated aniline (**204**) is first coupled with alkynyl cuprates (**205**) to form alkynyl aniline **206**. A subsequent Pd-mediated cyclization forms the indole structure (**207**). Ackermann has extended Larock's general strategy to a one-pot, multicomponent indole synthesis from chloroiodobenzene (**208**), alkynyl cuprates (**2-5**) and alkylamines.[20] Similarly, Willis demonstrated that styrene derivatives (**210**) couple twice with a single alkyl amine to construct 1,2,3-trisbustituted indoles.[21] Yu has reported a novel approach. Phenethyl trifluoromethanesulfonamides (**212**), in the presence of a Pd/Cu bimetallic catalyst system and an iodonium oxidant, will undergo a C–H bond functionalization and ring closure to form the indoline (**213**).[22]

Scheme 2.4. *Transition metal-catalyzed indole syntheses*



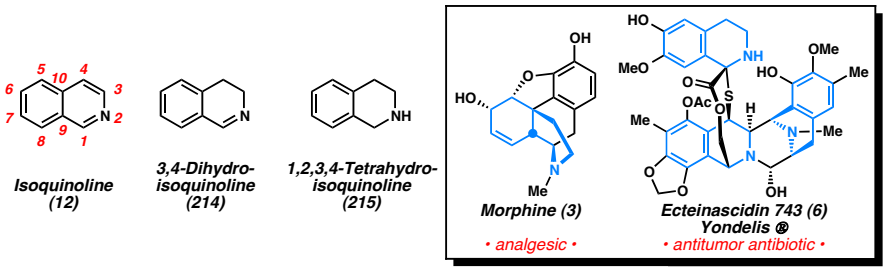
The growing body of methods for indole construction have very closely followed the history of synthetic strategies, transitioning from basic understanding, as in the case of the Fischer synthesis, to highly selective catalysis, as in the recent work done by Yu. The prolonged interest in this deceptively simple-looking bicyclic structure speaks to two points. First, indoles are extremely valuable structural motifs for their ubiquity in natural products and important bioactivity. Second, an ideal indole synthesis has not yet been developed, as there are specific limitations to each of these methods that will be addressed later in this chapter.

2.2.2 Isoquinoline Synthesis

2.2.2.1 Isoquinoline Background

Another exceptionally common benzannulated, nitrogen-containing heterocyclic motif is the isoquinoline (**12**, Figure 2.2).[5] This 6,6-bicyclic system has been the subject of a great deal of synthetic scrutiny, spanning a breadth of history comparable to indoles. This is largely because of the presence of isoquinoline motifs in molecules of tremendous societal importance, from the opiate morphine (**3**) to Et-743, the most potent broad-spectrum anticancer antibiotic approved for medical use (**6**). Isoquinolines are present in many oxidation states in nature, ranging from the parent molecule (**12**) to derivatives reduced on the heterocycle (**214** and **215**), and nearly saturated structures, as highlighted in morphine (**3**). The most common derivatives are di- and tetrahydroisoquinolines. As a consequence, the primary focus of the literature surveyed in the following section will be synthetic approaches to isoquinoline (**12**), dihydroisoquinoline (**214**, DHIQ) and tetrahydroisoquinoline (**215**, THIQ) structures.

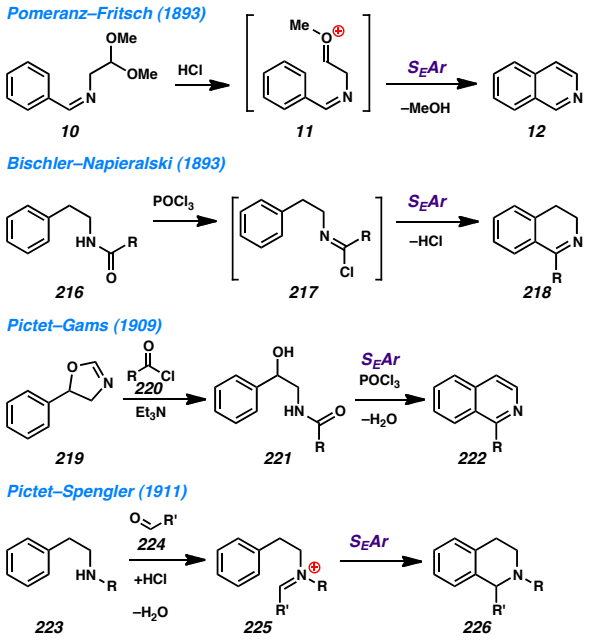
Figure 2.2. *The isoquinoline structure, its derivatives, and their appearance in natural products*



2.2.2.2 Isoquinoline Synthesis by Electrophilic Aromatic Substitution

As with some of the early indole syntheses, preliminary forays into isoquinoline synthesis were the result of serendipity more than experimental design (Scheme 2.5). However, these initial developments all followed an electrophilic aromatic substitution strategy that has enabled them to remain exceedingly effective throughout the surge of synthetic work over the last century. The first reported isoquinoline syntheses were disclosed separately by Pomeranz and Fritsch.[23] Benzaldimine **10**, in the presence of acid, undergoes C–C bond formation through oxocarbenium **11** to close the heterocyclic ring (**12**). The same year, Bischler and Napieralski disclosed a similar DHIQ synthesis (**218**) from phenethyl amides (**216**) through an intermediate chloroimidate (**217**) generated by phosphorus oxychloride.[24] Nearly two decades later, Amé Pictet published the first of his quintessential methods for isoquinoline construction.[25] The formal Pictet–Gams isoquinoline synthesis introduces a masked 1,2-amino alcohol (**221**) through a 3-aryl oxazoline (**219**). C–C bond formation through an electophilic aromatic substituton pathway (i.e. **221→222**), followed by acidic elimination of water, provides the isoquinoline (**222**) to complement the Bischler–Napieralski approach.

Scheme 2.5. *Isoquinoline synthesis by C–C bond formation via electrophilic aromatic substitution*



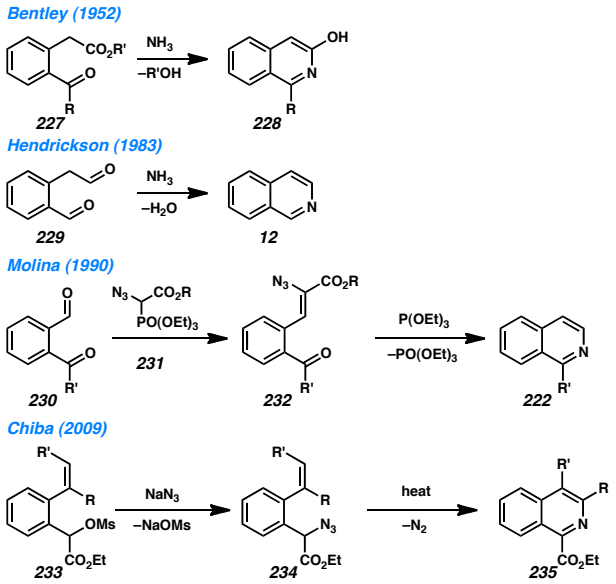
Pictet's 1911 demonstration that phenethylamine derivatives (**223**) and aldehydes (**224**), in the presence of strong acid, form *N*-acyliminium intermediates (**225**) was of seminal importance in the total synthesis of alkaloids.[26] These highly reactive species readily form C–C bonds and close to form THIQs (**226**). Pictet had unwittingly discovered the putative biosynthetic mechanism by which the broad range of THIQ natural products are generated.[27] This reaction has established itself as the gold standard for THIQ synthesis, and remains extremely relevant 101 years after its initial disclosure.[28]

2.2.2.3 Isoquinoline Synthesis by Late-Stage C–N Bond Formation

Since the discovery of the Pictet–Spengler THIQ synthesis, there have been a number of strategies explored to access the isoquinoline core structure that do not rely on electrophilic aromatic substitution reactions. Generally, these reactions have either relied upon a C–N bond forming cyclization at a late stage to close the heterocyclic ring of the

isoquinoline bicycle, or a transition metal catalyst to facilitate one of a series of possible bond-forming steps. While a great deal of effort has been invested in optimization of the Pictet–Spengler THIQ synthesis, efforts to advance the broad goal of isoquinoline synthesis have pursued an alternative tactical disconnection thru late-stage C–N bond formation (Scheme 2.6).[28b] Many of the 20th century efforts toward isoquinoline synthesis focused on this approach. Bentley proved that 2-acetyl phenylacetates (**227**) are converted to 3-hydroxyisoquinolines (**228**) in the presence of ammonia.[29] Henderson reported a similar isoquinoline synthesis from aryl di-aldehydes (**229**), again using ammonia as a nitrogen source.[30] More recently, Molina reported an intermolecular aza-Wittig reaction of *o*-acyl aryl aldheydes (**230**) with α-azidophosphonate **231** to generate intermediate styrenyl azide **232**, which, upon Staudinger reduction, furnishes the isoquinoline (**222**).[31] Chiba has reported another intermolecular reaction that effectively inverts the reactivity of intermediate azide intermediate **232** by beginning with benzyl mesylate **233** and in one pot, displacing it with sodium azide to form the stabilized benzyl azide intermediate (**234**), which cyclizes to produce the isoquinoline product (**235**).[32] This method is effective for generating fully substituted heterocyclic rings on isoquinolines.

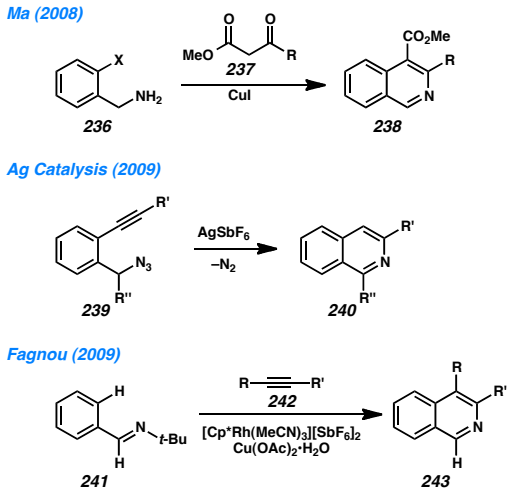
Scheme 2.6. *Synthesis of isoquinolines by C–N bond formation*



2.2.2.4 Isoquinoline Synthesis by Transition Metal-Catalyzed Processes

Outside of Chiba's report, most recent additions to the isoquinoline synthetic palette have used transition metal-catalyzed processes, following the trend observed in indole syntheses. Ma published the conversion of *o*-halogenated benzylamines (**236**) into 4-carboxyisoquinolines (**238**) through a copper catalyzed coupling with β-ketoesters (**237**, Scheme 2.7). The next year, Liang studied rearrangements of 2-alkynyl benzyl azides (**239**) with catalytic quantities of silver salts.[33] The resulting rearrangement provides 1,3-disubstituted isoquinolines (**240**) under mild conditions. Fagnou reported an interesting coupling of *tert*-butyl benzaldimines (**241**) with non-terminal alkynes (**242**) with a cationic rhodium catalyst that acts by a C–H functionalization to yield 3,4-difunctionalized isoquinoline (**243**).[34]

Scheme 2.7. *Transition metal-catalyzed isoquinoline syntheses*



2.2.3 Overview of Synthetic Approaches to Indoles and Isoquinolines

2.2.3.1 The Benefits of the Classical Methods

The effectiveness of the aforementioned strategies for the construction of indoles and isoquinolines is borne out by their manifold application in academic and commercial synthesis. For both systems, the classical methods (see Schemes 2.1, 2.3, and 2.5) embrace such fundamentally effective reaction pathways that entire research programs now focus on specific aspects of the transformation to marginally alter the reaction outcome.[28,35] Moreover, these well-worn processes combine largely abundant and inexpensive starting materials under reaction conditions that are reflective of the time in which the reactions were developed. The result is operationally simple, scalable synthesis. As a consequence, the large-scale synthesis of modestly functionalized indole and isoquinoline derivatives is still most effective using reactions that were discovered more than a century ago, when air-sensitive reagents and modern instrumentation were unknown.

The more recent approaches to these problems have emerged in a complementary role with their classical counterparts, and solve highly specific problems tailored to a subset of indoles and isoquinolines. Still, in combination with the highly effective classical approaches, transition metal catalyzed processes, and well-tailored metal-free transformations have broadened the pool of target molecules accessible through synthesis.

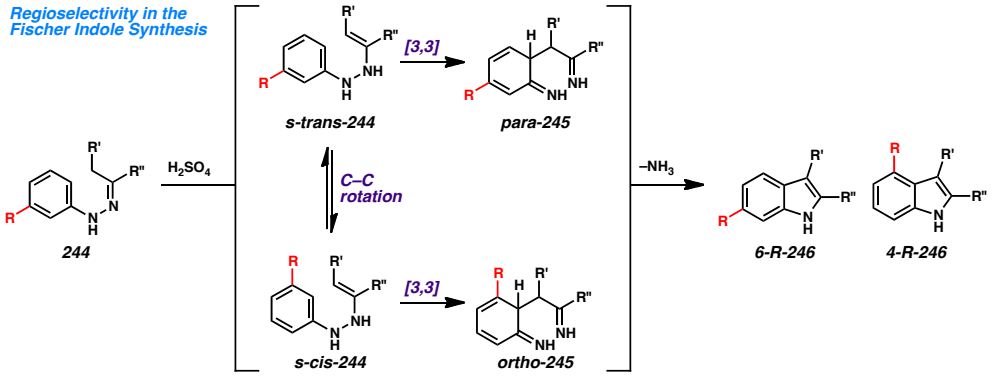
2.2.3.2 A Case for Further Reaction Discovery

In spite of the operational simplicity of the classical heterocycle syntheses, the field of chemical synthesis is advancing to a point where minute structural differences have a tremendous impact on the outcome of reactions and dramatically alter the effects of small molecules in biological systems.[36] Given the pressure on the synthetic community to produce greater quantities of more complex molecules in fewer steps with greater efficiency while simultaneously generating less waste, the beneficial operational simplicity of the classical heterocyclic syntheses is reaching a point where it is outweighed by these other concerns.[37] The shortcomings of such strategies are the direct result of the fundamental transformations that make these reactions so appealing in the first place.

Addressing these concerns for indole and isoquinoline substructures is more pressing than in most cases as a result of the popularity of these structures within bioactive natural products and drug agents.[5,27] In order to do so, methodologies must be developed that are high yielding, highly selective, and applicable to a wide variety of molecular targets. For instance, the Fischer indole synthesis is a high-yielding

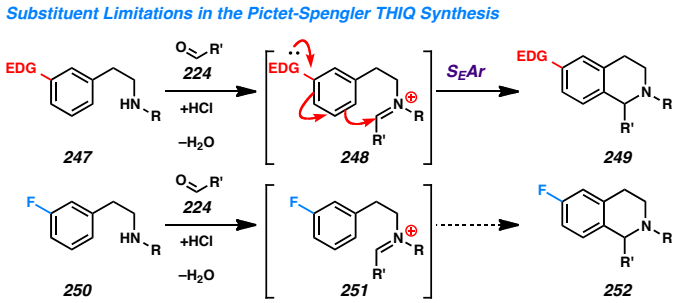
transformation that is applicable to a large number of indole substrates, helping it meet two of the three methodological criteria (Scheme 2.8). However, this strategy is poorly selective when *meta*-substituted aryl hydrazones (**244**) are used, yielding mixtures of 4- and 6-substituted indole products (**256**).[38] Typically, the 6-subtituted indoles are the preferred products, so a selective synthesis of 4-substituted indoles is an unmet need.

Scheme 2.8. *Systemic limitations of the Fischer indole synthesis*



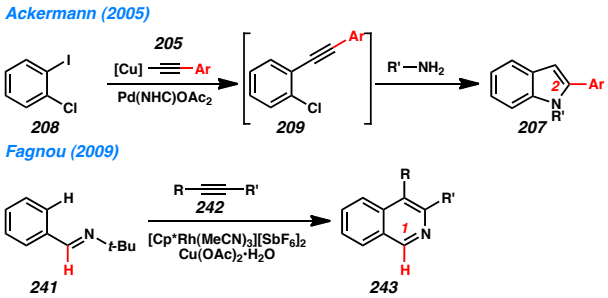
A different flaw exists in the venerable Pictet–Spengler THIQ synthesis, which proceeds through an electrophilic aromatic substitution to form the final C–C bond of the heterocycle (**248→249**, Scheme 2.9). While this process is also high yielding, it is highly selective at the cost of structural diversity. The terminal bond formation reaction requires electron-rich aromatic rings in order to yield the tetrahydroisoquinoline (**249**).[39] Installation of an electron-withdrawing substituent like a fluoride (**250**) will shut down the C–C bond-formation at acyliminium **251**, and will fail to produce the targeted THIQ (**252**). In order to include such a functional group, an extensive work-around with functional group manipulation must be employed, thereby negating the benefits of the Pictet–Spengler approach.[40]

Scheme 2.9. *Systemic limitations in the Pictet–Spengler THIQ synthesis*



In addition to the strategic flaws in these well-known methods for heterocycle synthesis, the shortcomings of many state-of-the-art methodologies are their substrate scope limitations. This is particularly true in transition-metal catalyzed processes, which employ starting materials that are designed to favor the desired bond-forming reactions (Scheme 2.10). In the Ackermann synthesis of indoles through a three-component reaction of *o*-chloro iodobenzene (**208**) with amines and alkynyl cuprates (**205**), the substituent on the alkyne component must be an arene, resulting exclusively in the synthesis of 2-aryl indoles (**207**).[20] Similarly, in Fagnou's isoquinoline synthesis, the *tert*-butyl aldimine substituent (**241**) is immutable for the reaction to occur. Thus, all products are C(1)-hydrogen-substituted isoquinolines (**243**).[34]

Scheme 2.10. *Limitations of transition metal-mediate indole and isoquinoline syntheses*



In order to address these concerns, a fundamentally new method needs to be investigated to form these heterocycles. To overcome the selectivity issues observed in the Fischer indole synthesis, the new approach requires a substrate that will be immune to electronic and steric effects. Similarly, to remove the electronic limitations of the Pictet–Spengler reaction, the method must include a reactive intermediate that is insensitive to the nature of functional groups. Finally, in order to emerge as a general approach to the synthesis of isoquinolines and indolines, the partners in this reaction must be easy to construct, readily functionalized, and capable of reacting in a number of combinations. Fortuitously, the research interests of the Stoltz lab had already encountered such an intermediate in previous work.[41]

2.3 ORTHOGONAL SYNTHESIS OF INDOLINES AND ISOQUINOLINES VIA ARYNE ANNULATION[42,43,†]

2.3.1 Design of an Aryne Annulation Reaction for the Synthesis of Indolines

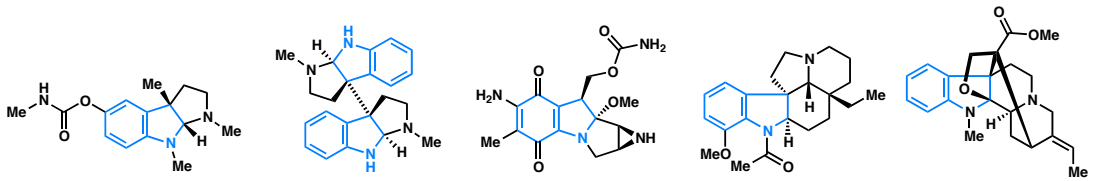
Given the opportunity to develop a broad-based approach to heterocyclic scaffolds, we reasoned that benzyne would be a suitable reaction partner in the belief that it is sufficiently active to generate a number of benzannulated heterocyclic products. Moreover, the historical importance of arynes highlights benzyne as a competent electrophile for a wide range of nucleophiles.[44,45,46,47,48] The intermediate aryl anions generated after addition of a nucleophile can readily participate in subsequent additions to other electrophiles, either in an intramolecular[49] or an intermolecular manner.[50] Our group had previously examined arynes as reaction intermediates by developing an acyl-

[†] This work was performed in collaboration with Dr. Kevin M. Allan, a fellow graduate student in the Stoltz research group.

alkylation of arynes,[41] and applying this methodology to the total synthesis of amurensinine, a tetrahydroisoquinoline alkaloid.[51] Because of the proven versatility of aryne reactive intermediates, and our group's ongoing interest in them, we elected to design an aryne-based synthesis of indolines.

Our interest in indolines stems directly from the presence of this motif in many natural products that have unique structural motifs and interesting biological activity (Figure 2.3). The examples below (**253**–**257**) showcase the diversity of naturally occurring indoline scaffolds. The widely varied structures also underscore the challenge to a synthetic chemist concerned with developing a new method for constructing indoline intermediate to be carried on to each of these target molecules. The successful development of such a direct method for their synthesis from easily prepared materials would reveal new approaches to unrelated substances relevant to the advancement of medicine.

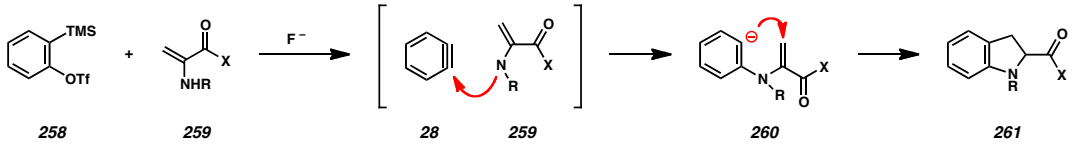
Figure 2.3. *Biologically active natural products containing indolines*



We envisioned a novel method for the synthesis of indolines (**261**) from arynes (**28**) and dehydro-amino acid species (**259**) (Scheme 2.11). Specifically, we expected the nitrogen atom of **259** to undergo nucleophilic addition to benzyne (**28**), to generate an intermediate aryl anion (**260**) that performs a conjugate addition to the α,β-unsaturated

carbonyl and closes the five-membered ring of indoline **261**. While we were confident that the initial addition of the nitrogen nucleophile (**260**) would occur, the conjugate addition was unprecedented as a means to quench the resultant anion.[52] We therefore examined the viability of our strategy for indoline synthesis.[53]

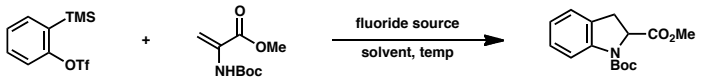
Scheme 2.11. *Proposed indoline synthesis via aryne annulation*



258 *259* *28* *259* *260* *261*

Our initial efforts focused on substrates derived from amino acids, specifically *N*-Boc dehydroalanine methyl ester (**262**) in combination with Kobayashi's *o*-silyl aryl triflate (**258**) (Table 2.1).[54,55] We first examined the conditions previously used to promote aryne acyl-alkylation (entry 1).[41] Gratifyingly, this initial attempt produced the desired indoline methyl ester (**263**) in 35% yield, confirming the viability of our aryne annulation strategy to these heterocycles. We proceeded to examine alternative sources of fluoride for generating benzyne. Both cesium fluoride (entries 1 and 2) and potassium fluoride (entries 3–6) promoted formation of the indoline, but tetra-*n*-butylammonium difluorotriphenylsilicate (TBAT) (entries 7–13) proved to be the optimal fluoride source. TBAT is soluble in several common organic solvents, which facilitates purification by eliminating the filtration or aqueous extractions required when using KF and CsF. TBAT performed well at room temperature (25 °C), with yields comparable to those obtained with other fluoride sources with heat. By lowering the molarity of the reaction to 0.02 M, the formation of minor undesired side products could be minimized, leading ultimately to the isolation of indoline **263** in 61% yield (entry 13).

Table 2.1. *Optimization of indoline synthesis via aryne annulation*

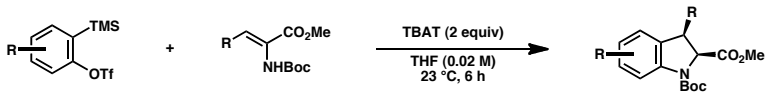


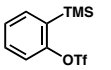
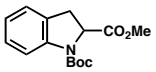
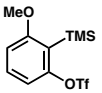
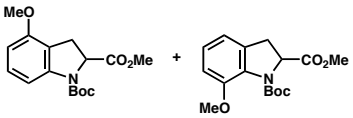
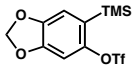
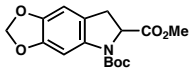
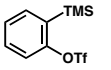
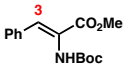
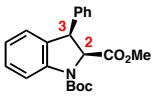
258 ***262*** ***263***

entry	aryne equivalents	fluoride source	fluoride equivalents	solvent	conc. [***258***] (M)	temp. (°C)	yield
1	1.5	CsF	2.0	MeCN	0.2	80	35%
2	1.5	CsF	2.0	MeCN	0.2	25	15%
3	1.5	KF / 18-Crown-6	2.0	THF	0.2	25	44%
4	1.5	KF / 18-Crown-6	2.0	THF	0.2	40	27%
5	1.0	KF / 18-Crown-6	1.5	THF	0.2	25	16%
6	2.0	KF / 18-Crown-6	2.0	THF	0.2	25	47%
7	2.0	TBAT	2.0	CH_2Cl_2	0.1	25	53%
8	2.0	TBAT	2.0	THF	0.2	25	45%
9	2.0	TBAT	2.0	THF	0.2	40	33%
10	2.0	TBAT	2.0	THF	0.1	25	45%
11	2.0	TBAT	2.0	THF	0.1	40	22%
12	2.0	TBAT	2.0	THF	0.02	40	47%
13	**2.0**	**TBAT**	**2.0**	**THF**	**0.02**	**25**	**61%**

With these optimal conditions, we examined a series of substituted aryne precursors and enamines (Table 2.2). Symmetrical aryne precursors produced the expected indolines in good yield (entries 1 and 3). Surprisingly, the unsymmetrically substituted *ortho*-methoxy aryne precursor, 3-methoxy-2-(trimethylsilyl)phenyl triflate (**264**), generated a 2.3:1 mixture of isomeric products, **265a** and **265b** (entry 2). Interestingly, installing a phenyl substituent at the β-position of the enamine (**268**) furnished 2,3-disubstituted indoline **269** in 40% yield. This result suggests that substitution at C(3) does not substantially impact reactivity. Notably, the syn disposition of the C(2) ester and the C(3) phenyl ring hints that the reaction proceeds through a polar mechanism; the product of a concerted reaction would reflect the anti relationship of the ester and phenyl groups in the enamine substrate (**268**).

Table 2.2. *Substrate scope for indolines by aryne annulation*[a]

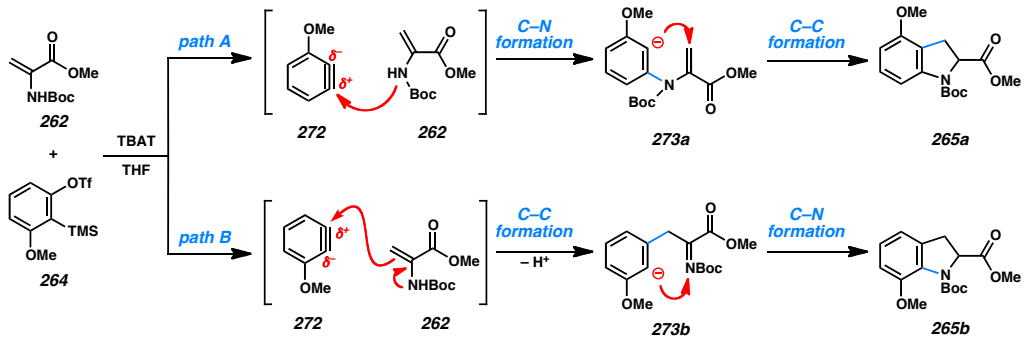


entry	silyl aryl triflate	ene carbamate	product	yield
1	 ***258***	 ***262***	 ***263***	61%
2	 ***264***	 ***262***	 ***265a*** **2.3 : 1** ***265b***	49%
3	 ***266***	 ***262***	 ***267***	39%
4	 ***258***	 ***268***	 ***269***	40%

[a] Reaction performed with 2.0 equiv ortho-silyl aryl triflate **258** relative to enamine **262**.

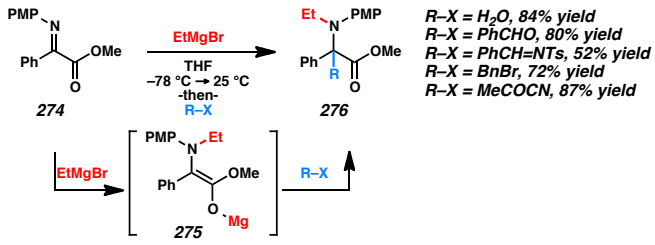
The result of the reaction with 3-methoxy-substituted aryne (from **264**) produced a mixture of isomeric indolines (**265a** and **265b**) in spite of literature precedent that this aryne promotes high levels of regioselectivity in several other reactions.[56,57] In order to reconcile this result with our initial mechanism, we considered that this poor regioselectivity might be attributable to alternative reaction pathways leading to the same product (Scheme 2.12). The initially proposed nucleophilic attack of nitrogen *meta* to the methoxy substitutient on aryne **272** (path A) might be competing with enamine addition to the aryne from C(β) of the starting material (path B).[58] If this is the case, an iminoester (**273b**) is generated as an intermediate anion instead of acrylate **273a**. Then, similarly to the proposed intramolecular conjugate addition that forms indoline **265a**, the umpolung addition of the aryl anion to the imine nitrogen would form a C–N bond to complete the five-membered ring, yielding indoline **265b**.

Scheme 2.12. *Competing reaction pathways for indoline formation*



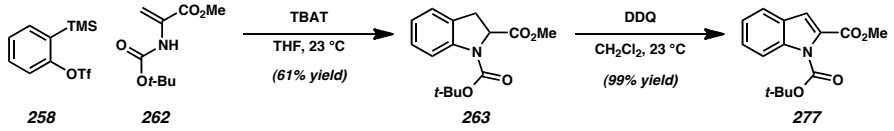
The observed product ratio seems to indicate that initial nucleophilic addition by the carbamate nitrogen is the more favorable mechanistic pathway (path A). Interestingly, this combination of mechanisms likely contributes to the formation of all observed indolines, but is only apparent when unsymmetrical arynes such as **264** are employed. The proposed nucleophilic addition directly to nitrogen (**273b→265b**) is unusual, but similar umpolung pathways have been reported with α-iminoesters[59] (e.g., **274**) and 2-iminomalonates[60] using Grignard and alkylaluminum reagents (Scheme 2.13).[61] Koslowski has demonstrated that intermediate magnesium ketene acetates (**275**) can actually be intercepted by electrophiles, in very close analogy to our proposal for the alternative reaction mechanism (path B).

Scheme 2.13. *Koslowski's umpolung nucleophilic C–N bond formation in α-iminoesters*



Given our initial interest in developing an indole synthesis to complement the many existing approaches to this heterocycle, we were pleased to discover that our indoline products (**263**), when treated with an equivalent of the mild oxidant DDQ, can be rapidly converted to their indole analogues (**277**) in nearly quantitative yield (Scheme 2.14). Through this two-step procedure, we believe that our convergent aryne annulative path to indole synthesis is an effective platform for futher development.

Scheme 2.14. *Two-step indole synthesis by aryne annulation*



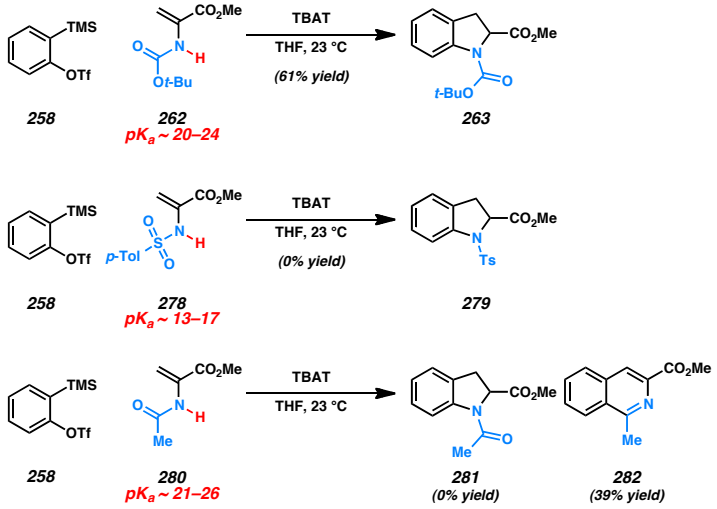
258 *262* *263* *277*

2.3.2 Synthesis of Isoquinolines via Aryne Annulation

In an effort to favor one reaction pathway over the other and increase the yield of the overall process, we examined alternative nitrogen functional groups that would impact the nucleophilicity of the enamine π-system by altering the pK_a of the N–H bond. As a result of the fluoride sources required for aryne generation, the reaction conditions are mildly basic. Thus, we reasoned that an electron-withdrawing nitrogen group might be sufficient to enable deprotonation to an amide, and favor pathway A over pathway B (see Scheme 2.12).[62] We considered a tosylamide (**278**) because of its increased electron withdrawing potential relative to the *tert*-butyl carbamate (**262**) used thus far to form the *N*-Boc indoline (**263**, Scheme 2.15). When subjected to the reaction conditions with TBAT and silyl aryl triflate **258**, the tosylamide rapidly decomposed, and none of the desired tosylindoline (**279**) was isolated. At this point we recognized that an *N*-acetyl

group might be capable of accomplishing the same goal of modulating nitrogen nucleophilicity. Thus, commercially available methyl-2-acetamidoacrylate (**280**) was subjected to our optimized conditions for indoline formation. To our surprise, instead of isolating the expected *N*-acetyl indoline (**281**), we found that methyl 1-methylisoquinoline-3-carboxylate (**282**) was the sole product generated.

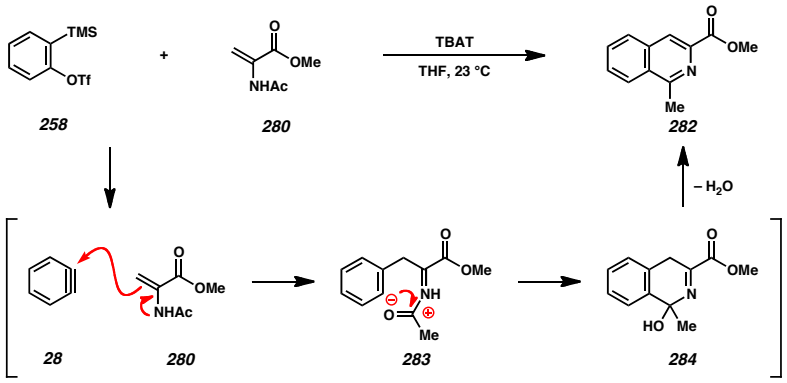
Scheme 2.15. *Examining the impact of the nitrogen functional group*



This unexpected heterocycle is most likely formed by nucleophilic addition of the enamine carbon to benzyne (**28**), followed by intramolecular addition of the aryl anion (**283**) to the carbonyl of the intermediate *N*-acetylimine (Scheme 2.16). Subsequent aromatization through dehydration of dihydroisoquinoline **284** produces the isoquinoline.[63] If this mechanism is operative, exchange of the carbamate for the acetamide leads to favorable C–C nucleophilic attack instead of initial C–N bond formation as we had anticipated. Moreover, the *N*-acetyl α-imino ester proves to be an inferior electrophile for intramolecular aryl anion addition in comparison to the acetyl

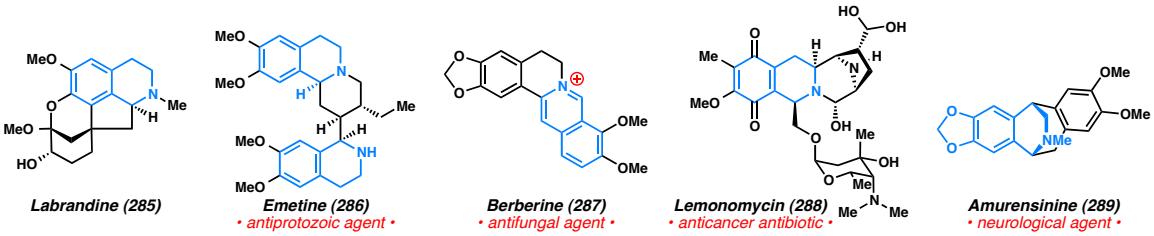
group. Our further insights into this reaction mechanism will be presented in more detail later in this chapter.

Scheme 2.16. *Unexpected formation of an isoquinoline through an alternative aryne annulation*



This serendipitous result caused us to immediately pursue this new reactivity. The isoquinoline structure is unique in its presence among the biologically active alkaloids (Figure 2.4).[5] Moreover, the Stoltz group had an outstanding interest in such structures, including our previously reported total syntheses of the THIQ alkaloids lemonomycin (**288**) and amurensinine (**289**). With an eye toward these synthetic applications, we turned our attention to optimizing this new reaction pathway.

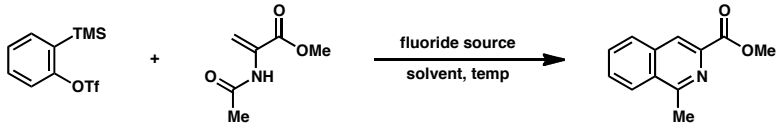
Figure 2.4. *Bioactive natural products containing isoquinolines and isoquinoline derivatives*



In order to exploit this unforeseen reactivity, we initiated a screen of reaction conditions to improve the yield of isoquinoline **282** (Table 2.3). Cesium fluoride once again was effective as a fluoride source (entries 1–6), forming the desired isoquinoline in

up to 65% yield at room temperature (entry 3). Potassium fluoride was less competent for the transformation than cesium fluoride (entries 7–9). As in the indoline methodology, however, TBAT proved to be a superior fluoride source (entries 11–14). Using this reagent, isoquinoline **282** could be synthesized in up to 87% yield when the reaction was performed in THF at a low concentration (0.01 M) (entry 14).

Table 2.3. *Optimization of reaction conditions for isoquinoline synthesis via aryne annulation*



258 ***280*** ***282***

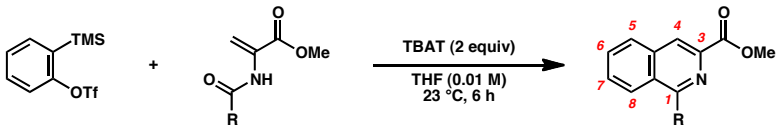
entry	aryne equivalents	fluoride source	fluoride equivalents	solvent	conc. [***258***] (M)	temp. (°C)	yield
1	1.5	CsF	2.0	MeCN	0.2	25	57%
2	1.5	CsF	2.0	MeCN	0.1	25	61%
3	2.0	CsF	2.0	MeCN	0.2	25	65%
4	1.5	CsF	2.0	MeCN	0.1	25	30%
5	1.25	CsF	2.0	MeCN	0.2	25	50%
6	1.25	CsF	2.0	THF	0.2	25	0%
7	2.0	KF / 18-C-6	3.0	THF	0.2	25	36%
8	1.5	KF / 18-C-6	2.0	THF	0.2	25	34%
9	2.0	KF / 18-C-6	3.0	THF	0.2	40	40%
10	2.0	TBAF	2.0	CH_2Cl_2	0.2	25	13%
11	2.0	TBAT	2.0	CH_2Cl_2	0.2	25	71%
12[a]	2.0	TBAT	2.0	CH_2Cl_2	0.2	120	56%
13	2.0	TBAT	2.0	THF	0.2	40	77%
14	**2.0**	**TBAT**	**2.0**	**THF**	**0.01**	**25**	**87%**

[a] Performed in a microwave reactor.

From a synthetic standpoint, the isoquinoline structure contains a number of sites for introduction of synthetic functionality, and this aryne annulation enables a convergent assembly of these functionalized derivatives. For example, isoquinolines bearing substitution at carbons 1, 3, and 4 are accessible through manipulation of the dehydroamino ester, while functionality at carbons 5–8 can be introduced through the

aryne. To systematically confirm this approach, we prepared a series of *N*-acyl dehydroalanine methyl esters (**290**) for the synthesis of C(1)-substituted isoquinolines (**291**) (Table 2.4). To our delight, the reaction proved quite tolerant to the introduction of a wide variety of functionality at this position, ranging from linear and branched alkyl chains (entries 1–4) to aryl groups (entries 5 and 6) and even heteroatom-functionalized sidechains (entries 7–9). Importantly, the carbon atom α to the amide carbonyl can be introduced in several different oxidation states—from alkane (entries 1–5) to alcohol (entries 6 and 8) to carboxylic acid (entries 7 and 9)—without diminishing product yields. Moreover, benzyne is competent in a reaction with *N*-formyl enamides (**290i**) to generate the C(1)-*H* product (entry 10).

Table 2.4. *Synthesis of C(1)-substituted isoquinolines via aryne annulation*[a]



258 ***290*** ***291***

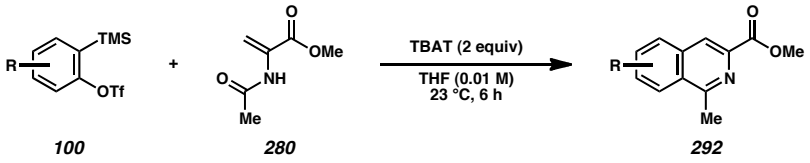
entry	*N-acyl enamine (**290**)*	*isoquinoline (**291**)*	*yield*
1	***280*** **R = Me**	***282*** **R = Me**	87%
2	***290a,*** **R = *n*-Bu**	***291a,*** **R = *n*-Bu**	76%
3	***290b,*** **R = *i*-Pr**	***291b,*** **R = *i*-Pr**	66%
4	***290c,*** **R = *c*-Hex**	***291c,*** **R = *c*-Hex**	65%
5	***290d,*** **R = Bn**	***291d,*** **R = Bn**	72%
6	***290e,*** **R = Ph**	***291e,*** **R = Ph**	55%
7	***290f,*** **R = CF_3**	***291f,*** **R = CF_3**	57%
8	***290g,*** **R = CH_2OMe**	***291g,*** **R = CH_2OMe**	68%
9	***290h,*** **R = CO_2Me**	***291h,*** **R = CO_2Me**	51%
10	***290i,*** **R = H**	***291i,*** **R = H**	71%

[a] Reaction performed with 2.0 equiv *ortho*-silyl aryl triflate **258** relative to enamine **290**.

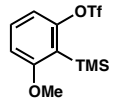
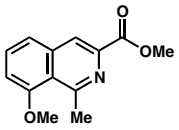
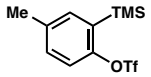
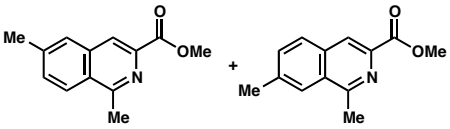
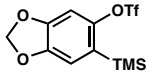
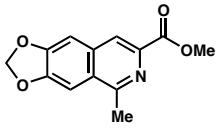
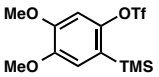
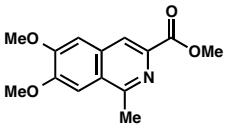
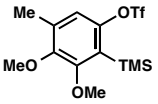
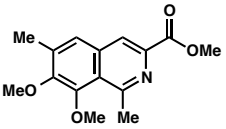
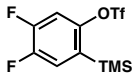
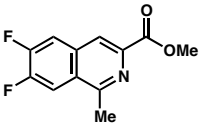
Next, we turned our attention to the effect of aryne substitution on reactivity. Using methyl 2-acetamidoacrylate (**280**) as a base *N*-acyl enamine, we examined a pair of monosubstituted arynes displaying functionality *ortho* and *meta* to the reactive aryne

bond (**264** and **293**) in addition to three disubstituted arynes (**266**, **294**, and **296**) and one trisubstituted aryne (**295**, Table 2.5). All six substrates provided the expected isoquinolines (**292a**–**g**) in good yield. Significantly, both electron-rich (entries 1–4) and electron-deficient (entry 5) arynes successfully underwent aryne annulation. Interestingly, difluoroaryne **296** reacted most rapidly, likely because of enhanced electrophilicity imparted by the inductively withdrawing fluoride substitution. We were also delighted that *o*-methoxy aryne generated from precursor **264** formed only one product isomer (**292a**) derived from the expected mode of nucleophilic attack *meta* to the ether. Importantly, the aryne generated from dimethoxymethyl precursor **295** does not produce an isomeric mixture of isquinolines, and instead yields only the product **292f** (entry 5). To illustrate the negligible effects of *meta*-alkyl substituents upon aryne reactivity, the *meta*-methyl aryne (**293**) provided a 1:1 mixture of 5- and 6-methyl isoquinolines (**292b** and **292c**).

Table 2.5. *Aryne substrate scope in isoquinoline synthesis*



100 ***280*** ***292***

entry	*substrate*	*product*	*yield*
1	 ***264***	 ***292a***	66%
2	 ***293***	 ***292b*** 1 : 1 ***292c***	59%
3	 ***266***	 ***292d***	63%
4	 ***294***	 ***292e***	60%
5	 ***295***	 ***292f***	69%
6	 ***296***	 ***292g***	78%

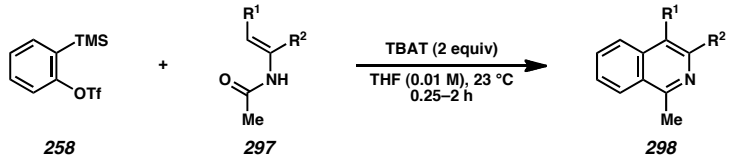
[a] Reaction performed with 2.0 equiv *ortho*-silyl aryl triflate **100** relative to enamine **292**.

Since the aryne annulation was capable of constructing several highly substituted isoquinoline esters, we re-examined the enamine substrates. Dehydroamino esters were originally selected because they contained both a nitrogen nucleophile and a conjugate acceptor in the form of the α,β-unsaturated ester required for C–C bond formation in indolines (see Scheme 2.11). Our investigations had thus far employed this scaffold

because of the easy diversification of the *N*-acyl moiety. But, the heretofore ubiquitous C(3) ester substituent in our isoquinoline products might be interchangeable with other functional groups. The mechanism we have proposed for the formation of isoquinolines does not directly benefit from the conjugate acceptor. We therefore set out to determine whether removing or replacing this group would have any effect upon reactivity.

The first substrates we tested were derivatives of 3-pentanone and pinacolone, acetamides **297a** and **297b**, respectively (Table 2.6).[64] As anticipated, both compounds produced the corresponding isoquinolines (**297a** and **297b**) far more rapidly than the isoquinoline esters **291a–i** (entries 1 and 2).[65] We hypothesize that this rate increase is the result of ester inhibition of the enamine reactivity in the dehydroamino esters (e.g., **280**) by withdrawing electron density from the nucleophilic carbon terminus. To extend our investigation of these ester-free substrates, we prepared cyclic enamines **297c–f**, which furnished a series of tricyclic isoquinolines (**298c–f**) upon aryne annulation (entries 3–6). Importantly, it is possible to incorporate both endocyclic (entry 5) and exocyclic (entry 6) carbonyl functionality without impacting reactivity.

Table 2.6. *N-Acyl enamine substrate scope*[a]



258 ***297*** ***298***

entry	*substrate*	*product*	*yield*
1	***297a***, R^1 = Et, R^2 = Me	***298a***, R^1 = Et, R^2 = Me	72%
2	***297b***, R^1 = H, R^2 = *t*-Bu	***298b***, R^1 = H, R^2 = *t*-Bu	83%
3	***297c***, *n* = 1, X = H_2	***298c***, *n* = 1, X = H_2	66%
4	***297d***, *n* = 2, X = H_2	***298d***, *n* = 2, X = H_2	67%
5	***297e***, *n* = 2, X = O	***298e***, *n* = 2, X = O	66%
6	***297f***	***298f***	71%

[a] Reaction performed with 2.0 equiv *ortho*-silyl aryl triflate **258** relative to enamine **297**.

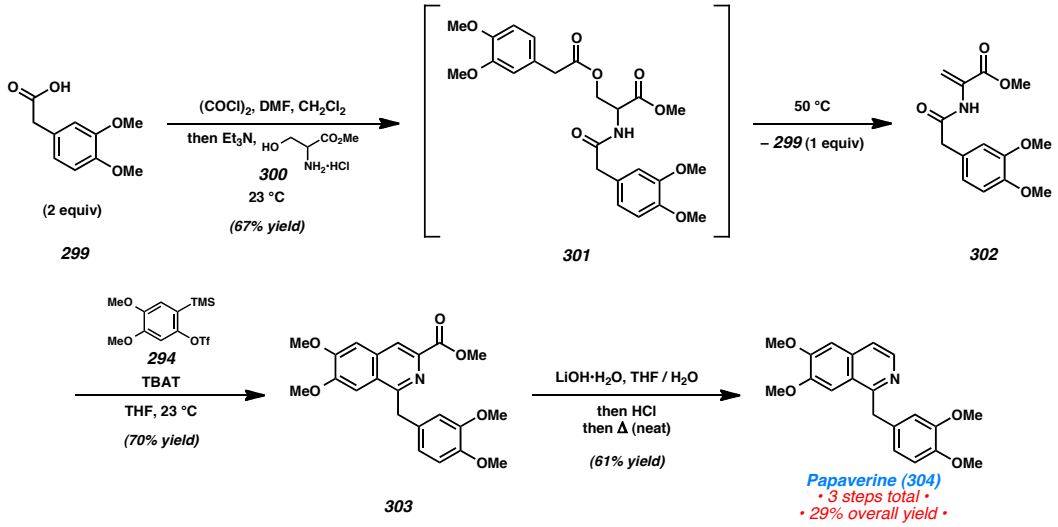
Considering that the goals at the outset of this project were to develop a broad based synthesis of indolines and isoquinolines that would allow the incorporation of a number of substituents, while being selective so as to avoid isomeric mixtures of products, we were satisfied with the development of our isoquinoline approach thus far. By aryne annulation, we are able to substitute isoquinolines at each carbon position around the ring, in a convergent manner, and do so regioselectively by uniting two synthetically accessible functionalized components. Further development of this methodology will occur in the context of its application to total synthesis.

2.3.3 Total Synthesis of Papaverine

With this powerful condensation reaction for generating isoquinolines, we elected to demonstrate its value by a rapid total synthesis of papaverine[66] (**304**), a clinically used non-narcotic antispasmotic agent that is a biosynthetic precursor to several of the pavine

alkaloids and one of the four major constituents of opium (Scheme 2.17).[67] Our synthesis began with the condensation of homoveratric acid (**299**) and serine methyl ester•HCl (**300**), followed by elimination to provide *N*-acyl enamine **302**.[68] In the key annulation, enamide **302** underwent dehydrative addition to the aryne generated from *ortho*-silyl aryl triflate **294** to construct isoquinoline ester **303** in 70% yield. Finally, saponification and thermal decarboxylation[69] afforded papaverine (**304**) in 29% overall yield. Our synthesis totals three steps from commercially available materials, which marks the shortest reported synthesis of this important alkaloid.[70,71]

Scheme 2.17. *Total synthesis of papaverine*

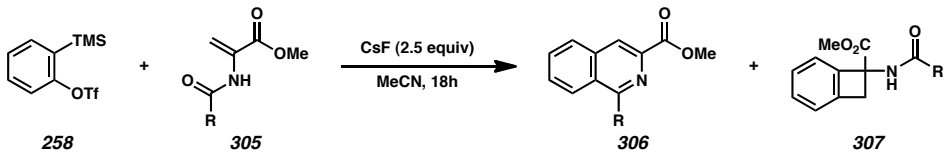


2.3.4 An Alternative Approach to the Synthesis of Isoquinolines and Benzocyclobutenes via Aryne Annulation

Following our report of two orthogonal aryne annulation methods, Blackburn and Ramtohul disclosed an approach to the synthesis of isoquinoline esters (**306a–k**) (Table 2.7).[72] However, in addition to the heterocycle, the authors also identified a second annulation product: a benzocyclobutene amino ester (**307**). In contrast to the

isoquinoline, which forms through a formal dehydrative [4 + 2] addition, the benzocyclobutene is the product of a formal [2 + 2] cycloaddition between enamine **305** and the aryne generated from *ortho*-silyl aryl triflate **258** using cesium fluoride in acetonitrile. The substrate scope of this reaction is similar to the one we reported, furnishing isoquinolines **305a–k** in good yield alongside modest yields of the corresponding benzocyclobutenes (**307a–k**).

Table 2.7. *Ramtohul's Isoquinoline and benzocyclobutene synthesis via aryne annulation*



258 ***305*** ***306*** ***307***

entry	*R*	*yield (**306**)*	*yield (**307**)*
1	***305a***	64% ***306a***	24% ***307a***
2	***305b***	59% ***306b***	21% ***307b***
3	***305c***	64% ***306c***	22% ***307c***
4	***305d***	62% ***306d***	18% ***307d***
5	***305e***	51% ***306e***	21% ***307e***
6	***305f***	66% ***306f***	25% ***307f***
7	***305g***	69% ***306g***	24% ***307g***
8	***305h***	56% ***306h***	22% ***307h***
9	***305i***	42% ***306i***	12% ***307i***
10	***305j***	66% ***306j***	22% ***307j***
11	***305k***	42% ***306k***	11% ***307k***

[a] Reaction performed with 1.25 equiv *ortho*-silyl aryl triflate **258** relative to enamine **305**.

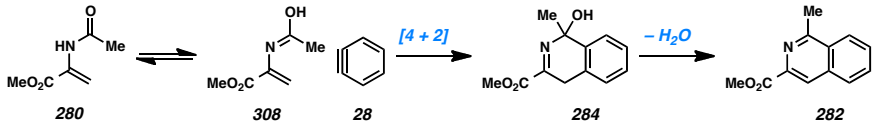
2.3.5 Orthogonality in the Synthesis of Indolines and Isoquinolines

The highly reactive nature of the benzyne intermediates used in the aryne annulations makes direct observation of the reaction mechanism exceedingly difficult. However, by modifying reaction conditions and performing subtle alterations of our substrates, we have been able to develop a working hypothesis for the mechanism through which these reactions proceed.

2.3.5.1 The Impact of C(β)-Substitution on Reactivity

Our initial mechanistic hypothesis regarding the formation of isoquinolines was through a direct [4 + 2] cycloaddition of the acyl imidate tautomer (**308**) of our acetamidoacrylate starting material (**280**) with benzyne to produce the imino alcohol (**284**). This intermediate aromatizes to the isoquinoline (**282**) after elimination of water (Scheme 2.18).

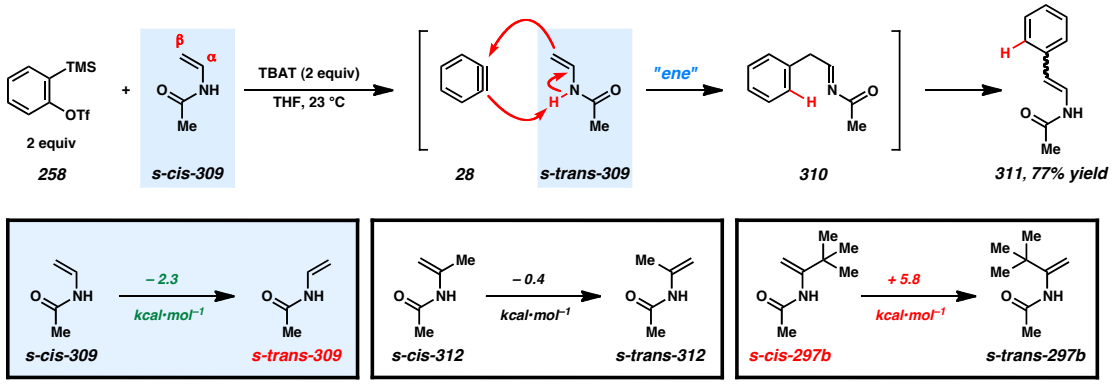
Scheme 2.18. *Originally proposed concerted [4 + 2] mechanism for isoquinoline formation*



We began to question this hypothesis as a result of our efforts to expand the isoquinoline substrate scope. In order to test the lower limit of substitution on the *N*-acyl enamine substrate structure, we attempted an aryne annulation using *N*-vinyl acetamide (**309**), a compound that lacks substitution at the enamine α-position (Scheme 2.19). Instead of isolating the desired 1-methylisoquinoline, the substrate underwent exclusive arylation at the carbon terminus to produce enamine **311** as an inseparable mixture of

olefin isomers in 77% yield.[73] This surprising result underscored the importance of substitution on our reaction partners in the context of acyl-enamide conformation. Specifically, a rotation about the C(α)–N bond of **309**, would generate an "*s*-trans-like" conformation.[74] This orientation would allow an ene reaction with benzyne (**28**) to generate intermediate *N*-acetyl imine **310**. Tautomerization would then yield the observed enamine (**311**).[75] It is unclear whether the β-arylation reaction proceeds through a concerted ene mechanism or by stepwise enamine attack and proton transfer. However, Ramtohul's studies on similar systems suggest that such a stepwise process is possible.[72,73]

Scheme 2.19. *The impact of acyl enamine conformation on reaction outcome*

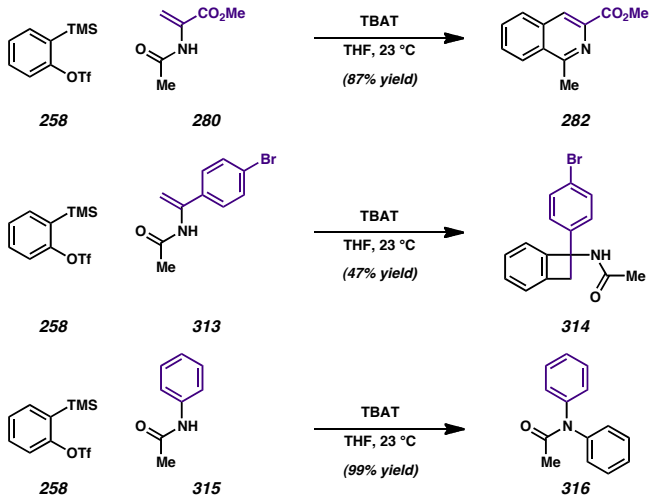


Arylation of *N*-vinyl acetamide through an "*s*-trans-like" conformation indicates a need for some form of substitution at C(α) in order to induce an "*s*-cis-like" conformation by steric interaction between the acetyl group and the C(α) substituent. To better appreciate the relationship between enamine substitution and conformational preference, we calculated the ground state energies of each of the rotational conformers of *N*-vinyl acetamide (**309**), *N*-(2-propenyl)acetamide (**312**), and *N*-(3,3-dimethyl-2-butenyl)acetamide (**297b**).[76] In accordance with the postulated ene mechanism for *C*-

arylation, the "*s*-trans-like" conformation of *N*-vinyl acetamide is preferred by 2.3 kcal·mol^{-1}. A methyl group at C(α) lowers the energy difference to 0.4 kcal·mol^{-1}, only slightly in favor of the "*s*-trans-like" conformation. Conversely, the presence of a *tert*-butyl group at C(α) produces a strong preference for the "*s*-cis-like" conformer (5.8 kcal·mol^{-1}), which helps to explain the observation that **297b** reacts faster than any other substrate we have tested to date.

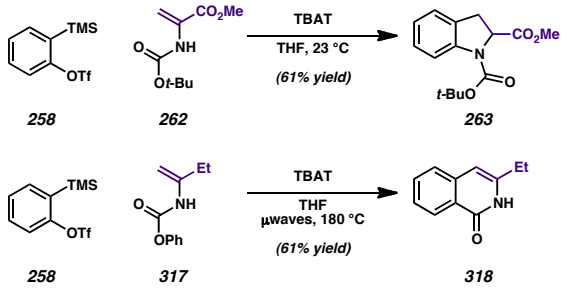
These low-level computational models have helped to explain the impact of C(α)-substitution on the mechanism of the reaction, and are largely borne out by experimental results (Scheme 2.20). The *N*-acyl enamines bearing α-esters (**280**) have given exclusively isoquinoline products (**282**) in all reactions we have attempted. Surprisingly, a *p*-bromophenyl group (**313**) gave exclusively the benzocyclobutenyl product **314**. This result indicates that there is an electronic component to the regioselectivity in addition to the steric aspect that has been discussed. An obvious example of this sort of electronic limitation is the reaction of acetanilide (**315**) with benzyne, which is not sufficient to disrupt aromaticity, and provides diphenylacetamide (**316**) exclusively.

Scheme 2.20. *Acyl enamide α-substitution and its influence on reactivity in the aryne annulation*



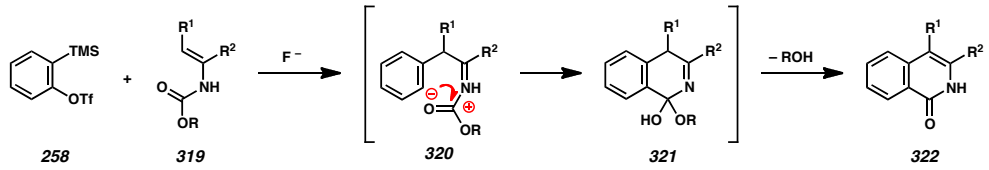
The functional group orthogonality that allows us to specifically target indolines or isoquinolines is also impacted by the C(α)-substituent effect (Scheme 2.21). Both *tert*-butyl and phenyl carbamates, when appended to the dehydroalanine backbone (**262** and **270**), generate indoline products (**263** and **271**, respectively). Interestingly, phenyl carbamoyl α-ethyl enamine **317** generates a completely different product in combination with benzyne, isoquinolone **318**. Presumably, the ethyl substituent on **317** enhances enamine nucleophilicity, favoring C–C bond formation.

Scheme 2.21. *Impact of* N*-substitution on carbamate-enamine substrates for aryne annulation*



Discovery of the isoquinolone highlights the interplay between the C–C and N–C bond forming pathways introduced in Scheme 2.12. Omission of the ester substituent removed any electrophiles for 5-endo cyclization. Consequently, this reaction allows a direct comparison of C and N nucleophilicity. To form the isoquinolone, enamine attack of the aryne by the substrate (**320**) must initiate the reaction (Scheme 2.22). Next, quenching of the aryl anion (**321**) occurs at the only available electrophilic position, the carbamate carbonyl. Elimination of an equivalent of alkoxide unveils the isoquinolone product (**322**).

Scheme 2.22. *Mechanism for isoquinolone formation*



The observed difference in reactivity between dehydroalanine **270** and enamine **317** underscores the electronic impact of the ester substituent on bond formation in these annulation methodologies (see Scheme 2.21). Clearly, the electron-withdrawing ester in **270** mitigates the nucleophilic capacity of the enamine in both the isoquinoline and indoline forming reactions. In the original indoline reaction design, we anticipated nucleophilic C–N bond formation to occur much more rapidly than enamine C–C bond formation. If these processes were even competitive, we would have isolated *N*-arylated side products from the conversion of **317** to the isoquinolone (**318**). Since no such byproducts have been recovered, we believe that the ester's attenuating effect on the enamine is so significant that it slows initial C–C bond formation to the point that C–N bond formation can occur at a comparable rate.

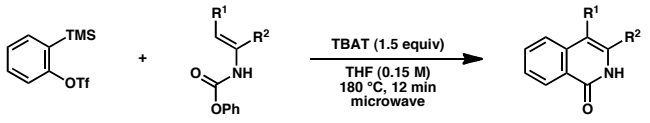
2.3.5.2 An Aryne Annulation Approach to Isoquinolones[†]

The discovery of isoquinolones suggested that a useful synthetic method for these heterocycles might be viable using the same general mechanism (see Scheme 2.22).[77] Indeed, the reaction was marginally successful at elevated temperatures, allowing the convergent assembly of several functionalized isoquinolone derivatives (Table 2.8). What has hindered the further exploitation of this methodology is the tendency of the

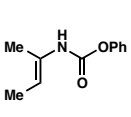
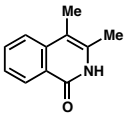
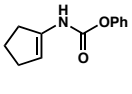
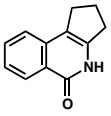
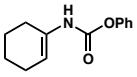
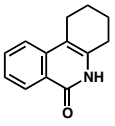
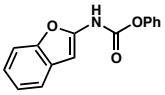
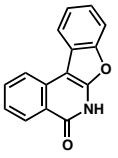
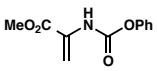
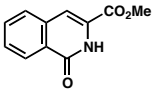
[†] The developmental work for this reaction was performed with Dr. K. M. Allan.

isoquinolones to participate in *N*-arylation reactions with benzyne after their formation, leading to diminished product yields.

Table 2.8. *Isoquinolones produced by aryne annulation*



258 ***319*** ***322***

entry	*substrate*	*product*	*yield*
1			**46%**
	319a	***322a***	
2			**68%**
	319b	***322b***	
3			**64%**
	319c	***322c***	
4[b]			**35%**
	319d	***322d***	
5[c]			**57%**
	319e	***322e***	

[a] Reaction performed with 1.5 equiv *ortho*-silyl aryl triflate **258** relative to enamine **319**.
[b] Reaction performed at 120 °C for 10 min with 1.1 equiv carbamate **319d** relative to **258**.
[c] Reaction performed at room temperature.

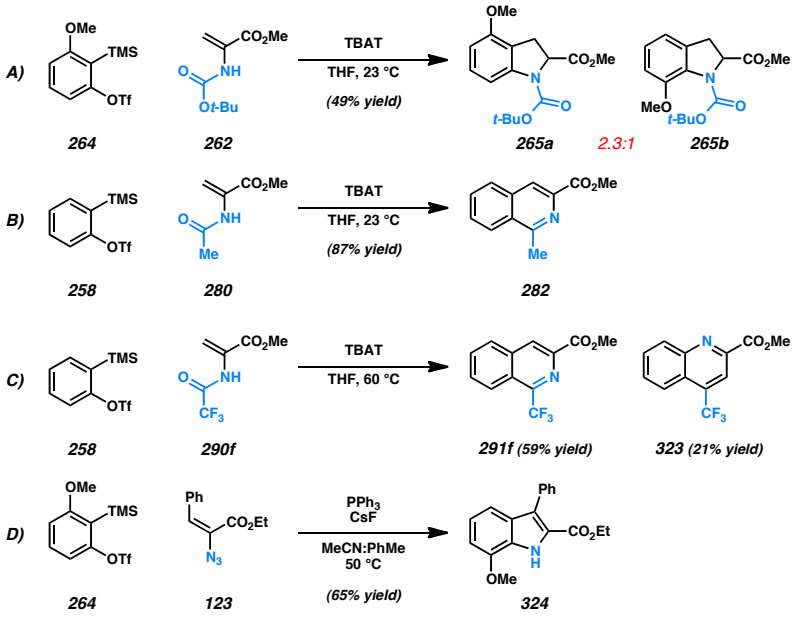
2.3.5.3 An Inherent Bias Toward Enamine Reactivity

While subtle alterations of the enamine substrates have helped to clarify the preference for our aryne annulations to proceed by one path or another, the serendipitous decision that led to our development of these parallel methodologies is still relatively poorly understood. To adequately identify why only carbamates generate indolines, but

amides give only products of C(β) arylations, we have to rely on trends obtained in disparate experiments.

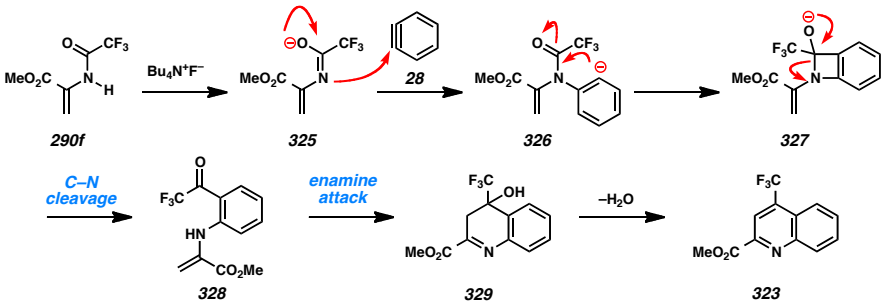
From our experiments on C(α)-functionalization of both enamides and ene-carbamates, we can infer that all of our substrates generally behave as good carbon nucleophiles. Moreover, C–N bond formation through the originally invoked nucleophilic mechanism (see Scheme 2.11) has only been observed by the mixture of C(4)- and C(7)-methoxy indolines (**265a** and **265b**, Scheme 2.23a). Our original efforts to optimize for the indoline synthesis led us to consider the impact nitrogen substitution has on reactivity in the context of proton acidity. This initially provided us with no greater understanding of the properties of *N*-functionalized dehydroalanines (Scheme 2.23b). However, in the aryne annulation of methyl-2-trifluoroacetamidoacrylate (**290**), the reaction produces the anticipated 1-trifluoromethyl-isoquinoline **291f** alongside a significant quantity of 2-carboxymethyl-4-trifluoromethyl-quinoline **323** (Scheme 2.23c). More recently, Wang has reported a 2-carboxyethyl-3-arylindole (**324**) synthesis inspired by our aryne annulation work, using azidoacrylate substrates (**123**) in combination with arynes (**264**, Scheme 2.23d).[78]

Scheme 2.23. *Nitrogen functional group manipulation and its impact on reaction outcome*



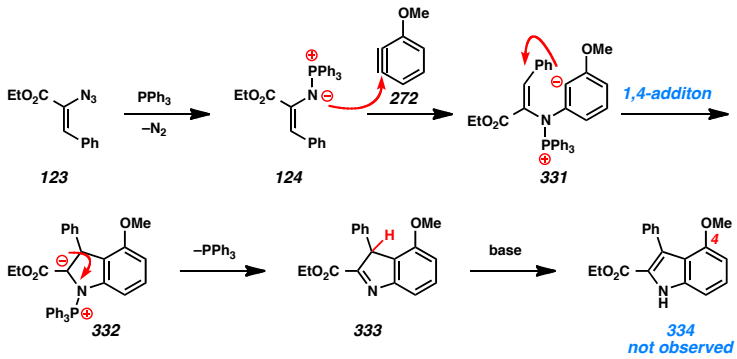
The quinoline formed with the trifluoroacetyl substrate is unique, because it is the only evidence for C–N bond formation within the *N*-acyl enamine substrate class (Scheme 2.24). It likely forms by nitrogen nucleophilic attack of the aryne (**28**), followed by anionic closure to an intermediate 4-membered hemiaminal (**327**). This strained ring fragments to the vinyl aniline (**328**), which can cyclize via enamine addition to the aryl ketone (**329**) and form the quinoline (**323**) following loss of water. This differs from the mechanism we propose for isoquinoline synthesis by initiating bond formation with nitrogen attack on the aryne (**325→326**). The more electron-deficient trifluoroacetyl group should diminish the nucleophilicity of protonated nitrogen, so the observed reactivity likely results from amide deprotonation.[79,80] Only in this case is it completely clear that the quinoline (**323**) is not formed as the result arylation by enamine attack of the aryne. Moreover, the quinoline result implies that, were significant deprotonation to occur in these annulation reactions, the outcomes would be drastically different from those we observe.

Scheme 2.24. *Proposed mechanism for quinoline side product formation*



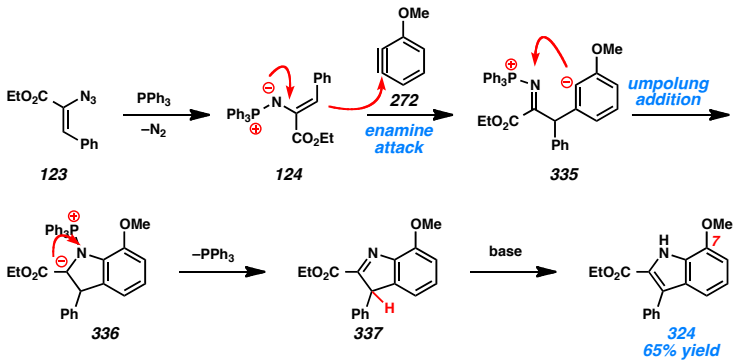
While isolation of quinoline **323** suggests that deprotonation of the amide nitrogen is possible and alters the reactivity of the system, we were intrigued by the notion of a direct indole synthesis by aryne annulation. In Wang's report, azidoacrylates are used to form indoles. As a result, there is no acidic proton to interfere with the nitrogen's activity. If the nitrogen is sufficiently nucleophilic, Wang's proposed mechanism would produce 4-methoxy indole (**334**) by initiating attack meta to the methoxy substituent of the substituted aryne (**272**), and following this with C–C bond formation (Scheme 2.25). Unfortunately, his results do not bear out the proposed mechanism, as the 4-methoxy-indole is not observed.

Scheme 2.25. *Wang's proposed mechanism for indole formation by aryne annulation of azidoacrylates*



We attribute this inconsistency to the same assumption we made when designing our indoline synthesis—that the nitrogen would inherently be the most nucleophilic component of the amidoacrylate starting material (see Scheme 2.12). In order to explain Wang's high regioselectivity for 7-methoxy indole **324**, we believe that the reaction commences with enamine attack (**335**) at the electophilic meta position on the methoxy aryne (**272**), followed by an umpolung C–N bond formation (**336**) as we previously proposed (Scheme 2.26). Our revision provides a rationale for the observed product of the reaction, and the selectivity in this process. Ultimately, what this work illustrates is that the enamine character of these systems is so great, that even after Staudinger-type activation of the azide to an azaphosphonium ylide (**124**), the nitrogen will still preferentially react through the conjugated olefin (e.g., **124→335**) instead of a direct nucleophilic addition to the aryne (e.g., **124→331**, Scheme 2.25).

Scheme 2.26. *Our mechanistic revision for indole formation by aryne annulation of azidoacrylates*

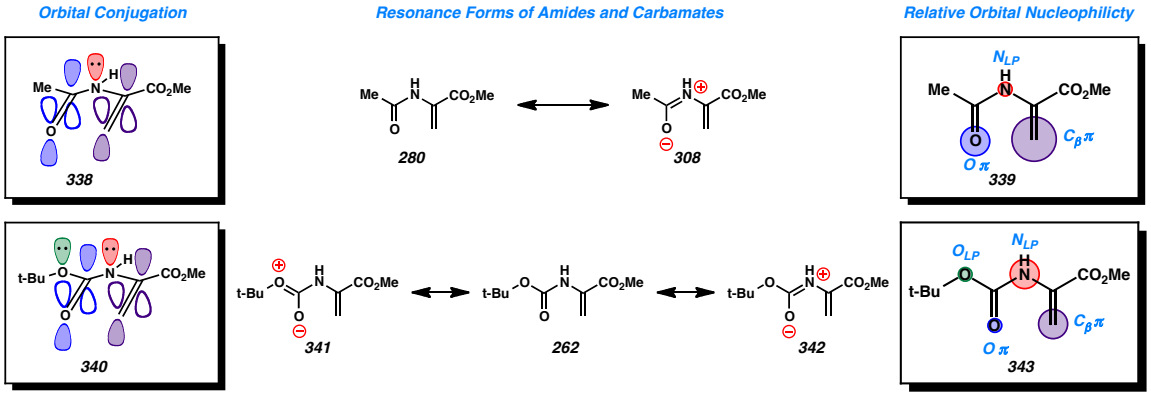


2.3.5.4 A Hypothesis Regarding Orthogonality

Given the inherent bias of our *N*-functionalized enamine substrates toward enamine addition to arynes, our explanation for the differences in reactivity we observe (indolines arising from carbamates, isoquinolines arising from amides) has a fundamental

electronic explanation. Amides are notoriously stable bonds because of resonance delocalization (**280↔308**) of the nitrogen lone pair into the adjacent carbonyl π* orbital (**338**, Figure 2.5). For our amidoacrylate system, the adjacent alkene has a similar, complementary influence through orbital overlap. These two features have the overarching effect of delocalizing most lone pair character on the nitrogen. Thus, the lone pair electron contribution of the nitrogen atom is so stabilized that it is essentially locked into the enamine system (**339**).

Figure 2.5. *Electronic considerations for enamides and ene-carbamates*



Similarly, the carbamate (**262**) is stabilized by resonance delocalization of the nitrogen's lone pair electrons (e.g., **262↔342**). However, competitive electron donation from the oxygen lone pair (**262↔341**) makes this a weaker stabilizing effect than the amide, and contributes to *N*-centered electron density. By this logic, however, ene-carbamates should be more active carbon nucleophiles than their enamide counterparts. In that case, impaired nitrogen lone pair delocalization in the carbamates would seem to favor enamine reactivity, it also enhances nitrogen nucleophilicity. This effect is most apparent in the isoquinolone synthesis (see Scheme 2.22), where a C(α) ester substituent

can sufficiently hinder C(β) nucleophilicity, and allow competitive nitrogen nucleophilic attack to occur.

With these data in mind, we have come to believe that the orthogonal reactivity is not due to amide suppression of nitrogen nucleophilicity relative to the carbamate's promotion of a more electron-rich amine. Instead, it appears to be the opposite scenario: our aryne annulation to form isoquinolines from enamides is assisted by resonance delocalization that allows highly regioselective processes to develop (**340**). The impact of the carbamate is the opposite—this comparatively more electron-rich functional group's contribution of greater electron density presents a more nucleophilic nitrogen, and results in lower selectivity with more unpredictable reactivity than its amide counterpart (**280**).

2.4 CONCLUDING REMARKS

In our efforts to develop a heterocycle synthesis using arynes as reactive intermediates, we have uncovered a new methodology capable of convergently constructing a number of nitrogen-containing heterocycles, including indolines, isoquinolines, isoquinolones, and quinolines. This approach has circumvented some of the problems with the previously known synthetic methodologies by providing a regioselective synthesis of electronically diverse heterocycle derivatives. By understanding some basic aspects of the reactivity in this system, we have pursued the synthesis of a simple natural product, papaverine. Moreover, our success in this realm has led us to pursue synthetic goals far beyond the initial scope of this methodology, whose outcomes will be discussed in the next chapter.

2.5 EXPERIMENTAL SECTION

2.5.1 Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Commercially obtained reagents were used as received. Tetrabutylammonium difluorotriphenylsilicate (TBAT) was purchased from Sigma-Aldrich Chemical Company and azeotropically dried three times from acetonitrile prior to use. Brine solutions are saturated aqueous sodium chloride solutions. Known dehydroamino ester starting materials were prepared by the methods of Kobayashi[81] or Parsons[68] unless otherwise specified. 3-methoxy-2-(trimethylsilyl)phenyl triflate (**264**),[82] 4-methyl-2-(trimethylsilyl) phenyl triflate (**293**),[83] 4,5-dimethoxy-2-(trimethylsilyl) phenyl triflate (**294**),[84] 6-(trimethylsilyl) benzo[*d*][1,3]dioxol-5-yl triflate (**266**),[41a] and 4,5-difluoro-2-(trimethylsilyl)phenyl triflate (**296**)[55] were prepared according to literature procedures. Reaction temperatures were controlled by an IKAmag temperature modulator. Microwave reactions were performed with a Biotage Initiator Eight 400 W apparatus at 2.45 GHz. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or CAM staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040–0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz, respectively) or a Varian Inova 500 (at 500 MHz and 125 MHz, respectively), with usage specified in each case, and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Data

for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the Caltech Mass Spectral Facility.

2.5.2 Preparative Procedures and Spectroscopic Data

2.5.2.1 Representative Procedures for the Synthesis of Indolines and Isoquinolines via Aryne Annulation

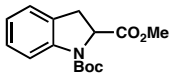
Method A

To a solution of TBAT (0.756 g, 1.40 mmol, 2.0 equiv) and enamine (0.70 mmol) in THF (35 mL) was added *ortho*-silyl aryl triflate **258** (0.340 mL, 1.40 mmol, 2.0 equiv) dropwise via syringe. The reaction was stirred under nitrogen at ambient temperature for 6 h, at which point the reaction was concentrated under reduced pressure and purified via flash chromatography.

Method B

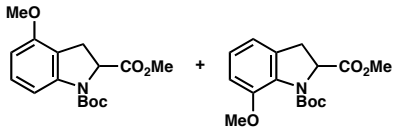
To a solution of TBAT (0.756 g, 1.40 mmol, 2.0 equiv) and enamine (0.70 mmol) in THF (70 mL) was added *ortho*-silyl aryl triflate **258** (0.340 mL, 1.40 mmol, 2.0 equiv) dropwise via syringe. The reaction was stirred under nitrogen at ambient temperature for 6 h, at which point the reaction was concentrated under reduced pressure and purified via flash chromatography.

2.5.2.2 Spectroscopic Data for Indolines



Indoline 263 (Table 2.2, Entry 1)

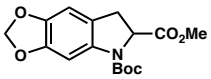
Reaction performed via Method A. Purified by flash chromatography (SiO_2, 10:90 → 30:70 EtOAc/hexanes). 61% yield. R_f = 0.35 (30:70 EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 6.5 Hz, 1H), 7.19 (d, *J* = 4.5 Hz, 1H), 7.12 (d, *J* = 4.2 Hz, 1H), 6.96 (t, *J* = 4.0 Hz, 1H), 4.89 (br t, *J* = 2.0 Hz, 1H), 3.77 (s, 3H), 3.65 (dd, *J* = 10.2, 8.0 Hz, 1H), 3.51 (dd, *J* = 9.0, 2.5 Hz, 1H), 1.49 (br s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.3, 128.2, 124.7, 122.5, 117.5, 81.7, 60.3, 52.2, 32.4, 28.6; IR (Neat Film, NaCl) 3066, 2928, 1754, 1603, 1485, 1289, 1319, 1277, 1203, 1169, 1046, 1022, 848, 751 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{19}NO_4$ $[M^{\bullet}]^+$: 277.1314, found 277.1323.



Indolines 265a and b (Table 2.2, Entry 2)

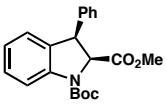
Reaction performed via Method A. Purified by flash chromatography (SiO_2, 0:100 → 30:70 EtOAc/hexanes). 49% yield, isolated as a 2.3:1 mixture of inseparable 4- and 7-methoxyindolines. R_f = 0.21 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.0 (t, *J* = 7.3 Hz, 1H), 6.80 (d, *J* = 3.6 Hz, 2H), 6.78 (d, *J* = 2.9 Hz, 1H), 5.08 (dd, *J* = 10.2, 2.2 Hz, 1H), 3.86 (s, 3H), 3.71 (s, 3H), 3.55 (dd, *J* = 16.8, 5.0 Hz, 1H), 3.07 (d, *J* = 16.8, 1.0 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 153.5, 149.8, 133.4, 130.8, 125.7, 117.1, 112.8, 81.3, 62.6, 55.7, 53.1, 33.9, 28.3; IR (Neat Film, NaCl) 2976,

2838, 1733, 1695, 1609, 1595, 1490, 1461, 1367, 1275, 1164, 1027, 947, 867, 766 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{21}NO_5$ $[M^{\bullet}]^+$: 307.1420, found 307.1418.



Indoline 267 (Table 2.2, Entry 3)

Reaction performed via Method A. Purified by flash chromatography (SiO_2, 10:90 → 30:70 EtOAc/hexanes). 39% yield. R_f = 0.33 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (s, 1H), 6.58 (s, 1H), 5.89 (s, 2H), 4.84 (d, *J* = 11.0 Hz, 1H) 2.78 (s, 1H), 3.55 (dd, *J* = 12.1, 5.7 Hz, 1H), 3.07 (d, *J* = 15.9, 1.0 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 151.9, 147.6, 143.3, 145.6, 128.2, 119.6, 105.0, 101.5, 98.3, 81.7, 61.7, 52.7, 33.0, 28.3; IR (Neat Film, NaCl) 2949, 1753, 1706, 1477, 1405, 1367, 1303, 1258, 1166, 1081, 1037, 938 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{16}H_{19}NO_6$ $[M^{\bullet}]^+$: 321.1212, found 321.1224.

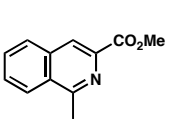


Indoline 269 (Table 2.2, Entry 4)

Reaction performed via Method A. Purified by flash chromatography (SiO_2, 10:90 → 20:80 EtOAc/hexanes). 40% yield. R_f = 0.23 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.0 Hz, 1H), 7.48 (dd, *J* = 7.6, 2.2 Hz, 1H), 7.37 (comp m, 4H), 7.23 (d, *J* = 8.9 Hz, 2H), 6.90 (t, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 7.6 Hz, 1H) 3.86 (t, *J* = 5.3 Hz, 1H), 3.82 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 158.9, 155.8, 135.2, 133.9, 133.0, 130.2, 129.9, 129.6, 129.0, 128.8, 128.0, 120.9, 115.1, 80.9,

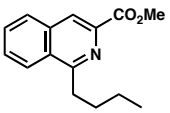
67.5, 52.8, 47.8, 21.4; IR (Neat Film, NaCl) 2947, 1723, 1707, 1638, 1600, 1496, 1448, 1391, 1366, 1245, 1170, 1143, 755, 692 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{21}H_{23}NO_4$ $[M+H]^+$: 352.1549, found 352.1564. Relative stereochemistry of substituents at C(2) and C(3) confirmed by 1D NOESY NMR studies.

2.5.2.3 Spectroscopic Data for Isoquinolines



Isoquinoline 282 (Table 2.4, entry 1)

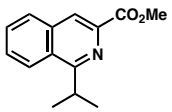
Reaction performed via Method B. Purified by flash chromatography (SiO_2, 10:90 → 30:70 EtOAc/hexanes). 87% yield. R_f = 0.33 (30:70 EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.20 (d, *J* = 9.2, 1H), 7.97 (d, *J* = 6.7 Hz, 1H), 7.76 (app ddd, *J* = 5.2, 3.2, 1.9 Hz, 2H), 4.04 (s, 3H), 3.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 158.6, 141.4, 135.4, 131.0, 129.1, 128.6, 127.4, 125.4, 123.5, 51.5, 21.4; IR (Neat Film, NaCl) 2953, 1731, 1569, 1501, 1448, 1337, 1391, 1291, 1230, 1210, 795 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_{11}NO_2$ $[M^{\bullet}]^+$: 201.0790, found 201.0797.



Isoquinoline 291a (Table 2.4, entry 2)

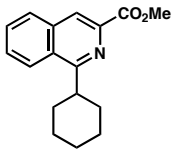
Reaction performed via Method B. Purified by flash chromatography (SiO_2, 10:90 → 30:70 EtOAc/hexanes). 76% yield. R_f = 0.40 (30:70 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.18 (d, *J* = 9.6 Hz, 1H), 7.93 (d, *J* = 9.2 Hz, 1H), 7.70 (ddd,

J = 5.0, 3.6, 2.3 Hz, 2H), 4.01 (s, 3H), 2.89 (d, *J* = 6.3 Hz, 2H), 1.63 (q, *J* = 5.2 Hz, 2H), 1.12 (app dt, *J* = 5.5, 3.3 Hz, 2H), 0.88 (t, *J* = 3.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 163.8, 141.4, 135.9, 131.0, 129.8, 129.1, 128.6, 126.0, 123.5, 53.5, 36.1, 33.2, 23.8, 14.3; IR (Neat Film, NaCl) 2855, 2870, 1721, 1449, 1293, 1246, 1213, 1175, 749 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{17}NO_2$ $[M^{\bullet}]^+$: 243.1259, found 243.1256.



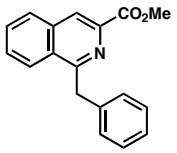
Isoquinoline 291b (Table 2.4, entry 3)

Reaction performed via Method B. Purified by flash chromatography (SiO_2, 10:90 → 30:70 EtOAc/hexanes). 66% yield. R_f = 0.37 (30:70 EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 8.41 (s, 1H), 8.29 (d, *J* = 4.5 Hz, 1H), 7.96 (d, *J* = 3.5 Hz, 1H), 7.73 (app dt, *J* = 5.5, 3.3 Hz, 2H), 4.03 (s, 3H), 3.97 (m, 1H), 1.50 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 145.0, 140.8, 135.3, 130.4, 129.7, 129.3, 128.2, 125.2, 122.9, 53.0, 31.4, 22.7; IR (Neat Film, NaCl) 3965, 2929, 1718, 1565, 1501, 1449, 1323, 1267, 1221, 1207, 1150, 1117, 1077, 987, 781 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{15}NO_2$ $[M^{\bullet}]^+$: 229.1103, found 229.1100.



Isoquinoline 291c(Table 2.4, entry 4)

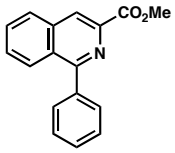
Reaction performed via Method B. Purified by flash chromatography (SiO_2, 10:90 EtOAc/hexanes). 65% yield. R_f = 0.49 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) 8.44 (s, 1H), 8.28 (d, J = 4.3 Hz, 1H), 7.4 (d, J = 3.5 Hz, 1H), 7.73 (app dt, J = 5.2, 3.1 Hz, 2H), 4.02 (s, 3H), 3.59 (m, 1H), 1.98 (m, 8H), 1.57 (q, J = 5.1 Hz, 1H), 1.41 (q, J = 3.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 166.1, 140.7, 136.0, 129.9, 129.1, 127.8, 124.6, 122.2, 52.0, 42.1, 32.1, 27.1, 26.0; IR (Neat Film, NaCl) 2927, 2852, 1739, 1718, 1567, 1502, 1449, 1325, 1311, 1271, 1243, 1204, 1150, 1000, 780, 750 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{15}NO_2$ $[M^{\bullet}]^+$: 269.1416, found 269.1424.



Isoquinoline 291d(Table 2.4, entry 5)

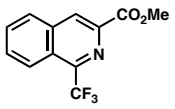
Reaction performed via Method B. Purified by flash chromatography (SiO_2, 0:100 → 30:70 EtOAc/hexanes). 72% yield. R_f = 0.47 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.20 (d, J = 6.7, 1H), 8.02 (d, J = 5.1 Hz, 1H), 7.74 (t, J = 7.1 Hz, 1H), 7.63 (t, J = 6.6 Hz, 1H), 7.22 (m, 4H), 7.18 (m, 1H), 4.80 (s, 2H) 4.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 163.7, 141.4, 139.5, 135.4, 131.7, 129.8, 129.1, 128.3, 128.0, 126.3, 124.0, 53.5, 42.9; IR (Neat Film, NaCl) 2946, 2929, 1731,

1716, 1551, 1455, 1380, 1301, 1230, 1210, 995 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{18}H_{15}NO_2$ $[M+H]^+$: 278.1103, found 278.1181.



Isoquinoline 291e (Table 2.4, entry 6)

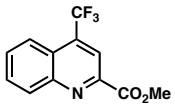
Reaction performed via Method B. Purified by flash chromatography (SiO_2, 0:100 → 10:90 EtOAc/hexanes). 55% yield. R_f = 0.52 (30:70 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 8.05 (d, *J* = 8.3 Hz, 1H), 7.78 (t, *J* = 7.7 Hz, 1H), 7.71, (dd, *J* = 7.7, 4.3 Hz, 2H), 7.66 (d, *J* = 7.7 Hz, 1 H), 7.57 (t, *J* = 6.0 Hz, 1H), 7.53 (d, *J* = 6.8, 1H), 7.49 (t, *J* = 4.3 Hz, 1H), 4.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 162.2, 141.2, 139.3, 137.7, 131.0, 130.4, 129.7, 128.6, 128.3, 128.2, 128.0, 127.8, 124.0; IR (Neat Film, NaCl) 2949, 1725, 1715, 1493, 1449, 1376, 1339, 1292, 1242, 1217, 1148, 1102, 997, 798, 766, 700 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{17}H_{13}NO_2$ $[M+H]^+$: 264.1025, found 264.1020.



Isoquinoline 291f (Table 2.4, entry 7)

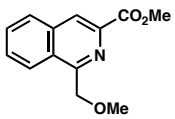
Reaction performed via Method B. Purified by flash chromatography (SiO_2, 20:80 → 30:70 EtOAc/hexanes). 57% yield. R_f = 0.22 (30:70 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.42 (d, *J* = 7.9 Hz, 1H), 8.21 (d, *J* = 9.3 Hz, 1H), 7.91 (t, *J* = 8.4, Hz, 1H), 7.81 (t, *J* = 7.1 Hz, 1H), 4.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

165.6, 148.3, 135.9, 135.1, 132.1, 131.4, 130.6, 124.6, 122.1, 118.2, 54.5; IR (Neat Film, NaCl) 2924, 2102, 1730, 1643, 1462, 1275, 1252, 1155, 1126, 897, 726 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_8F_3NO_2$ $[M^{\bullet}]^+$: 255.0507, found 255.0500.



Quinoline 323 (Scheme 2.23)

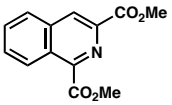
Reaction performed via Method B. Purified by flash chromatography (SiO_2, 20:80 → 30:70 EtOAc/hexanes). 21% yield. R_f = 0.22 (30:70 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.39 (d, *J* = 8.7 Hz, 1H), 8.10 (d, *J* = 6.7 Hz, 1H), 7.89 (dt, *J* = 6.9, 4,8 Hz, 2H), 4.08 (s, *3*H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 147.0 (q, *J* = 35 Hz), 139.9, 137.3, 132.0, 129.3, 127.8, 126.2, 125.2, 123.1, 53.4; IR (Neat Film, NaCl) 3081, 1717, 1625, 1501, 1455, 1394, 1377, 1315, 1262, 1234, 1187, 1156, 1113, 1030, 997, 974, 802, 782 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{12}H_8F_3NO_2$ $[M^{\bullet}]^+$: 255.0507, found 255.0502.



Isoquinoline 291g (Table 2.4, entry 8)

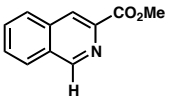
Reaction performed via Method B. Purified by flash chromatography (SiO_2, 25:75 → 50:50 EtOAc/hexanes). 68% yield. R_f = 0.50 (50:50 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.43 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.99 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.78 (ddd, *J* = 8.0, 6.0, 1.0 Hz, 1H), 7.77 (ddd, *J* = 9.0, 6.5, 1.5 Hz, 1H), 5.13 (s,

2H), 4.06 (s, 3H), 3.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ□166.6, 158.0, 140.4, 136.4, 131.2, 130.0, 128.9, 128.8, 126.4, 125.0, 75.5, 58.9, 53.2□ IR (Neat Film, NaCl) 2950, 1736, 1718, 1450, 1295, 1248, 1210, 1100, 779 cm^{-1}; HRMS (ES+) *m/z* calc'd for $C_{13}H_{14}NO_3$ $[M+H]^+$: 232.0974, found 232.0968.



Isoquinoline 291h (Table 2.4, entry 9)

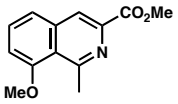
Reaction performed via Method B. Purified by flash chromatography (SiO_2, 20:80 → 30:70 EtOAc/hexanes). 51% yield. R_f = 0.21 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.85 (d, *J* = 8.2 Hz, 1H), 8.78 (s, 1H), 8.05 (t, *J* = 3.5 Hz, 1H), 7.81 (m, 2H), 4.13 (s, 3H), 4.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 165.4, 149.1, 139.6, 136.3, 134.2, 131.0, 131.4, 128.4, 128.0, 127.2, 126.6, 53.6; IR (Neat Film, NaCl) 2959, 2924, 1725, 1713, 1449, 1300, 1251, 1232, 1205, 1146, 1055, 786, 760 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{11}NO_4$ $[M^{\bullet}]^+$: 245.0688, found 245.0679.



Isoquinoline 291i (Table 2.4, entry 10)

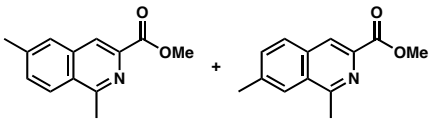
Reaction performed via Method B. Purified by flash chromatography (1:1 hexanes:ethyl acetate eluent). 72% yield. R_f = 0.16 (1:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.52 (s, 1H), 8.05–7.94 (m, 1H), 7.94–7.82 (m, 1H), 7.69 (m, 2H), 3.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.36, 152.74, 141.54, 135.53, 131.27,

130.01, 129.71, 128.09, 127.77, 124.14, 52.96; IR (NaCl/film) 2994, 2951, 1726, 1577, 1497, 1452, 1387, 1328, 1291, 1228, 1202, 1139, 1095, 970, 901, 795, 769 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{10}O_2N$ $[M+H]^+$: 188.0706, found 188.0709.



Isoquinoline 292a (Table 2.5, entry 1)

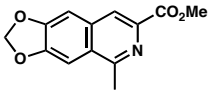
Reaction performed via Method B. Purified by flash chromatography (SiO_2, 20:80 → 20:80 EtOAc/hexanes). 66% yield. R_f = 0.32 (30:70 EtOAc/hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 3.83 (s, 3H), 3.03 (s, 3H), 2.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 159.8, 158.3, 140.6, 138.6, 131.4, 122.8, 121.8, 121.0, 109.0, 55.9, 53.0, 29.2; IR (Neat Film, NaCl) 2936, 2852, 1734, 1708, 1616, 1566, 1455, 1435, 1363, 1275, 1252, 1214, 1140, 1088, 1012, 787 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{13}NO_3$ $[M^{\bullet}]^+$: 231.0895, found 231.0889.



Isoquinolines 292b and c (Table 2.5, entry 2)

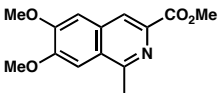
Reaction performed via Method B. Purified by flash chromatography (SiO_2, 10:90 → 20:80 EtOAc/hexanes). 59% yield as a 1:1 mixture of isomers. R_f = 0.40 (30:70 EtOAc/hexanes); Isolated as 1:1 mixture of isomers. ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 8.00 (s, 1H), 8.34 (s, 1H), 8.04 (s, 1H), 8.02 (s, 1H), 7.90, (s, 2H), 7.82 (s, 1H),

7.80, (s, 1H), 7.67 (s, 2H), 7.56 (d, J = 8.7 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H) 4.02 (s, 6H), 2.99 (d, J = 1.8 Hz, 6H), 2.57 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 167.1, 159.3, 158.9, 141.6, 140.1, 139.9, 133.8, 133.6, 132.0, 129.1, 128.5, 128.0, 127.8, 125.9, 125.0, 123.8, 122.6, 53.3, 23.1, 22.1, 21.9; IR (Neat Film, NaCl) 2951, 1718, 1438, 1392, 1287, 1245, 1212, 1116, 1009, 818 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{13}H_{13}NO_2$ $[M^{\bullet}]^+$: 215.0946, found 215.0898.



Isoquinoline 292d (Table 2.5, entry 3)

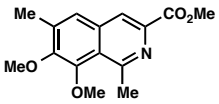
Reaction performed via Method B. Purified by flash chromatography (SiO_2, 10:90 → 40:60 EtOAc/hexanes). 63% yield. R_f = 0.25 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.31 (s, 1H), 7.06 (s, 1H), 5.87 (s, 2H), 3.85 (s, 3H), 3.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 157.1, 150.2, 149.3, 141.3, 133.6, 121.9, 104.2, 101.0, 100.7, 68.3, 51.7, 22.2; IR (Neat Film, NaCl) 2903, 2833, 1755, 1609, 1522, 1461, 1430, 1244, 1170, 1026, 931, 733 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{13}H_{11}NO_4$ $[M^{\bullet}]^+$: 245.0688, found 245.1003.



Isoquinoline 292e (Table 2.5, entry 4)

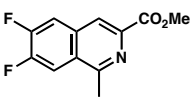
Reaction performed via Method B. Purified by flash chromatography (SiO_2, 10:90 → 40:60 EtOAc/hexanes). 60% yield. R_f = 0.34 (30:70 EtOAc/hexanes); ^{1}H NMR (500

MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.34 (s, 1H), 7.20 (s, 1H), 4.08 (s, 3H), 4.05 (s, 6H), 4.03 (s, 3H), 2.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 156.6, 154.2, 152.1, 139.7, 132.1, 125.8, 123.9, 111.8, 105.2, 56.1, 51.5, 21.4; IR (Neat Film, NaCl) 2952, 2840, 1730, 1618, 1511, 1465, 1426, 1256, 1161, 1028, 733 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{15}NO_4$ $[M^{\bullet}]^+$: 261.1001, found 261.1012.



Isoquinoline 292f (Table 2.5, entry 5)

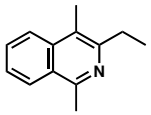
Reaction performed via Method B. Purified by flash chromatography (2.5% → 10% EtOAc:CH_2Cl_2) 71% yield R_f = 0.35 (1:1 hexanes:EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.51 (s, 1H), 4.04 (s, 3H), 3.99 (s, 3H), 3.98 (s, 3H), 3.09 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.62, 157.80, 152.53, 149.72, 139.37, 138.12, 133.88, 125.11, 124.12, 122.20, 60.82, 60.19, 52.80, 27.49, 16.92; IR (NaCl/film) 2948, 2852, 1735, 1715, 1617, 1559, 1487, 1450, 1437, 1396, 1355, 1328, 1261, 1218, 1194, 1131, 1091, 1057, 1010, 998, 907, 874, 782 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{10}O_2N$ $[M+H]^+$: 276.1230, found 276.1245.



Isoquinoline 292g (Table 2.5, entry 6)

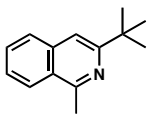
Reaction performed via Method B. Purified by flash chromatography (SiO_2, 30:70 EtOAc/hexanes). 66% yield. R_f = 0.29 (1:1 EtOAc/hexanes); ^1H NMR (500 MHz,

$CDCl_3$) δ 8.40 (s, 1H), 7.93 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.70 (t, *J* = 8.7 Hz, 1H), 4.05 (s, 3H), 3.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 122.23, 115.1, 114.9, 113.9, 113.0, 60.7, 53.3, 31.3, 23.2, 21.4, 14.5; IR (Neat Film, NaCl) 2920, 1716, 1514, 1426, 1281, 1258, 1228, 1181, 1144, 1125, 928, 851, 792, 738, 611 cm^{-1}; HRMS (ES+) *m/z* calc'd for $C_{19}H_{23}NO_2$ $[M^{\bullet}]^+$: 237.0601 found 237.0591.



Isoquinoline 298a (Table 2.6, entry 1)

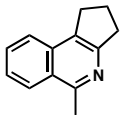
Reaction performed via Method B. Purified by flash chromatography (SiO_2, 0:100 → 20:80 EtOAc/hexanes). 72% yield. R_f = 0.45 (30:70 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.68 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 7.52 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 3.00 (q, *J* = 7.8 Hz, 2H), 2.92 (s, 3H), 2.58 (s, 3H), 1.30 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 149.2, 129.5, 125.9, 125.3, 123.4, 29.3, 22.3, 14.3, 13.4; IR (Neat Film, NaCl) 2965, 1618, 1570, 1443, 1395, 1339, 1270, 755 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{15}N$ $[M^{\bullet}]^+$: 185.1204, found 185.1266.



Isoquinoline 298b (Table 2.6, entry 2)

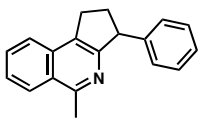
Reaction Performed via Method B. Purified by flash chromatography (SiO_2, 0:100 → 4:96 Et_2O/hexanes). 83% yield. R_f = 0.73 (15:85 EtOAc/hexanes); ^1H NMR (500 MHz,

$CDCl_3$) δ 8.07 (d, *J* = 9.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 7.0 Hz, 1H), 7.51 (t, *J* = 6.5 Hz, 1H), 7.45 (s, 1H), 2.95 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 157.2, 136.6, 129.4, 127.2, 125.9, 125.6, 125.3, 112.5, 36.9, 30.1, 22.6; IR (Neat Film, NaCl) 3058, 2954, 1626, 1573, 1481, 1390, 1356, 878, 748 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{17}N$ $[M^{\bullet}]^+$: 199.1361, found 199.1363.



Isoquinoline 298c (Table 2.6, entry 3)

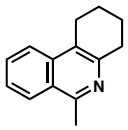
Reaction performed via Method B at 60 °C. Purified by flash chromatography (SiO_2, 0:100 → 20:80 EtOAc/hexanes). 66% yield. R_f = 0.29 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.5 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.67 (app t, *J* = 7.5 Hz, 1H), 7.52 (app t, *J* = 7.5 Hz, 1H), 3.20 (app dd, *J* = 9.0, 8.0 Hz, 4H), 2.95 (s, 3H), 2.26 (app quintet, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 156.4, 133.9, 130.1, 128.7, 126.6, 126.0, 125.7, 124.2, 35.1, 29.2, 22.7, 22.6; IR (Neat Film, NaCl) 2953, 1621, 1581, 1562, 1442, 1390, 1342, 1150, 755 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{13}N$ $[M^{\bullet}]^+$: 183.1048, found 183.1033.



A1-1

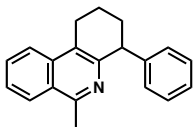
Reaction performed via Method B at 60 °C. Purified by flash chromatography (SiO_2, 0:100 → 20:80 EtOAc/hexanes). 21% yield, isolated as a side product of the reaction to

form Table 2, Entry 12. R_f = 0.80 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.3 Hz, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.72 (ddd, *J* = 8.3, 6.8, 1.0 Hz, 1H), 7.57 (ddd, *J* = 8.3, 6.8, 1.2 Hz, 1H), 7.27 (app t, *J* = 7.1 Hz, 2H), 7.19 (tt, *J* = 7.3, 1.2 Hz, 1H), 7.14 (app d, *J* = 7.1 Hz, 2H), 4.62 (dd, *J* = 8.8, 5.1 Hz, 1H), 3.36 (ddd, *J* = 15.9, 7.8, 7.3 Hz, 1H), 3.22 (ddd, *J* = 16.1, 9.0, 5.1 Hz, 1H), 2.91 (s, 3H), 2.85-2.77 (m, 1H), 2.26-2.19 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 157.5, 145.7, 135.5, 135.2, 130.3, 130.2, 128.7, 128.2, 128.1, 126.7, 126.4, 126.3, 126.2, 124.4, 52.6, 33.9, 27.8, 22.8; IR (Neat Film, NaCl) 3064, 2943, 1682, 1622, 1561, 1493, 1429, 1390, 1117, 1027, 758, 700 cm^{-1}; HRMS (ES+) *m/z* calc'd for $C_{19}H_{18}N$ $[M+H]^+$: 260.1439, found 260.1438.



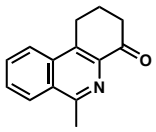
Isoquinoline 298d (Table 2.6, entry 4)

Reaction performed via Method B at 60 °C. Purified by flash chromatography (SiO_2, 10:90 → 40:60 EtOAc/hexanes). 67% yield. R_f = 0.33 (30:70 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.68 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 7.53 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 3.04 (app dd, *J* = 5.0, 2.0 Hz, 4H), 2.92 (s, 3H), 1.95 (app quintet, *J* = 3.0 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 148.9, 135.7, 129.9, 126.3, 126.0, 125.8, 123.2, 122.7, 33.0, 24.9, 23.4, 23.0, 22.6; IR (Neat Film, NaCl) 2930, 1616, 1570, 1443, 1392, 1332, 1030, 754 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{15}N$ $[M^{\bullet}]^+$: 197.1204, found 197.1213.



A1-2

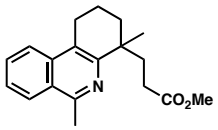
Reaction performed via Method B at 60 °C. Purified by flash chromatography (SiO_2, 10:90 →30:70 EtOAc/hexanes). 14% yield, isolated as a side product of the reaction to form Table 2, Entry 13. R_f = 0.84 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.3 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.73 (ddd, *J* = 8.3, 6.8, 1.2 Hz, 1H), 7.58 (ddd, *J* = 8.3, 6.8, 1.2 Hz, 1H), 7.23 (app t, *J* = 7.1 Hz, 2H), 7.16 (tt, *J* = 7.3, 1.2 Hz, 1H), 7.00 (app d, *J* = 7.1 Hz, 2H), 4.48 (app t, *J* = 4.6 Hz, 1H), 3.23 (dt, *J* = 16.9, 4.9 Hz, 1H), 3.05 (dt, *J* = 16.9, 8.3 Hz, 1H), 2.84 (s, 3H), 2.29-2.21 (m, 1H), 2.08 (app dq, *J* = 13.4, 4.2 Hz, 1H), 1.88-1.83 (comp m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6, 149.6, 146.6, 135.6, 135.2, 130.4, 130.0, 129.3, 128.2, 126.4, 126.3, 126.2, 125.9, 124.5, 123.0, 47.5, 32.4, 25.0, 22.7, 18.4; IR (Neat Film, NaCl) 3066, 2934, 1615, 1590, 1492, 1446, 1390, 1332, 1117, 1029, 756, 700 cm^{-1}; HRMS (ES+) *m/z* calc'd for $C_{20}H_{20}N$ $[M+H]^+$: 274.1596, found 274.1608.



Isoquinoline 298e (Table 2.6, entry 5)

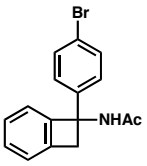
Reaction performed via Method B. Purified by flash chromatography (SiO_2, 1:1 EtOAc/hexanes). 66% yield. R_f = 0.21 (1:1 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J* = 9.8 Hz, 1H), 8.15 (d, *J* = 7.6 Hz, 1H), 7.84 (t, *J* = 6.1 Hz, 1H), 7.78

(t, J = 7.6 Hz, 1H), 3.38 (t, J = 6.8 Hz, 2H), 3.04 (s, 3H), 2.86 (d, J = 7.6, 2H), 2.33 (quintet, J = 4.5, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7, 158.6, 141.2, 136.0, 134.7, 130.9, 129.7, 128.9, 126.8, 124.7, 39.2, 25.2, 23.1, 22.5; IR (Neat Film, NaCl) 2944, 1682, 1628, 1407, 1385, 1164, 1129, 1031, 906, 759 cm^{-1}; HRMS (ES+) m/z calc'd for $C_{19}H_{23}NO_2$ $[M+H]^+$: 211.0997, found 211.0994.



Isoquinoline 298f (Table 2.6, entry 6)

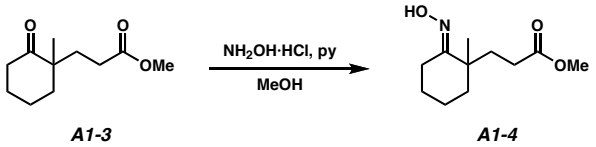
See below for synthesis of the enamide substrate A1-4. Purified by flash chromatography (SiO_2, 5:95 Et_2O/hexanes). 71% yield. R_f = 0.48 (15:85 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.65 (t, J = 7.0 Hz, 1H), 7.52 (t, J = 7.0 Hz, 1H), 3.62 (s, 3H), 3.11 (dt, J = 16.5, 5.5 Hz, 1H), 2.99-2.93 (m, 1H), 2.90 (s, 3H), 2.33 (app d, J = 12.0 Hz, 2H), 2.08 (app d, J = 12.0 Hz, 2H), 2.02-1.90 (comp m, 2H), 1.85 (td, J = 13.0, 3.0 Hz, 1H), 1.74-1.69 (m, 1H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 155.6, 153.9, 135.2, 129.3, 125.8, 125.5, 125.4, 122.9, 122.4, 51.4, 38.7, 36.5, 34.7, 29.9, 28.2, 25.5, 22.5, 18.9; IR (Neat Film, NaCl) 2934, 1737, 1570, 1439, 1205, 1171, 1118, 756, 710 cm^{-1}; HRMS (ES+) m/z calc'd for $C_{19}H_{23}NO_2$ $[M+H]^+$: 298.1807, found 298.1796.



Benzocyclobutene 314 (Scheme 2.20)

Reaction Performed via Method B. Purified by flash chromatography (SiO_2, 5:95 Et_2O/hexanes). 47% yield. R_f = 0.44 (30:70 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.47–7.28 (m, 6H), 5.61 (d, J = 9.0 Hz, 1H), 3.10 (ddd, J = 22.8, 15.5, 12.3, 2H), 1.9 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 135.5, 134.7, 133.2, 133.1, 132.2, 130.9, 130.0, 129.7, 128.7, 127.8, 127.1, 123.9, 122.8, 46.6, 34.8, 23.5; IR (Neat Film, NaCl) 3269, 1636, 1539, 1446, 1372, 1313, 1278, 1093, 1016, 819, 770, 732 cm^{-1}; HRMS (ES+) m/z calc'd for $C_{19}H_{23}NO_2$ $[M+H]^+$: 316.0337, found 316.0323.

2.5.2.4 Synthesis of Additional Substrates

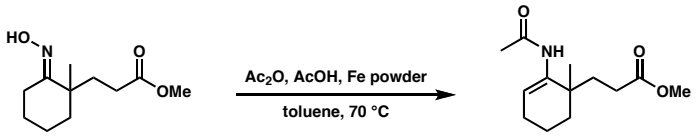


A1-3 *A1-4*

Oxime A1-4

To a solution of ketoester **A1-3** (1.36 g, 6.86 mmol) in MeOH (27 mL) was added $NH_2OH{\cdot}HCl$ (1.21 g, 17.4 mmol, 2.5 equiv) and pyridine (9.75 mL, 121 mmol, 17.6 equiv). The reaction was stirred at ambient temperature under nitrogen for 30 h, at which point it was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and washed sequentially with water (50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced

pressure to pink oil. Purification by flash chromatography (SiO_2, 10:90 EtOAc:hexanes) provided oxime **A1-4** as a colorless oil (1.22 g, 83% yield). R_f = 0.33 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (br s, 1H), 3.66 (s, 3H), 3.01 (dt, *J* = 14.5, 4.5 Hz, 1H), 2.31 (dt, *J* = 10, 5 Hz, 1H), 2.19-2.11 (comp m, 2H), 2.04 (ddd, *J* = 14.5, 11.0, 5.0 Hz, 1H), 1.77-1.58 (comp m, 5H), 1.50-1.42 (comp m, 2H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 163.9, 51.6, 40.0, 39.9, 32.5, 29.1, 25.8, 23.7, 21.1, 20.7; IR (Neat Film, NaCl) 3313, 2933, 2863, 1738, 1438, 1375, 1197, 1173, 936 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{11}H_{19}NO_3$ $[M^{\bullet}]^+$: 213.1365, found 213.1367.



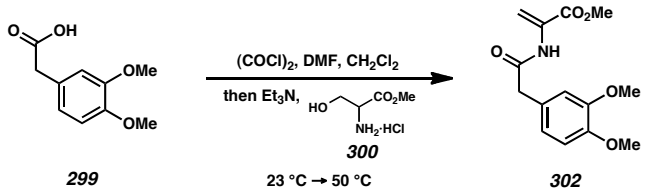
A1-4 *A1-5*

_N_-Acetyl enamine A1-5

Reaction performed according to the method of Burk.[64] Acetic anhydride (7.0 mL, 74.1 mmol, 2.8 equiv) was added dropwise to a solution of oxime **A1-4** (5.61 g, 26.3 mmol) in toluene (45 mL) over a period of 5 min. After an additional 5 min, acetic acid (4.5 mL, 78.6 mmol, 3.0 equiv) was added dropwise over 2 min, followed by 325 mesh iron powder (2.94 g, 52.6 mmol, 2.0 equiv). A reflux condenser was attached and the mixture was heated to 70 °C under a nitrogen atmosphere for 4 h, during which time the color changed from dark grey to orange-brown. The reaction was cooled to ambient temperature and passed through a plug of Celite. The filtrate was diluted with EtOAc (100 mL) and washed with saturated aqueous sodium bicarbonate (2 × 100 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL) and the combined organic layers

were washed with brine (100 mL), dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure to a yellow oil. Purification by flash chromatography (SiO_2, 25:75 → 60:40 EtOAc:hexanes) provided acetamide **A1-5** (3.74 g, 60% yield) as a colorless oil. R_f = 0.21 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.52 (br s, 1H), 6.16 (t, *J* = 4.0 Hz, 1H), 3.68 (s, 3H), 2.33 (dd, *J* = 9.5, 7.0 Hz, 1H), 2.26-2.09 (comp m, 3H), 2.05 (s, 3H), 1.88-1.82 (m, 1H), 1.64-1.56 (comp m, 4H), 1.44-1.39 (m, 1H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 168.8, 135.7, 120.1, 51.8, 37.0, 34.7, 33.8, 29.0, 26.0, 24.8, 24.5, 18.6; IR (Neat Film, NaCl) 3301, 2934, 1738, 1672, 1658, 1531, 1436, 1371, 1272, 1198, 1173, 1001 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{13}H_{21}NO_3$ $[M^{\bullet}]^+$: 239.1521, found 239.1527.

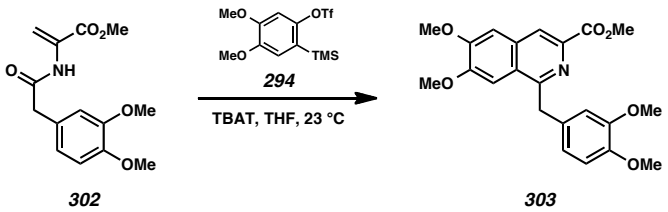
2.5.2.5 Total Synthesis of Papaverine



Methyl (3,4-dimethoxyphenyl)acetamidoacrylate (302)

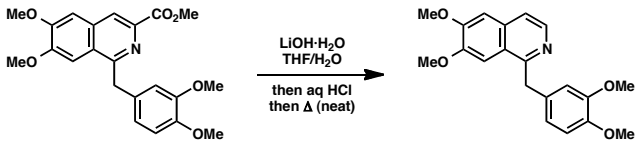
Oxalyl chloride (2.6 mL, 29.8 mmol, 2.3 equiv) was slowly added to a solution of acid **299** (5.55 g, 28.3 mmol, 2.2 equiv) in CH_2Cl_2 (40 mL), followed by DMF (0.10 mL, 1.29 mmol, 0.1 equiv). The solution was stirred at ambient temperature for 40 min, during which time it bubbled vigorously and the color changed from pale to bright yellow. In a separate flask, serine methyl ester·HCl (**300**) (2.02 g, 13.0 mmol) was suspended in CH_2Cl_2 (120 mL), and Et_3N (5.91 mL, 42.0 mmol, 3.2 equiv) and DMAP (77.6 mg, 0.64 mmol, 0.05 equiv) were added. The mixture was stirred for 15 min until

all solids had dissolved. The solution of acid chloride in the first flask was then transferred into the second flask via cannula under nitrogen over a period of 10 min, during which time the color of the serine methyl ester solution changed from colorless to orange. The reaction was maintained at ambient temperature under nitrogen for 2.5 h, at which time an additional portion of Et_3N (2.0 mL, 14.3 mmol, 1.1 equiv) was added. A reflux condenser was attached and the reaction was heated to 50 °C for 20 h. After cooling to ambient temperature, the solids were filtered off under vacuum and the filtrate was diluted in CH_2Cl_2 (100 mL), washed with saturated aqueous sodium bicarbonate (150 mL), brine (150 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a yellow oil. In order to retrieve excess acid **299**, the aqueous layer was acidified with concentrated HCl (5 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a pale yellow solid (crude **302**). Purification of the original yellow oil by flash chromatography (SiO_2, 25:75 → 45:55 EtOAc/hexanes) provided enamine **302** (2.43 g, 67% yield) as a colorless oil. R_f = 0.51 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (br s, 1H), 6.86 (s, 1H), 6.86 (d, *J* = 19.0 Hz, 1H), 6.82 (d, *J* = 19.5 Hz, 1H), 6.60 (s, 1H), 5.85 (d, *J* = 1.0 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.78 (s, 3H), 3.61 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ□169.9, 164.4, 149.4, 148.5, 130.8, 126.4, 121.6, 112.3, 111.6, 108.7, 55.9, 55.8, 52.9, 44.5; IR (Neat Film, NaCl) 3368, 2955, 1725, 1687, 1514, 1441, 1327, 1263, 1158, 1027 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{14}H_{17}NO_5$ $[M^{\bullet}]^+$: 279.1107, found 279.1118.



Methyl 1-(3'4'-dimethoxybenzyl)-6,7-dimethoxyisoquinoline-3-carboxylate (303)

To a solution of methyl (3,4-dimethoxyphenyl)acetamidoacrylate **302** (156 mg, 0.56 mmol, 2.0 equiv) in THF (20 mL) was added TBAT (166 mg, 0.31 mmol, 1.1 equiv) followed by *ortho*-silyl aryl triflate **294** (100 mg, 0.28 mmol) in THF (8 mL). The solution was stirred at ambient temperature under nitrogen for 72 h, at which point it was concentrated under reduced pressure to a yellow oil. Purification by flash chromatography (SiO_2, 50:50 → 60:40 EtOAc/hexanes) provided isoquinoline **303** (77.6 mg, 70% yield) as tan solid. R_f = 0.15 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.34 (s, 1H), 7.16 (s, 1H), 6.78 (app d, *J* = 6.5 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 1H), 4.63 (s, 2H), 4.05 (s, 3H), 4.01 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ□166.9, 158.2, 152.8, 151.5, 149.0, 147.6, 139.6, 133.0, 132.0, 124.8, 122.4, 120.5, 111.9, 111.1, 106.5, 104.8, 56.1, 56.0, 55.8, 55.7, 52.8, 42.8; δ; IR (Neat Film, NaCl) 2951, 2835, 1730, 1618, 1511, 1465, 1426, 1256, 1161, 1028, 733 cm^{-1}; HRMS (ES+) *m/z* calc'd for $C_{22}H_{23}NO_6$ $[M+H]^+$: 398.1604, found 398.1584.

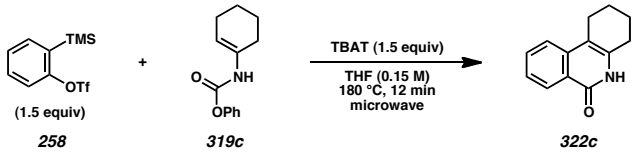


303 ***Papaverine (304)***

Papaverine (304)

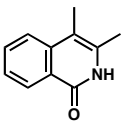
To a solution of isoquinoline ester **303** (20.0 mg, 50 μmol) in THF (1 mL) was added a solution of $LiOH{\cdot}H_2O$ (10.6 mg, 253 μmol, 5.0 equiv) in H_2O (0.5 mL). The biphasic mixture was vigorously stirred at ambient temperature under nitrogen for 3 h. The mixture was then concentrated under reduced pressure to remove the organic solvent and the aqueous layer was diluted with H_2O (1 mL). The pH was adjusted to 4 with conc. HCl (20 μL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a solid tan foam. The vial containing the crude foam under nitrogen was then heated by passing intermittently through a Bunsen burner flame over 45 sec. The resulting brown oil was purified by flash chromatography (SiO_2, 40:60 → 60:40 EtOAc/hexanes) to provide papaverine (**304**) (10.5 mg, 61% yield) as a yellow solid. R_f = 0.10 (50:50 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, J = 5.5 Hz, 1H), 7.43 (d, J = 5.5 Hz, 1H), 7.35 (s, 1H), 7.06 (s, 1H), 6.82 (app d, J = 7.0 Hz, 2H), 6.77 (d, J = 8.5 Hz, 1H), 4.54 (s, 2H), 4.01 (s, 3H), 3.91 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ□155.9, 150.5, 147.8, 147.1, 145.6, 139.2, 131.5, 130.4, 121.0, 118.6, 116.8, 109.9, 109.2, 103.4, 102.3, 54.1, 54.0, 53.9, 53.8, 40.4; IR (Neat Film, NaCl) 2930, 2832, 1511, 1478, 1421, 1269, 1235, 1158, 1026, 855 cm^{-1}; HRMS (ES+) *m/z* calc'd for $C_{20}H_{21}NO_4$ $[M+H]^+$: 340.1549, found 340.1553.

2.5.2.6 General Procedure for the Synthesis of Isoquinolones via Aryne Annulation



A flame-dried 3 mL microwave vial equipped with a magnetic stir bar was charged with TBAT (0.186 g, 0.345 mmol, 1.5 equiv) and carbamate **319c** (0.050 g, 0.230 mmol). The vial was sealed with a teflon-silicone septum, then evacuated and back-filled with argon (x2). Tetrahydrofuran (1.5 mL) was added via syringe and the mixture was stirred until the solids fully dissolved. 2-(trimethylsilyl)phenyl triflate (**258**) (0.084 mL, 0.346 mmol, 1.5 equiv) was then added via syringe and the reaction was immediately irradiated in a Biotage Initiator microwave reactor at 240 W until the temperature reached 180 °C. The reaction was stirred at 180 °C for 12 min, at which point the vial was cooled to room temperature, the septum was removed, and the contents of the vial were passed through a plug of silica (2 cm circular diameter × 2 cm height) under EtOAc elution (30 mL). The solvent was removed under reduced pressure and the resulting residue was purified via flash chromatography over silica gel.

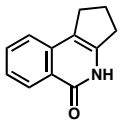
2.5.2.7 Spectroscopic Data for Isoquinolones



Isoquinolone 322a (Table 2.9, entry 1)

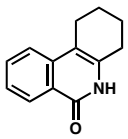
Purified by flash chromatography (SiO_2, 25:75 → 40:60 EtOAc/hexanes) to yield a white solid (46% yield). R_f = 0.10 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.93

(br s, 1H), 8.45 (dd, J = 7.8, 1.5 Hz, 1H), 7.71 (ddd, J = 7.8, 6.8, 1.5 Hz, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.47 (ddd, J = 7.8, 6.8, 1.5 Hz, 1H), 2.39 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 139.0, 132.9, 132.6, 127.6, 125.5, 124.7, 122.8, 108.4, 17.7, 12.5; IR (Neat Film, NaCl) 2988, 2866, 1712, 1654, 1637, 1607, 1548, 1477, 1347, 1316 cm^{-1}; HRMS (EI+) m/z calc'd for $C_{11}H_{11}NO$ $[M^{\bullet}]^+$: 173.0841, found 173.0852.



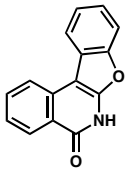
Isoquinolone 322b (Table 2.9, entry 2)

Purified by flash chromatography (SiO_2, 25:75 → 40:60 EtOAc/hexanes) to yield a white solid (68% yield). R_f = 0.07 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.08 (br s, 1H), 8.44 (d, J = 8.3 Hz, 1H), 7.68 (dd, J = 7.8, 7.3 Hz, 1H), 7.48–7.42 (comp m, 2H), 3.00 (t, J = 7.3 Hz, 2H), 2.94 (t, J = 6.8 Hz, 2H), 2.24 (app quintet, J = 7.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 140.6, 136.6, 132.6, 128.2, 125.3, 124.5, 123.0, 115.3, 31.6, 28.3, 22.0; IR (Neat Film, NaCl) 2899, 2849, 1657, 1643, 1606, 1545, 1476, 1386, 1339, 1324, 1154 cm^{-1}; HRMS (MM: ESI–APCI) m/z calc'd for $C_{12}H_{11}NO$ $[M+H]^+$: 186.0913, found 186.0916.



Isoquinolone 322c (Table 2.9, entry 3)

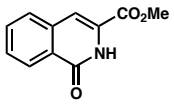
Purified by flash chromatography (SiO_2, 25:75 → 50:50 EtOAc/hexanes) to yield a white solid (64% yield). R_f = 0.10 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (br s, 1H), 8.43 (ddd, *J* = 8.1, 1.5, 0.5 Hz, 1H), 7.69 (ddd, *J* = 8.3, 6.8, 1.5 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.46 (ddd, *J* = 7.8, 7.1, 1.2 Hz, 1H), 2.74–2.69 (m, 2H), 2.68–2.63 (m, 2H), 1.94–1.86 (comp m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1, 138.5, 134.9, 132.5, 127.7, 125.6, 124.9, 121.8, 109.8, 27.5, 23.1, 22.6, 22.0; IR (Neat Film, NaCl) 2931, 2859, 1652, 1640, 1608, 1549, 1476, 1380, 1355, 1331, 1260, 1170 cm^{-1}; HRMS (MM: ESI–APCI) *m/z* calc'd for $C_{13}H_{13}NO$ $[M+H]^+$: 200.1070, found 200.1073.



Isoquinolone 322d (Table 2.9, entry 4)

Purified by flash chromatography (SiO_2, 2:98 → 5:95 EtOAc/hexanes) to yield a white solid (35% yield). R_f = 0.2 (25:75 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.51 (br s, 1H), 8.50 (dd, *J* = 7.8. 1.0 Hz, 1H), 8.11 (d, *J* = 7.8 Hz, 1H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.78 (ddd, *J* = 8.3, 7.8, 1.0 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.45 (dd, *J* = 7.8, 7.3 Hz, 1H), 7.37 (dd, *J* = 8.3, 7.3 Hz, 1H), 7.27 (app t, *J* = 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 159.4, 140.0, 135.5, 133.6, 129.6, 129.4, 129.3, 128.2, 125.3, 124.3, 122.7, 119.6, 111.7, 111.6; IR (Neat Film, NaCl) 2919, 2851, 1667, 1630, 1524,

1454, 1290, 1246, 1208, 1137 cm^{-1}; HRMS (ES+) *m/z* calc'd for $C_{15}H_9NO_2$ $[M+H]^+$: 236.0706, found 236.0709.



Isoquinolone 322e (Table 2.9, Entry 5)

Reaction performed at room temperature. Purified by flash chromatography (SiO_2, 10:90 → 30:70 EtOAc/hexanes). 57% yield. R_f = 0.35 (30:70 EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.46 (d, *J* = 5.9 Hz, 1H), 7.68 (m, 2H), 7.37 (s, 1H), 3.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 121.7, 136.0, 133.1, 129.4, 128.2, 127.9, 111.4, 53.2; IR (Neat Film, NaCl) 3168, 3060, 2953, 1726, 1662, 1602, 1496, 1466, 1433, 1304, 1215, 1149, 1005, 864, 769, 750 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{15}H_{19}NO_4$ $[M^{\bullet}]^+$: 203.0582, found 203.0511.

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(6) Sir William Henry Perkin famously attempted to synthesize the anti-malarial agent quinine (**5**) based on its empirical formula ($C_{20}H_{24}N_2O_2$), by combining 2 equivalents of the aniline-derived *N*-allyl toluidine ($C_{10}H_{13}N$) and $K_2Cr_2O_7$. Instead of isolating quinine as a product, however, Perkin discovered the purple,

heterogeneous dye mauveine, and became exceptionally wealthy. See: Perkin, W. H. *J. Chem. Soc. Trans.* **1879**, 717–732.

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(8) Robinson, B. *Chem. Rev.* **1969**, *69*, 227–250.

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(10) Madelung, W. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 1128–1134.

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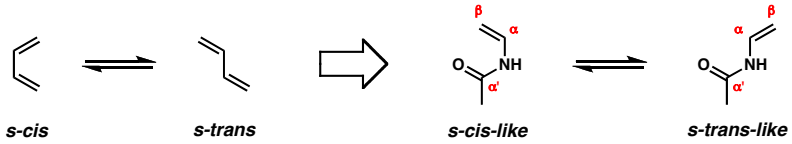

(75) As an alternative to the ene mechanism, nucleophilic attack as shown in Scheme 2.11 followed by protonation (either from an intramolecular or intermolecular proton source) would also generate styrene **311**.

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