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Applications of C−H Functionalization Logic to Cyclobutane Synthesis

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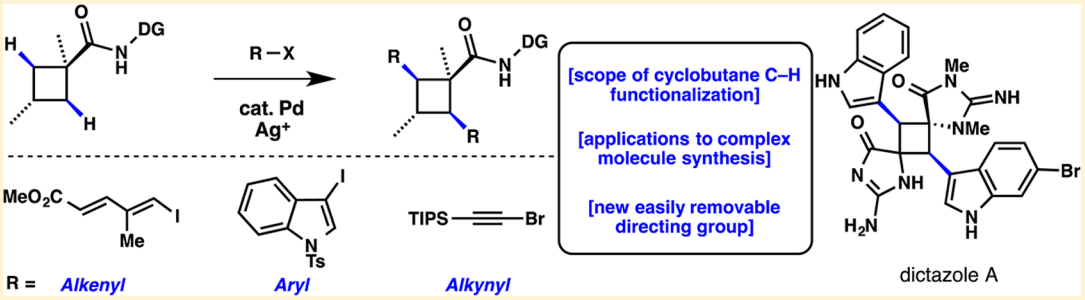
Supporting Information



ABSTRACT: The application of C−H functionalization logic to target-oriented synthesis provides an exciting new venue for the development of new and useful strategies in organic chemistry. In this article, C−H functionalization reactions are explored as an alternative approach to access pseudodimeric cyclobutane natural products, such as the dictazole and the piperarborenine families. The use of these strategies in a variety of complex settings highlights the subtle geometric, steric, and electronic effects at play in the auxiliary guided C−H functionalization of cyclobutanes.

INTRODUCTION

C−H functionalization logic is rapidly permeating the way organic chemists approach synthesis and deconstruct target molecules. With methodological advances developing at an increasing pace, new disconnections and strategies once thought impossible are now available for consideration during synthesis planning. While these methods have sporadically been utilized to great effect for decades, only recently have these strategies been formalized and articulated as an efficient and effective means to construct molecules of interest. In comparison to traditional prefunctionalization approaches, there are inherent benefits to using C−H bonds as latent functional groups in terms of redox, atom, and step economy. Furthermore, many issues of chemoselectivity are frequently mitigated by simply removing the functional groups from the equation altogether. C−H functionalization methods are particularly compelling from a strategic standpoint because they can challenge preconceived notions in order to provide solutions to longstanding problems in organic chemistry.[1]

Stereocontrolled synthesis of complex cyclobutanes is one such problem that was identified while surveying the wide diversity of cyclobutane-containing natural products that have been reported in the literature. Figure 1 shows a handful of these natural products. Common among all of these cyclobutanes, with the exception of tripartilactam[2] (**4**), is that they are pseudodimeric; they are composed of two similar, but distinct, olefin precursors. For instance, the piperarborenines (**1** and **2**) have differing degrees of oxidation on the aryl rings, with one ring containing two methoxy substituents and the other possessing three.[3] The dictazoles (**5** and **6**), anthocerotonic acid (**3**), and pipercyclobutanamide A (**8**), on the other hand, are fully unsymmetrical with four different substituents on the cyclobutane ring.[4] Additionally, a wide variety of cyclobutane stereochemistries are observed, furthering the difficulty of general strategies for their construction.

With increasing interest apparent in the fields of medicinal chemistry, polymer, and material science, a dearth of methods for the construction of cyclobutanes has been revealed, particularly in comparison to its smaller and larger homologues.[5] The most commonly considered and direct approach to cyclobutane synthesis is through a [2 + 2] photocycloaddition.[6] While this strategy has proven useful in many intramolecular contexts and homodimerizations, the successful *hetero*dimerization of two olefins is highly dependent upon the proper steric and electronic properties of the monomers. Additionally, the resulting stereochemistry is largely at the mercy of the substrates chosen. For the heterodimerization of two similar monomers, a photochemical approach could be highly inefficient, as illustrated in Figure 2. This first issue, presuming a photocycloaddition reaction is viable, is one of statistics. Since the two monomers are effectively identical in terms of steric and electronic parameters, there is likely no preference for heterodimerization over homodimerization. The orientation of the olefin monomers during the dimerization is another point of consideration, since both head-to-head and head-to-tail modes of cyclization are possible. When these factors are combined with facile *E*/*Z* isomerism of the starting

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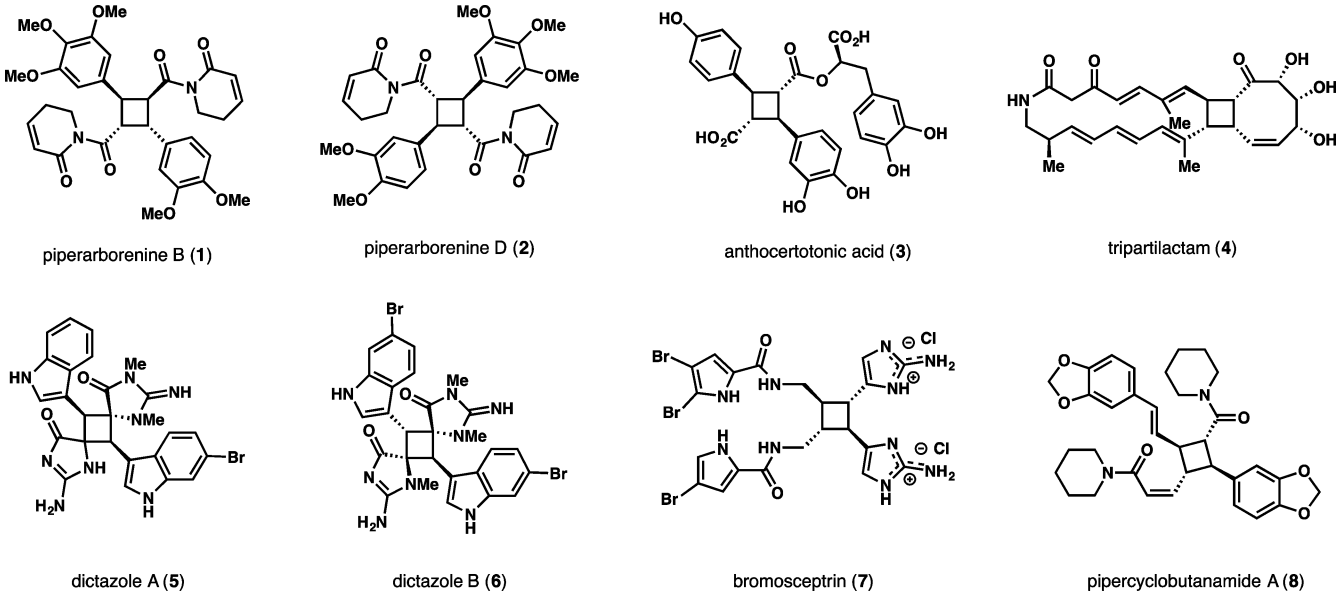

Figure 1. Complex cyclobutane natural products.

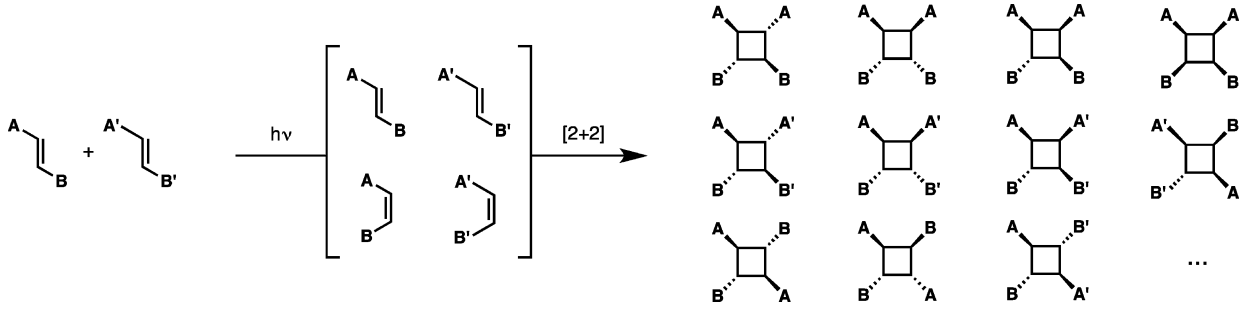

Figure 2. Potential products of a hypothetical photochemical [2 + 2] heterodimerzation reaction.

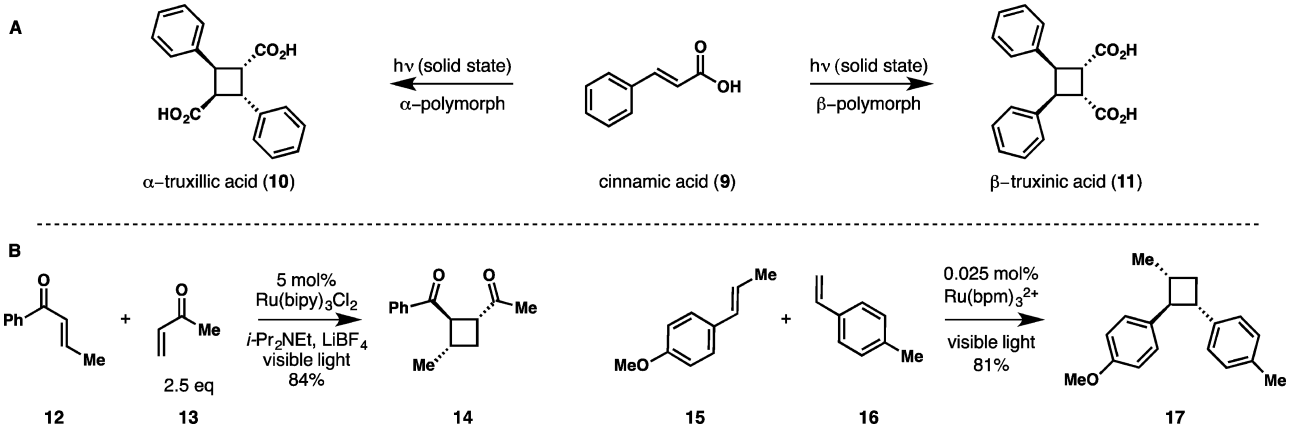

Figure 3. Examples of (A) solid-state photochemistry and (B) photoredox-catalyzed [2 + 2] cycloadditions.

materials under photochemical conditions, a potentially very complex mixture of dimeric products could arise that presumably would be very challenging to purify. Further supporting this line of reasoning, the *homodimerization* of methyl cinnamate in the presence of $BF_3{\cdot}Et_2O$ leads to 8 of the 11 possible isomeric cyclobutane products.[7]

Partial solutions to this problem have emerged from solid-state photochemistry, template-directed photochemistry, and photoredox catalysis. As shown in Figure 3A, seminal studies on topochemistry by Schmidt demonstrated that direct irradiation of different crystal polymorphs of cinnamic acid (**9**) in the solid state leads to different cyclobutane dimers.[8] The α polymorph leads to α-truxillic acid (**10**), while the β form gives exclusively β-truxinic acid (**11**). This chemistry was the basis for the syntheses of the symmetrical cyclobutane dimers dipiperamide A and incarvillateine.[9] Notably, the γ polymorph of cinnamic acid is photoinert due to improper olefin spacing and alignment in the solid state. This strategy is not well suited for heterodimerizations, however, since a 1:1 cocrystallization and precise packing of the two different olefins in the crystal lattice

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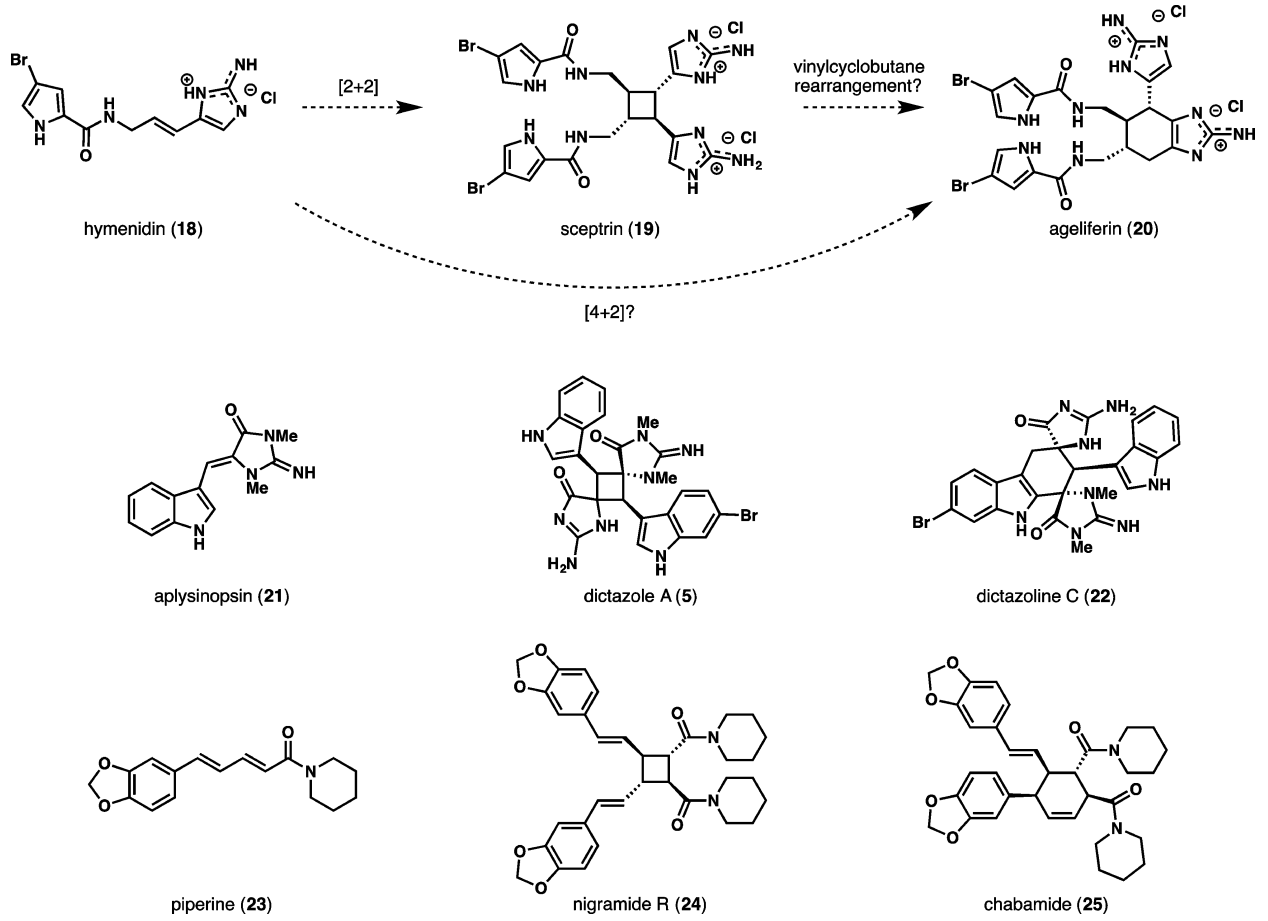

Figure 4. Biosynthetic relationships between various dimeric natural products.

would be required, a challenging crystal engineering problem that has only been observed in highly biased systems.[10] Template-directed photochemistry has also seen success in controlling the stereo- and regiochemistry of [2 + 2] reactions by placing two olefins in close proximity through molecular imprinting,[11] supramolecular encapsulation,[11b] or other noncovalent interactions (e.g., hydrogen bonding).[11c,d] While this approach has allowed the controlled dimerization of several cinnamic derivatives that are otherwise unreactive, the scope is still quite limited. Recently, impressive progress has been made using visible light photoredox catalysis for highly efficient and stereoselective dimerization of olefins, including reports of controlled heterodimerization by Yoon and co-workers (Figure 3B).[12] Currently, these methods are limited to aryl enone (e.g., **12**) or an electron-rich styrene (e.g., **15**) substrate for productive cyclization and only generate head-to-head adducts. Nonphotochemical methods are also available for the preparation of cyclobutanes. Direct ring-closing strategies are entropically disfavored and are frequently low yielding, even for simple substrates.[13] Ketene cycloaddition is one of the most useful methods for cyclobutane synthesis, due to the high levels of regio- and stereoselectivity frequently observed and a variety of methods for ketene formation, though the product always results in a cyclobutanone.[14]

Cyclobutane natural products also have proven to be challenging to properly elucidate using standard spectroscopic methods, particularly NMR.[15] Numerous stereochemical and constitutional errors have been made in the literature when attempting to determine the structure of cyclobutane-containing natural products.[16] These misinterpretations likely derive from the fluxional nature of the cyclobutane ring system that rapidly undergoes ring flipping, resulting in unpredictable NMR chemical shifts that have been described as "rather erratic".[17] Proton−proton coupling constants, which are routinely used as a diagnostic stereochemical tool in other cyclic systems, are widely varied for cyclobutanes, with *cis* and *trans* vicinal coupling ranging 4.6−11.5 and 2.0−10.7 Hz, respectively.[17] In combination with the frequently observed long-range $^4J_{H,H}$ coupling across the ring, compounds of mistaken identity are frequently proposed. From the viewpoint of structural confirmation, a direct dimerization strategy would be at a disadvantage, since the true structure would likely not be challenged if the spectral and physical data matched those which were reported. Reassignments are generally reliant upon X-ray crystallography,[9a,18] chemical synthesis,[19] and, more recently, computational methods.[20] Since the majority of cyclobutane-containing natural products have not been evaluated by one of these means, it stands to reason that many of the structures suggested in the literature are in fact incorrect.

While many terpene-derived cyclobutanes are produced through cationic polyolefin cyclization, the role of enzymes in the production of many cyclobutane dimers is unclear.[21] The marine natural products dictazole A (**5**), dictazole B (**6**), and sceptrin (**19**) are isolated from deep-sea sponges where very little sunlight penetrates, making a purely photochemical [2 + 2] pathway improbable. Furthermore, sceptrin (**19**) is isolated as an enantiopure molecule, almost certainly implying

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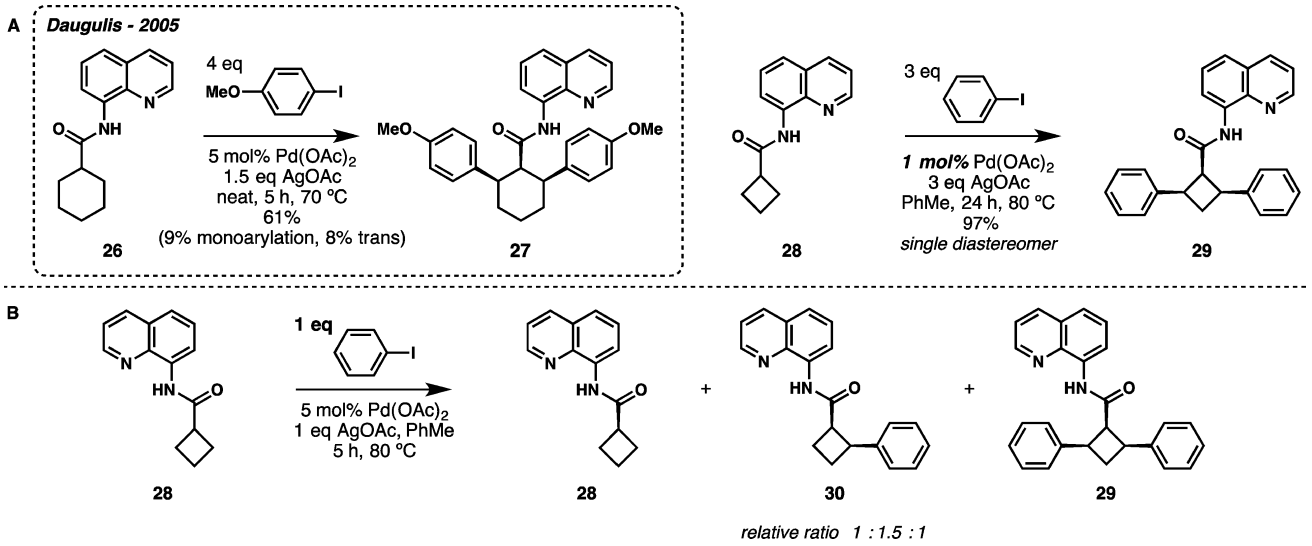

Figure 5. (A) Daugulis' methylene C−H arylation. (B) Statistical arylation of **28** with 1 equiv of iodobenzene.

enzymatic intervention.[22] A recent report by Molinski demonstrated the production of benzosceptrin C from its monomer, oroidin, using a "metabiosynthetic" approach with cell-free enzyme extracts.[23] This oxidative dimerization, proposed to occur through a series of single-electron-transfer events, suggests that a similar enzymatic pathway is operative for the conversion of hymenidin (**18**) to sceptrin (**19**) (Figure 4). Additional support for this arises from the reluctance of hymenidin (**18**) and aplysinopsin (**21**) to undergo photochemical [2 + 2] reactions.[22,24] The piperine cyclobutane natural products (**23**−**25**), on the other hand, are isolated from pepper plants and are necessarily exposed to light. These molecules are isolated as racemic mixtures and could be produced by unselective photochemical [2 + 2] photocycloaddition reactions, as a variety of dimeric products with differing stereochemical patterns have been isolated.[25] Curiously, the intermolecular [2 + 2] photocycloaddition of these monomers is highly inefficient; therefore, additional templating or intervention within the plant cell has been proposed.[26]

[4 + 2] adducts, such as ageliferin (**20**), dictazoline C (**22**), and chabamide (**25**), are also isolated alongside the cyclobutane dimers. Hymenidin (**18**) and aplysinopsin (**21**) also do not engage in Diels−Alder reactions when heated.[4a] Piperine (**23**) can undergo thermal dimerization to chabamide (**25**), but forcing conditions are required (>130 °C) and the reaction is unselective.[27] An alternate biosynthetic hypothesis for formation of these [4 + 2] dimers has been proposed by our group, in which a vinyl cyclobutane rearrangement (VCB) gives the six-membered-ring natural products from the respective cyclobutane dimers. Experimental support for this pathway has been provided by the direct conversion of sceptrin (**19**) into ageliferin (**20**) and the epimeric nagelamide E in 50% and 28% yields, respectively, after microwave irradiation in water at 200 °C.[28] Williams also suggested this as a possible pathway for the biogenesis of dictazoline C (**22**) on the basis of preliminary experiments with naturally isolated dictazole A (**5**).[4a]

RESULTS AND DISCUSSION

C−H Functionalization Approach to Cyclobutane Synthesis. Taking into account the limitations of regio- and stereocontrol of a direct dimerization strategy, an unconventional retrosynthesis of unsymmetrical cyclobutane dimers was considered using C−H functionalization logic as an alternative to intermolecular photocycloaddition. Common among many of the cyclobutane natural products shown in Figure 1 is a carbonyl group attached directly to the cyclobutane ring. This led us to consider a general cyclobutane strategy in which the carbonyl is viewed as a latent directing group for C−H functionalization. This would permit the direct installation of the desired functionality in a facially controlled manner, guided by the preexisting stereocenter. If two C−H functionalization reactions could be employed sequentially, the synthetic challenge of pseudosymmetry and stereochemistry would be greatly simplified. While C−H functionalization of cyclopropanes had received some attention at the time,[29] examples of direct cyclobutane functionalization were limited to a harsh magnesiation procedure described by Eaton and co-workers.[30] Other examples of cross-coupling to sp^3 C−H bonds in the literature were generally limited, but a seminal report by Daugulis and co-workers in 2005 appeared promising (Figure 5A).[31] Employing an aminoquinoline directing group, a wide variety of methylene C−H bonds could be arylated under palladium (II/IV) catalysis. Furthermore, the only cyclic substrate examined, cyclohexane **26**, delivered the bis-arylated product **27** in 61% yield as the all-*syn* isomer. To test the competence of four-membered rings in this methodology, cyclobutane **28** was prepared and subjected to the reaction conditions with iodobenzene. Encouragingly, this substrate outperformed any of the examples described in the original report, giving the bis-phenylated cyclobutane **29** in 97% isolated yield and as a single diastereomer. Additionally, the palladium loading could be lowered to 1 mol %, making this one of the most efficient sp^3 C−H functionalization reaction reported to date using a Pd (II/IV) manifold.

Following this initial proof of concept, studies were directed toward two potential problems: sequential cross-coupling reactions and the scope of coupling partners. In order to access the unsymmetrical cyclobutane targets in Figure 1, the C−H functionalization reactions would need to be performed sequentially in a controlled manner. To test the viability of a monofunctionalization, the phenylation reaction was repeated with 1 equiv of iodobenzene (Figure 5B). A statistical mixture (1:1.5:1) of starting material **28**, monoarylated cyclobutane **30**, and bis-arylated cyclobutane **29** resulted, implying that the rate

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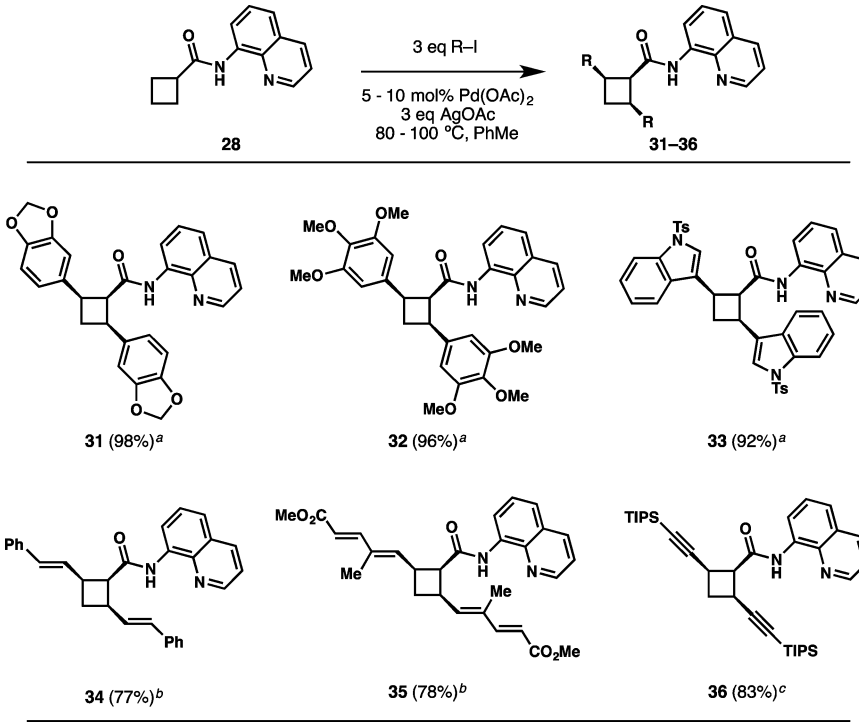
Scheme 1. Coupling Partner Scope for Cyclobutane C−H Functionalization[a]



[a]Reagents and conditions: (a) 5 mol % of $Pd(OAc)_2$, 80 °C, 5 h. [b]Reagents and conditions: 10 mol % of $Pd(OAc)_2$, 80 °C, 12 h. [c]Reagents and conditions: 5 mol % of $Pd(OAc)_2$, LiCl (3 equiv), 100 °C, 12 h.

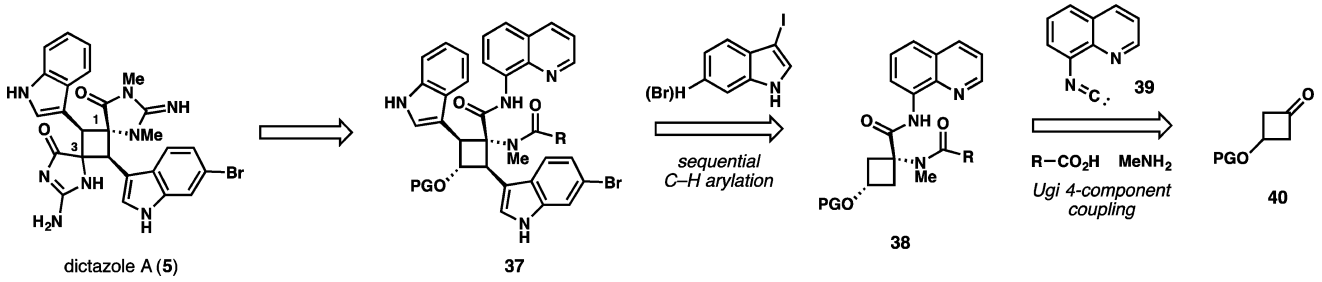


Figure 6. Retrosynthesis of dictazole A (**5**) employing C−H arylation and an Ugi reaction.

of the second arylation is nearly identical with that of the first arylation. While this was initially discouraging, we were hopeful that the issue could be overcome through alteration of the reaction conditions or substrate control on a more functionalized system.

To test the generality of the C−H cross-coupling reaction, other coupling partners were explored and the scope was found to be broad (Scheme 1). Electron-rich arenes, such as those found in the piperarborenine natural products (**1** and **2**), performed excellently to give **31** and **32** in 98% and 96% yield, respectively. Two *N*-tosylated indoles were introduced onto the cyclobutane ring in 92% yield, encouraging potential access to the dictazole natural products (**5** and **6**). Additionally, the C−H olefination reaction needed for pipercyclobutanamide A (**8**) was successful in the Daugulis chemistry, with iodostyrene giving **34** in 77% yield. Even the bis-dienoate **35** could be prepared using this strategy, introducing a substructure found in tripartilactam (**4**). Finally, alkynylation proved facile according to Chatani's protocol to give **36** in 83% yield,[32] which could serve as an alternate entry to the dictazole natural products through a Larock indole synthesis. With these preliminary results, efforts were directed toward the total synthesis of the dictazole and piperarborenine families of natural products.

Studies toward Dictazole A. The structure of dictazole A (**5**) offers a number of difficulties for synthesis; the most notable is the four contiguous stereocenters around the congested cyclobutane core, two of which are quaternary spiroiminoimidazolidinone rings.[4a] Furthermore, each of the substituents is unique, as only one of the indoles is brominated and a single spiro ring bears methyl groups. To add to this challenge, the spiro stereocenter at C-3 could not be determined by standard spectroscopic means and its relative configuration is unknown. Applying the cyclobutane C−H functionalization strategy, a retrosynthesis of dictazole A (**5**) was devised (Figure 6). The spiroiminoimidazolidinone rings were first deconstructed; one could arise through Strecker type chemistry (further disconnected to a protected alcohol) and another from an aminoquinoline amide, leading back to intermediate **37**. Two sequential C−H arylation reactions with appropriate 3-iodoindoles would remove two of the stereocenters and lead back to symmetrical cyclobutane **38**.

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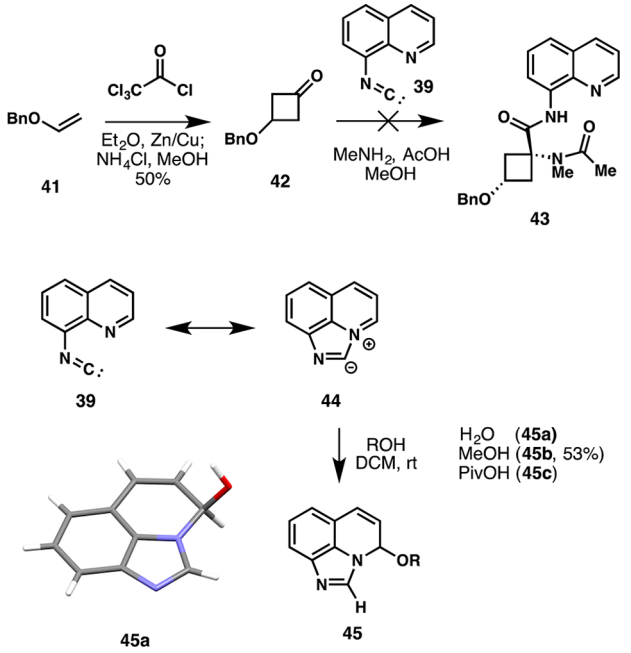
Notably, the bromide present on one of the indoles in dictazole A (**5**) should be tolerated in the arylation chemistry, since it proceeds through a palladium (II/IV) catalytic cycle.[33] Finally, the quaternary amino-amide stereocenter at C-1 could arise from an Ugi four-component coupling of cyclobutanone **40**, 8-isocyanoquinoline **39**, methylamine, and a suitable carboxylic acid.[34]

To test the viability of this approach, (benzyloxy)-cyclobutanone **42** was prepared by thermal [2 + 2] cyclo-addition of benzyl vinyl ether (**41**) and in situ formed dichloroketene following Poisson's one-pot procedure[35] in 50% yield (Scheme 2). Unfortunately, it was wholly ineffective

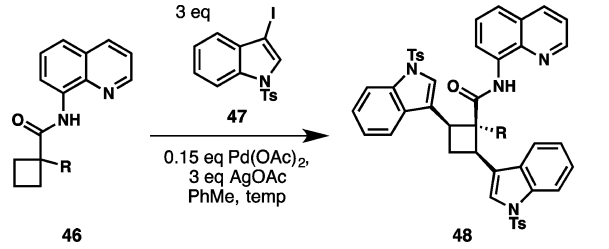
Scheme 2. Attempted Ugi Reaction and Abnormal Reactivity of Isonitrile 39[a]



in the Ugi reaction under a variety of reaction conditions explored, despite ample precedent for the use of cyclobutanones in Ugi reactions.[36] Interestingly, the side reactions were determined to be direct addition reactions of isonitrile **39** with the carboxylic acid or an alcoholic solvent to give dearomatized benzimidazoles (**45**). While the pivalic acid adduct **45c** could be observed by crude ^{1}H NMR, it was not isolable and hydrolyzed to **45a**, which was characterized by X-ray crystallography. These bizarre addition reactions can be rationalized by considering the cyclized zwitterionic isomer **44**, wherein a deprotonation/addition mechanism would generate the observed products.

During the exploration of an Ugi strategy, a model study was also under investigation to examine the effect of quaternary α-amino substituents in the Daugulis C−H arylation reaction.[37] A series of substrates were synthesized from commercially available ethyl 1-amino-1-cyclobutanecarboxylate (see the Experimental Section for preparations). Surprisingly, these proved to have highly deleterious effects on the C−H arylation chemistry. Azide **46a** and Cbz-protected amine **46b** gave no detectable arylated products on reaction with iodoindole **47**, simply decomposing or remaining unreactive after prolonged heating, respectively (Table 1). Phthalimide-derived **46c** required heating to 130 °C to initiate the reaction and was

Table 1. Surprising Effects of α Substituents on C−H Arylation Chemistry



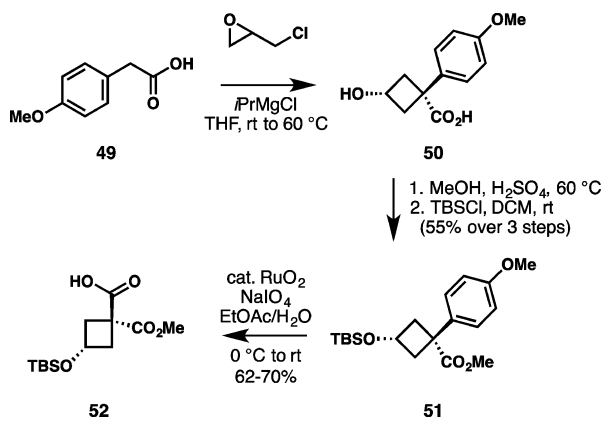
entry	R	temp (°C)	% yield (%)
1	N_3 (**46a**)	130	decomp
2	NHCbz (**46b**)	140	NR
3	NPhth (**46c**)	130	14 (**48c**)[a]
4	CO_2Me (**46d**)	90	21 (**48d**)[b]

[a]Starting material fully consumed. [b]62% starting material recovered.

accompanied by nonspecific decomposition, yielding only 14% of bis-indolated **48c** with full consumption of the starting material. This lowered reactivity was attributed to the coordinating nature of the nitrogen substituents, generating an unreactive chelate with the directing group and preventing cyclometalation.[38] Ester-derived cyclobutane **46d** was examined next, since it is less coordinating and could be converted to the requisite amine through a Curtius rearrangement. While this substrate was also significantly less reactive than the parent cyclobutane **28**, it performed the arylation chemistry at much lower temperature (90 °C) than phthalimide **46c** and the mass balance was largely unreacted starting material. Therefore, a 1,1-cyclobutanedicarboxylate derivative was targeted for the second-generation approach to dictazole A (**5**).

A diastereoselective synthesis of the C−H activation precursor began following a report from Merck for the preparation of cyclobutane hydroxy acids that is scalable and employs inexpensive starting materials.[39] In this reaction, the dianion of 4-methoxyphenylacetic acid (**49**) was treated with epichlorohydrin in a double-alkylation reaction to deliver hydroxy acid **50** as a single diastereomer (Scheme 3). The observed relative stereochemistry can be rationalized by invoking a magnesium chelate that templates the final ring-closing alkylation. Fischer esterification and alcohol protection with TBSCl generated cyclobutane **51** in 55% yield over the three steps. The electron-rich methoxyarene was selected in anticipation of the ruthenium tetroxide catalyzed arene

Scheme 3. Diastereoselective Synthesis of 52



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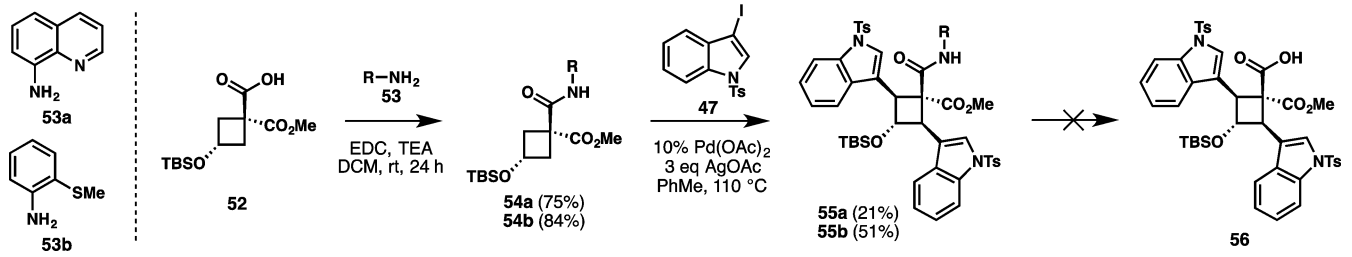
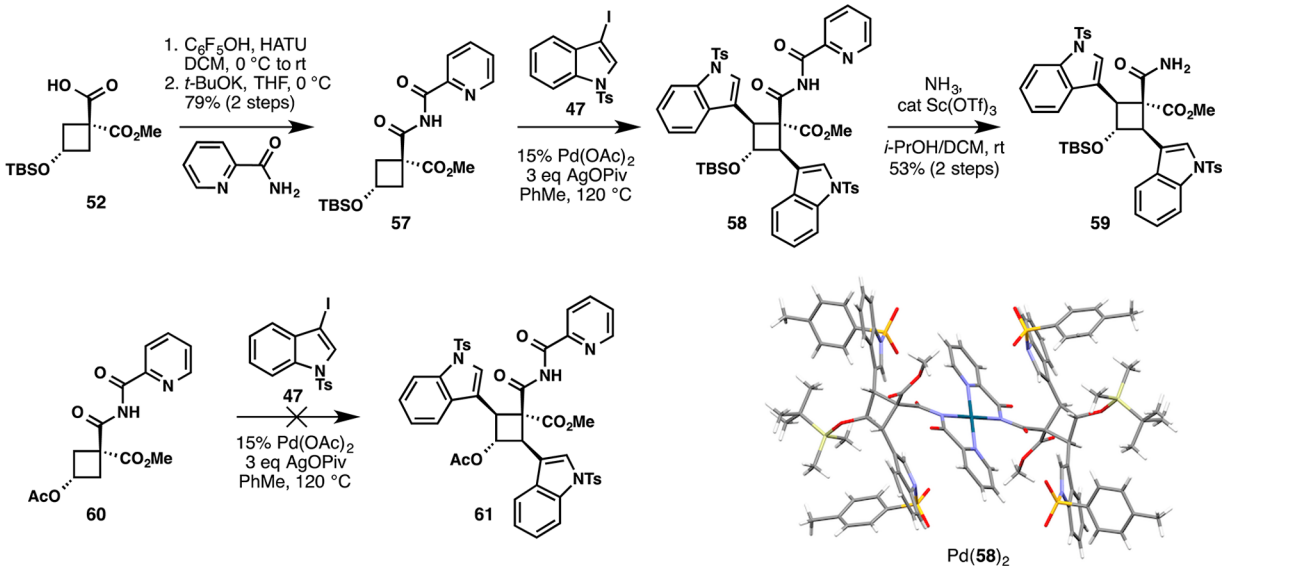
Scheme 4. Successful C−H Arylation Reaction, but Unsuccessful Directing Group Deprotection



Scheme 5. Successful Deprotection of the Picolinimide Directing Group



degradation, which gave acid **52** in 70% yield. Notably, performing the reaction in the absence of acetonitrile and at dilute concentrations were necessary to avoid overoxidation of the TBS alcohol to the corresponding cyclobutanone.

With the key cyclobutane substrate **52** prepared, studies on the C−H functionalization chemistry commenced. Two directing groups developed by Daugulis and co-workers, 8-aminoquinoline (**53a**) and *o*-thioanisidine (**53b**), were tested in the arylation reaction and were coupled to the carboxylic acid with EDC to give **54a** and **54b** in 75% and 84% yields, respectively (Scheme 4).[33] Similar to the case for **46d**, aminoquinoline **54a** was found to be poorly suited for the direct arylation chemistry, delivering bis-indolated cyclobutane **55a** in 21% yield (unoptimized) with primarily starting material remaining. The thioanisidine **54b**, on the other hand, performed better. Under the same reaction conditions, the starting material was fully consumed to give **55b** in 51% yield. This was especially peculiar, because the thioanisidine-derived directing group was reported to generally be less reactive toward methylene C−H bonds in comparison to the aminoquinoline directing group.[33] This observation, combined with the significant effect of α substitution, highlights the subtle geometric factors at play in the C−H functionalization chemistry.

Temporarily bypassing the problem of sequential arylation of the two different indoles, attention was directed at removal of the directing groups for the construction of the guanidine-containing spirocycle. Removal of the directing group proved to be very challenging, since the inherently strong amide bond is quite sterically hindered after introduction of the indoles. Many conditions explored for amide deprotection met with failure,[40] and even hydrolysis of the ester in **55a** for a Curtius rearrangement resulted in primarily decarboxylation of the generated acid. The difficulty in removal of the amide-based directing groups is consistent with previous studies by Chen and co-workers, in which considerable functional group manipulation was required to cleave the aminoquinoline auxiliary.[38]

Recognizing the need for a new directing group that could be more easily deprotected, we considered an imide-based strategy. Since picolinamide was reported to be a competent directing group by Daugulis in his 2005 communication, a picolin*imide*-based directing group seemed logical.[31] Imides in general are much more susceptible to hydrolysis than amides, and this would give a second, less hindered carbonyl group for reaction and removal. To test this hypothesis, picolinimide **57** was prepared via the pentafluorophenyl ester according to the Andrus protocol in 79% yield over two steps (Scheme 5).[41] Gratifyingly, this directing group was found to be competent in the C−H arylation chemistry, giving the bis-indolated imide **58** along with the corresponding palladium complex Pd(**58**)$_2$ (confirmed by X-ray crystallography). As anticipated, the imide motif was found to be much more easily cleaved than then traditional amide-based systems. Treating the mixture of **58** and Pd(**58**)$_2$ with a DCM/2-propanol solution saturated with ammonia in the presence of catalytic scandium triflate generated the primary amide **59** in 53% yield from **57**. While it was possible to separate **58** from its palladium complex, it was more convenient to subject both to the ammonolysis, as they converge to the same product. The acetate derivative of **60** was

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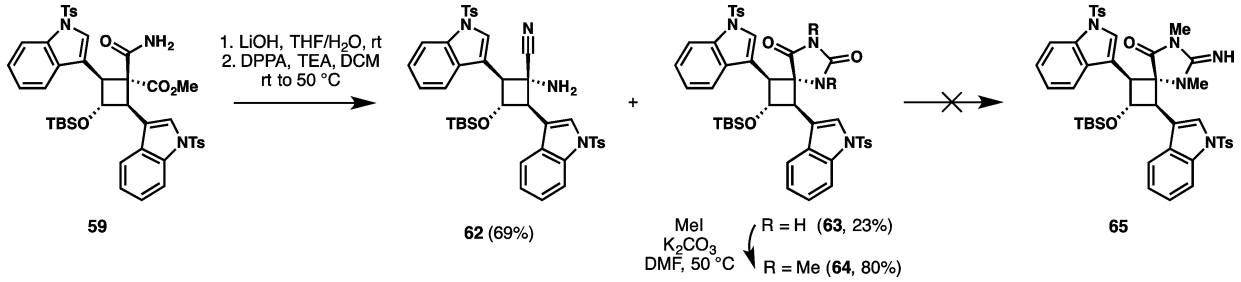
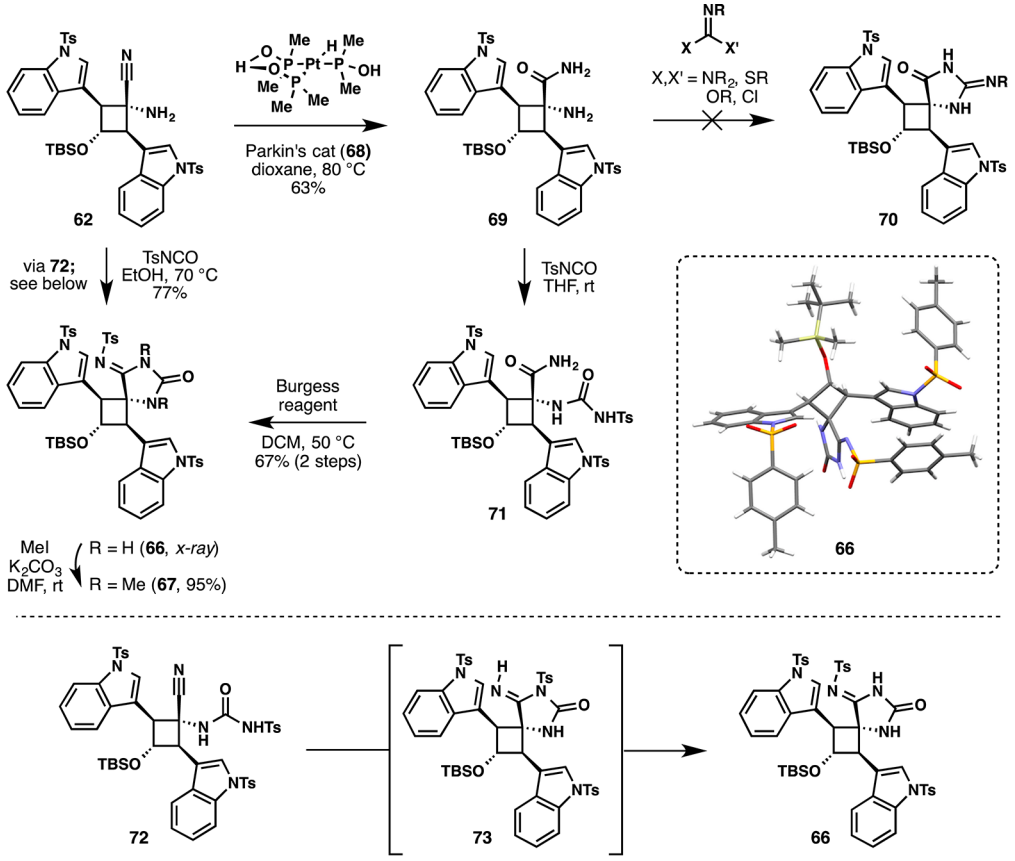
Scheme 6. Unexpected Curtius Rearrangement Product



Scheme 7. Failure of Aza-Bucherer–Bergs Reaction and Unexpected Dehydration of 71



prepared in an analogous fashion (see the Experimental Section for details) but strangely proved unsuccessful in the C–H arylation chemistry under the same reaction conditions. It is possible that the inductive effect of the acetate influences the efficiency of the reaction or the larger TBS ether locks the ring into a more favorable geometry for C–H insertion and cross-coupling.

With the successful deprotection of the picolinimide directing group, the synthesis of the C-1 spirocycle using a Curtius strategy was investigated. Since this ring required regioselective methylation, attempts were made to prepare substrates that would allow for selective alkylation, through either a hydantoin or an appropriately protected spiroguanidine. Hydantoin **63** was the expected product from a Curtius rearrangement of **59**, since the primary amide could intramolecularly collapse onto the intermediate isocyanate (Scheme 6). Unexpectedly, hydantoin **63** was isolated as the minor product (23% yield) and aminonitrile **62** was isolated as the major product (69% yield) when the carboxylic acid was treated with excess diphenylphosphoryl azide (DPPA). This suggests that the hindered primary amide dehydrates competitively with the rearrangement of the intermediate acyl azide under the reaction conditions. Interested in moving forward, we alkylated hydantoin **63** with methyl iodide to give **64** in 80% yield, but conversion of the carbonyl to the imino group of **65** through activation with Meerwein's salt or Lawesson's reagent met with failure.

Reconsidering the strategy, we turned our attention to the major product of the Curtius reaction, aminonitrile **62**, as an intermediate to carry forward. An aza variant of the Bucherer–Bergs hydantoin synthesis was envisioned in which an isocyanate would replace carbon dioxide to directly generate the desired heterocycle. In this reaction, **62** was treated with tosyl isocyanate and heated in ethanol to produce the undesired spirocycle **66**. The true identity of the product was initially uncertain because of the ambiguous spectroscopic and mass spectrometry (MS) data (Scheme 7). Spirocycle **66** could be dimethylated with methyl iodide to give **67**, which also

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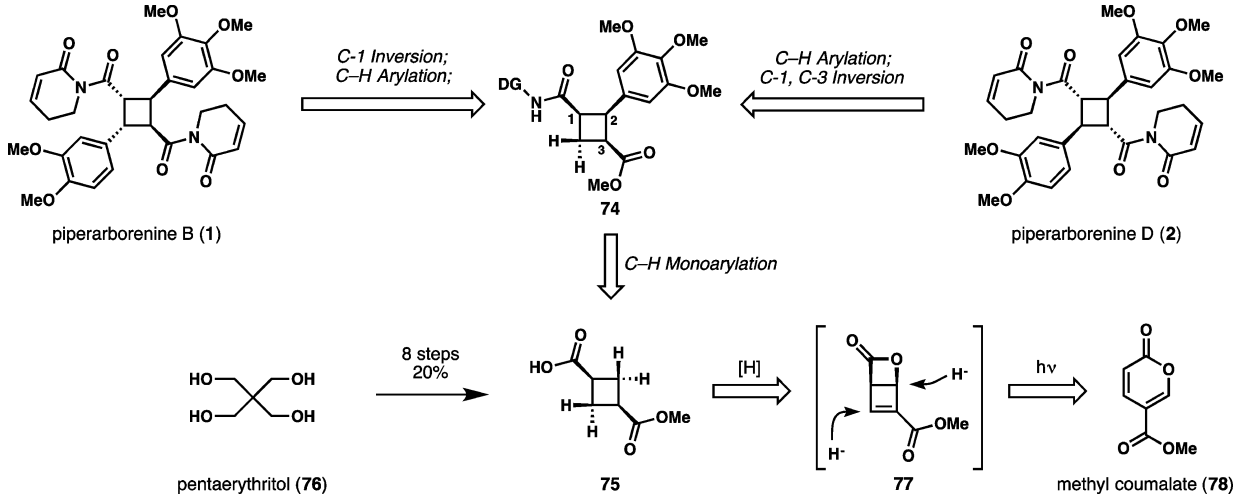
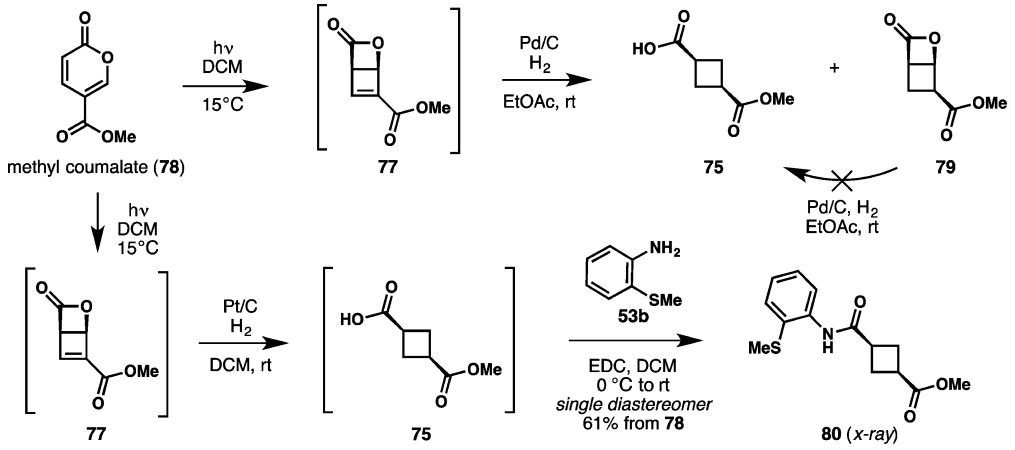


Figure 7. Retrosynthesis of the piperarborenines from methyl coumalate (78).

Scheme 8. New Synthesis of 1,3-Cyclobutanedicarboxylates



appeared to be in agreement with the desired ring system (e.g., **65**). During this time, however, crystals were obtained of **66**, and the aza-Bucherer–Bergs reaction was demonstrated to be unsuccessful through X-ray crystallographic analysis. Instead of the desired oxygen closure, the nitrogen of urea **72** cyclized onto the nitrile to give intermediate **73**, which underwent additional sulfonyl migration to produce the observed product **66**.

Still interested in utilizing aminonitrile **62**, we were successful in hydrating amide **69** using Parkin's platinum catalyst (**68**), tolerating the free primary amine (Scheme 7).[42] Unfortunately, this amine was reluctant to react with a number of electrophiles for spirocycle synthesis (isothioureas, cyanogen bromide, bis(methylthio)methylenesulfonamides, etc.) even when combined with a range of bases and salt additives (Ag^+, Hg^{2+}, etc.). Recalling the facile reaction of **62** with tosyl isocyanate, amide **69** was also found to react to give urea **71**. Dehydration of this urea was expected to generate a carbodiimide that would cyclize to the desired product (**70**), but treatment with Burgess reagent gave **66** as the exclusive product in 67% yield for the two steps. Again, the hindered primary amide was surprisingly susceptible to dehydration, leading to intermediate **72**.

Given the unforeseen difficulty in constructing the requisite spirocycles, efforts at this time were directed to a separate set of pseudodimeric cyclobutane natural products, the piperarborenines, whose synthesis was being explored concurrently. Despite the initial challenges in the synthesis of dictazole A (**5**), further efforts are aimed at construction of the spirocycles at an earlier stage in the synthesis and application of knowledge gained during the piperarborenine projects for sequential introduction of the differentiated indole substituents.

Synthesis and Revision of the Piperarborenines and Pipercyclobutanamide A. Contemporaneous with the dictazole studies, efforts were also being directed toward the synthesis of stereoisomeric piperarborenines B (**1**) and D (**2**). The central challenge associated with the piperarborenine natural products is the controlled, sequential installation of the two different aryl rings on the cyclobutane core. Piperarborenine B (**1**) has a *cis,trans,cis* relative configuration with the two aryl substituents on opposite sides of the cyclobutane ring, whereas the arenes are on the same face of the cyclobutane in the *trans,trans,trans* piperarborenine D (**2**) (Figure 7).[3] Continuing with our general C–H functionalization strategy, we viewed the dihydropyridone motif as a latent directing group for C–H arylation and devised a divergent strategy from the all-*cis* cyclobutane **74**. From this intermediate, piperarborenine B (**1**) could be prepared by an epimerization at C-1, directed C–H arylation, and further functional group manipulations to install the imide side chains. Alternatively, piperarborenine D (**2**) could be accessed by performing a C–H

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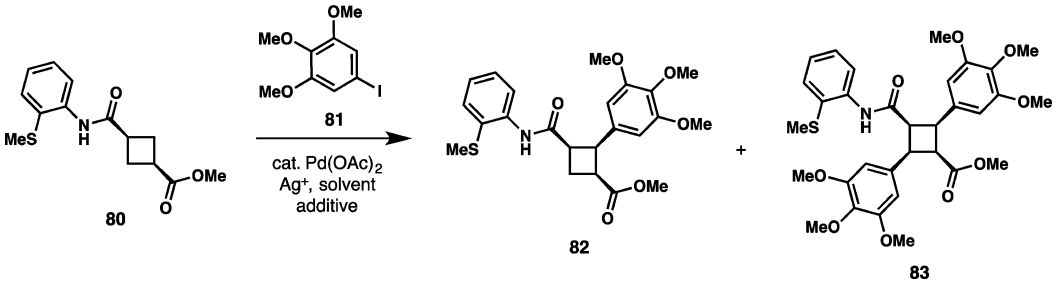
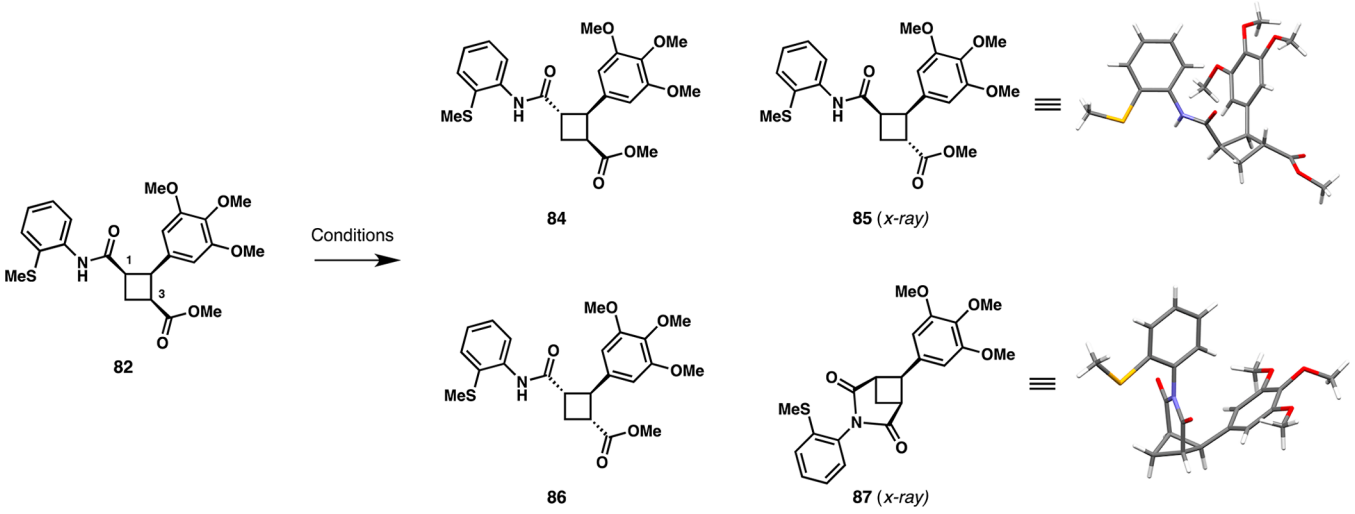
Table 2. Optimization of the Monoarylation Reaction



entry	conditions	yield of **82** (%)	**80:82:83**
1	6 equiv ArI, 0.2 equiv $Pd(OAc)_2$, 2 equiv AgOAc, 110 °C, neat	30	0:2:1
2	2 equiv ArI, 0.2 equiv $Pd(OAc)_2$, 1 equiv Ag_2CO_3 ***1 equiv PivOH***, 100 °C, *t*-BuOH	42	1:4:0.4
3	2 equiv ArI, 0.15 equiv $Pd(OAc)_2$, 1 equiv Ag_2CO_3 1 equiv PivOH, 100 °C, ***TFE***	48	1:5:1.5
4	2 equiv ArI, 0.15 equiv $Pd(OAc)_2$, 1.5 equiv Ag_2CO_3 1 equiv PivOH, 100 °C, ***HFIP***	65	1:6:trace
5	2 equiv ArI, 0.15 equiv $Pd(OAc)_2$, 1.5 equiv Ag_2CO_3 1 equiv PivOH, 100 °C, HFIP ***(gram scale)***	52	1:5:trace

Table 3. Selective C-1 Epimerization of 82



entry	conditions	conversion (%)	**84:85:86:87**
1	1 equiv NaOMe, MeOH/THF, room temp, 16 h	55	1:1:0:0
2	3 equiv DBU, THF, 80 °C, 24 h	66	5.4:1:0.7:0
3	1 equiv *t*-BuOK, THF, room temp, 3 h	72	2:3:0.1:0.1
4	1 equiv *t*-BuOLi, THF, room temp, 3 h	47	3.3:1:0:0.5
5	1 equiv *t*-BuOLi, PhMe, room temp, 24 h	15	1:0:0:0
6	1 equiv *t*-BuOLi, PhMe (0.3 M), 50 °C, 36 h	95	20:1:1:2

arylation directly on **74**, followed by epimerization of both C-1 and C-3 stereocenters. The divergent intermediate **74** was envisioned arising from a desymmetrizing monoarylation reaction of a cyclobutanedicarboxylate derived from **75**. While the 1,3-cyclobutanedicarboxylate **75** appears to be quite simple, the shortest synthesis reported in the literature was eight steps in 20% overall yield starting from pentaerythritol (**76**).[43] Viewing this route unsuitable for our needs, we envisioned a new synthesis of 1,3-cyclobutanedicarboxylates starting from methyl coumalate (**78**).

Inspired by Corey's seminal work on pyrone photochemistry and more recent studies by Maulide and co-workers, we selected methyl coumalate (**78**) as a potential starting material to solve the 1,3-cyclobutanedicarboxylate problem.[44] Upon irradiation with ultraviolet light, methyl coumalate (**78**) was reported to undergo a successful photochemical 4π electrocyclization reaction to generate photopyrone **77**.[45] This intermediate was attractive, since only two reductions would be needed to arrive at the desired cyclobutane monocarboxylic acid **75**. In practice, it was found that the intermediate photopyrone **77** is quite reactive, rapidly decomposing when treated with acid/base and thermally reverting back to the parent coumalate along with nonspecific decomposition. Consistent with earlier reports by Corey, hydrogenation of photopyrone **77** with palladium on carbon resulted in varying mixtures of β-lactone **79** and the desired acid **75** (Scheme 8).[44a] Resubjection of β-lactone **79** to the reaction conditions did not result in further reduction, implying that the C−O bond must be reduced first to produce **75**. Gratifyingly, switching the heterogeneous catalyst to platinum on carbon consistently gave the monoacid **75** as the sole product and diastereomer observed by ^{1}H NMR. Furthermore, both the 4π electrocyclization and the hydrogenation reactions could be performed with DCM as the solvent, allowing the sequence to be further

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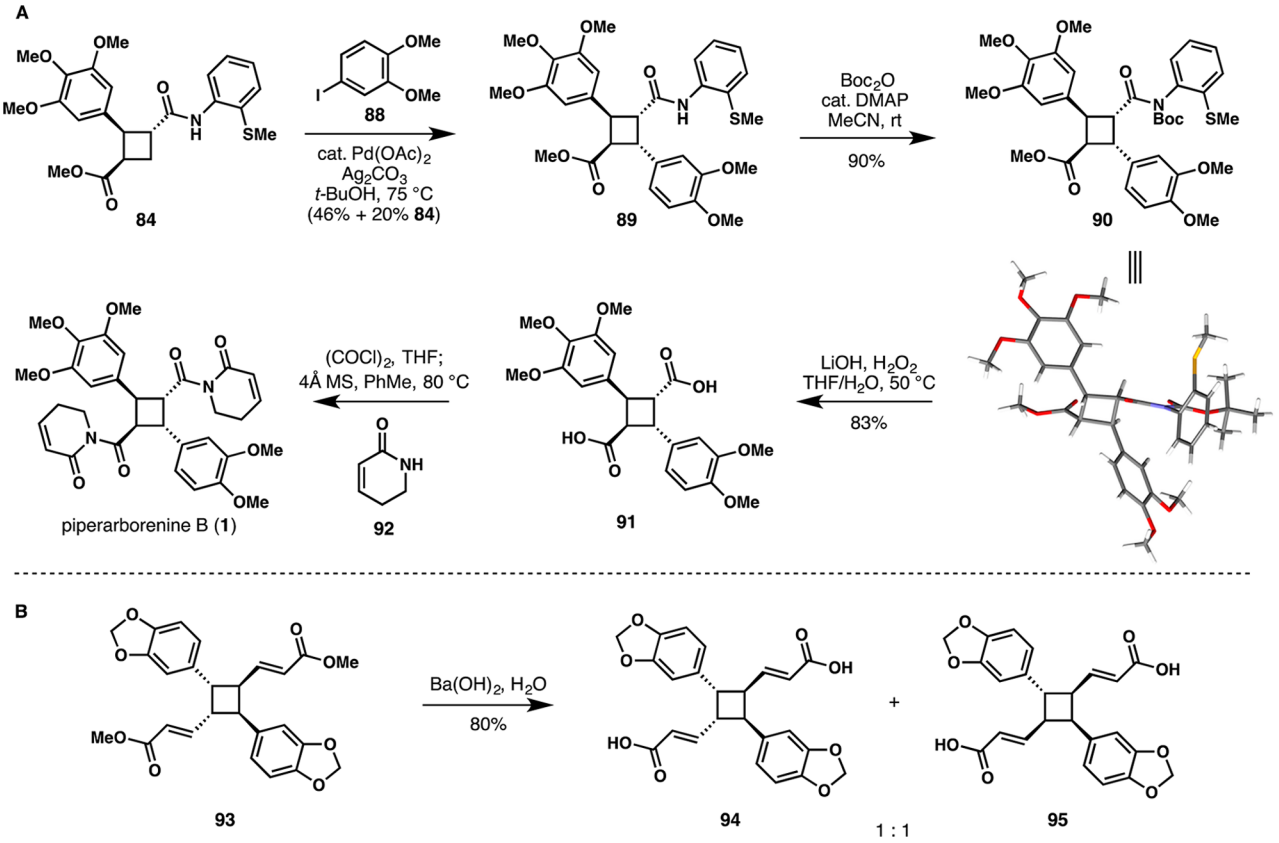
Scheme 9. Completion of Piperarborenine B (1)



telescoped to an EDC coupling with *o*-thioanisidine (**53b**), giving **80** in 61% yield in a single operation from methyl coumalate (**78**).

With the cyclobutanedicarboxylate problem resolved, studies commenced toward the development of a desymmetrizing C−H monoarylation reaction of cyclobutane **80** with 3,4,5-trimethoxyiodobenzene (**81**). Preliminary results were promising, with the conditions originally reported by Daugulis and coworkers (6 equiv of ArI, no solvent, 110 °C) giving the desired monoarylated cyclobutane **82** in 30% isolated yield (Table 2, entry 1). Since the carboxylate ligands on the palladium are proposed to be directly involved in the C−H cleavage event, it was reasoned that a bulkier carboxylate could hinder the second cyclometalation event and the production of doubly arylated **83**. Indeed, pivalic acid in combination with *tert*-butyl alcohol as a solvent proved to be effective (entry 2), though the overall conversion of the reaction was also lowered.[46] Further screening of solvents revealed that trifluoroethanol (TFE) improved the reaction, permitting the temperature and catalyst loading to be lowered slightly, but more of the overarylation byproduct **83** was produced (entry 3). Switching the solvent to hexafluoro-2-propanol (HFIP) maintained the accelerating effects of TFE but almost fully suppressed the second arylation, possibly due to the increased steric bulk. With these optimized conditions, monoarylated cyclobutane **82** was obtained in 65% isolated yield, though the conversion dropped slightly when the reaction was scaled up, leading to a 52% yield on a gram scale. Additionally, the beneficial effects of fluorinated alcoholic solvents on C−H activation reactions has been reported in other palladium-catalyzed systems since the disclosure of this work.[47]

In order to access piperarborenine B (**1**), a selective inversion of the directing group stereocenter at C-1 was needed, followed by a second C−H arylation reaction. While the epimerization of the amide is energetically favorable to create a *trans* relationship to the aryl ring, the issue is complicated by the presence of the also epimerizable ester moiety at C-3. Since inversion of both of the stereocenters is the most thermodynamically favorable result, initial experiments were stopped at incomplete conversion of the starting material to observe the selectivity of the initial epimerization. Upon screening various bases, C-3 epimer **85** and double epimer **86** were observed, along with an unexpected transannular cyclization to form imide **87** (Table 3). Sodium methoxide in MeOH/THF showed very little selectivity, resulting in roughly equal quantities of **84** and **85** (entry 1). The hindered amine base DBU showed some selectivity for C-1 epimerization (3/1), though more forceful reaction conditions were required. Interestingly, a counterion effect was observed with hindered alkoxide bases (entries 3 and 4). Potassium *tert*-butoxide slightly favored ester epimer **85**, while lithium *tert*-butoxide favored C-1 epimer **84**. Extending the reaction time of entry 3 to 24 h resulted in nearly full conversion to **86**, as anticipated. Encouraged by the lithium *tert*-butoxide result, the solvent was changed to toluene (entry 5). This slowed the reaction rate (15% conversion in 24 h) but only the desired **84** was detectable in the crude ^{1}H NMR, in addition to starting material. Further optimization of temperature, concentration, and reaction time resulted in entry 6, which minimized undesired side reactions while maintaining high conversion of starting material to give **84** in 79% yield. The origins of selectivity in this system are uncertain and are currently under investigation.

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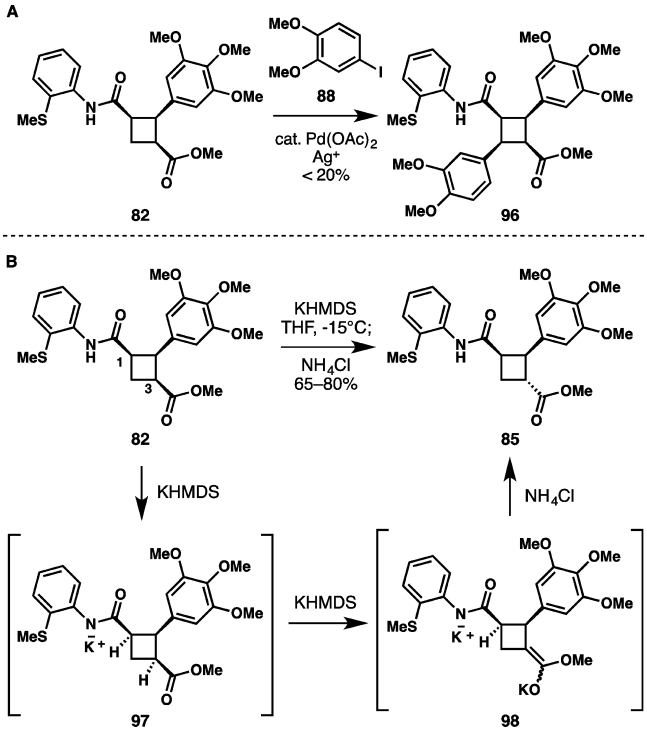
Completion of the piperarborenine B (**1**) synthesis is shown in Scheme 9A. A second, directed C−H arylation reaction with 3,4-dimethoxyiodobenzene (**88**) provided **89** in 46% yield. The reaction conditions developed for C−H monoarylation of **80** proved ineffective for this reaction, but performing the reaction in *tert*-butyl alcohol at high reaction concentrations (1 M) gave acceptable results. Attempts to further conversion of the reaction by raising the temperature to 110 °C resulted in the production of tris- and tetraarylated cyclobutanes (tentatively assigned by ^{1}H NMR and LC-MS) in small quantities, along with significant decomposition. With the second C−H arylation secured, all that remained to complete piperarborenine B (**1**) was the conversion of the directing group and ester moieties to dihydropyridone imides. This could also prove problematic, since methods for direct amide bond cleavage are generally very harsh, requiring strong acid or base and heat. This is further complicated by the stereochemical lability of the ester and amide functionalities. While 1,2-*trans* relationships in cyclobutanes are energetically favored over *cis* relationships, the 1,3-*cis* and *trans* orientations are nearly thermoneutral (0.1 kcal/mol difference for dimethyl 1,3-cyclobutanedicarboxylate).[43a] Kibayashi and co-workers observed this problem during the synthesis of the natural product dipiperamide A, wherein hydrolysis of **93** with barium hydroxide resulted in equal amounts of the two inseparable epimers **94** and **95** (Scheme 9B).[9a] Fortunately, the two-step deprotection strategy developed by Grieco and Evans allowed for retention of the carefully constructed stereotetrad.[40,48] In this reaction, DMAP-catalyzed carbamoylation with Boc anhydride generated **90** in 90% yield, with X-ray crystallographic analysis confirming the presumed stereochemistry. Warming **90** in the presence of lithium hydroperoxide resulted in the hydrolysis of both the amide directing group and the methyl ester in 83% yield. Bis-acid **91** was converted to the corresponding bis-acid chloride and heated with dihydropyridone **92** to give piperarborenine B (**1**) in 77% isolated yield, which matched the spectral and experimental data reported in the isolation paper. The use of 4 Å molecular sieves as an acid scavenger was uniquely effective for this reaction, with traditional bases resulting in low yields and significant formation of byproducts (possibly resulting from epimerization and ketene generation).[49]

Initial attempts to synthesize piperarborenine D (**2**) focused on the resubjection of **82** to the C−H arylation reaction conditions (Scheme 10A). Unfortunately, this consistently resulted in low yields (<20%) and significant decomposition. The presence of the methyl ester substituent on the same face as the directing group and aryl ring, which was critical for monoarylation, presumably hindered the second reaction. Taking this into consideration, we hypothesized that epimerization of the ester stereocenter (C-3) would alleviate this issue. Previous epimerization studies (vide supra) suggested that thermodynamically controlled conditions would not deliver epimer **85** selectively; therefore, an alternative approach was devised. Treating **82** with 2.2 equiv of KHMDS and quenching the resulting dianion with ammonium chloride, delivered C-3 epimer **85** in 65−80% yield as the only observable product. The rationalization of this selectivity is shown in Scheme 10B. Initial amide N−H deprotonation allows for exclusive formation of ester enolate **98** as a result of charge separation. When this dianion was quenched with ammonium chloride, the C-3 epimer was produced as a single diastereomer. The somewhat low and ranging yield of this transformation results from the rapid

Scheme 10. Controlled C-3 Epimerization of 82



decomposition of intermediate dianion **98**, along with a sluggish second deprotonation at reduced temperatures. In agreement with the proposed blocking role of the methyl ester, C-3 epimer **85** readily underwent the desired C−H arylation reaction. Notably, the combination of HFIP and pivalic acid again proved superior to all other reaction conditions examined and delivered the bis-arylated **99** in 81% yield (Scheme 11). Refluxing **99** in an ethanolic solution of sodium hydroxide effected epimerization at C-1, hydrolysis of the amide directing group, and hydrolysis of the methyl ester to produce the bis-acid in 86% yield. Conversion to the bis-acid chloride and heating according to the piperarborenine B protocol gave piperarborenine D (**2**), which did *not* match the spectroscopic data from the original isolation report.[3b] Examination of the isolation data revealed a number of inconsistencies—particularly the number of unique peaks in the ^{13}C NMR for a compound containing a σ_v plane of symmetry. Further analysis led to the consideration of a head-to-head type dimer (**100**) for piperarborenine D that was more consistent with the data provided, and this structure was confirmed through synthesis using an intramolecular photocycloaddition strategy.[50]

Synthesis of the Proposed Structure of Pipercyclobutanamide A. After the successful synthesis of the piperarborenine natural products, we were interested in extending our general C−H functionalization strategy to more complex members of the family, and pipercyclobutanamide A (**8**) was selected to further explore the cyclobutane C−H olefination chemistry.[4c] Additionally, if this C−H functionalization strategy could be coupled to a vinylcyclobutane rearrangement, access to unsymmetrical [4 + 2] adducts in the natural product family could also be possible.[27] The general synthetic strategy is analogous to the approach used for the piperarborenines, involving controlled, sequential C−H functionalizations and epimerizations.

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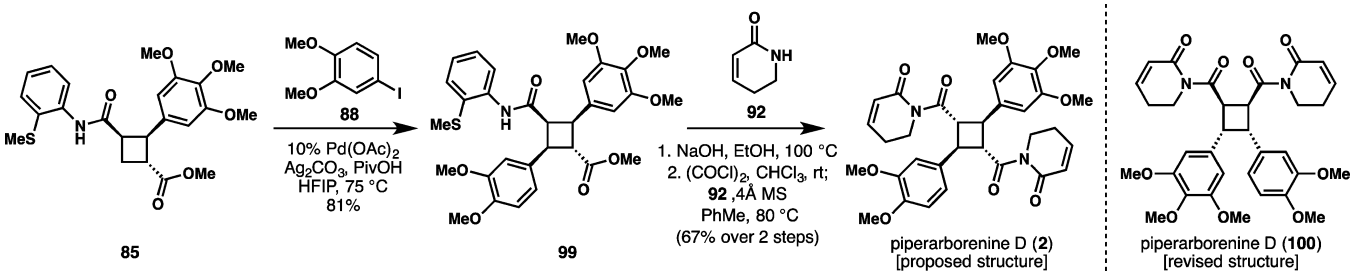
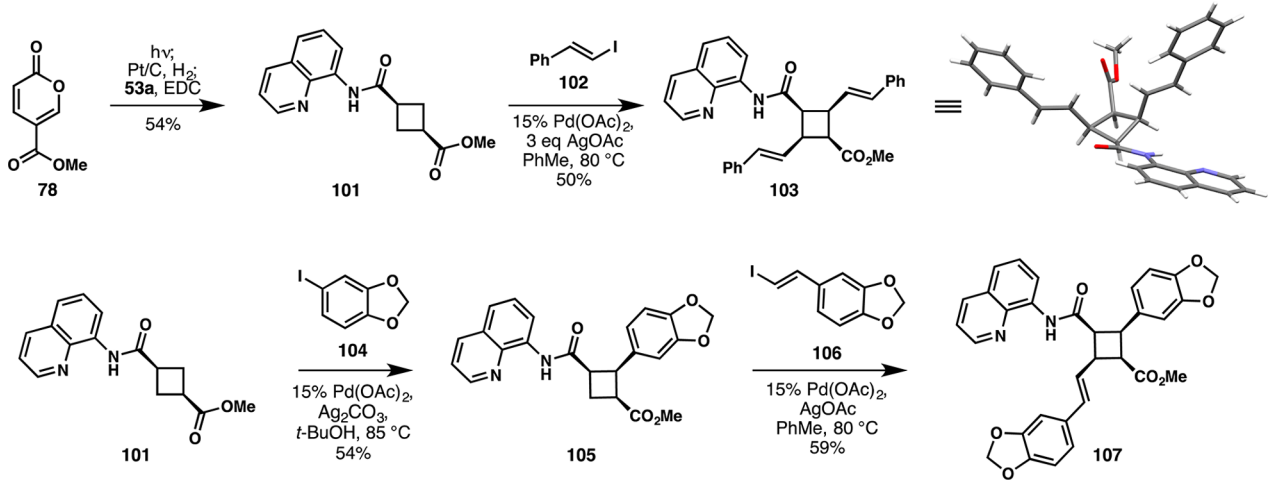
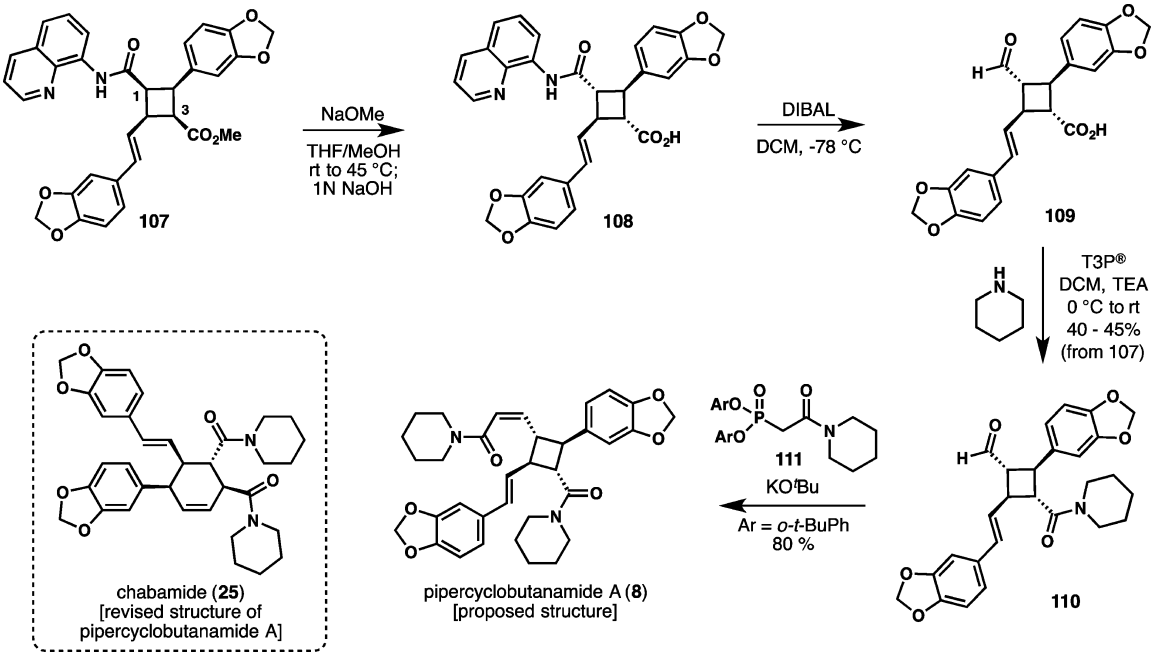
Scheme 11. Structural Revision of Piperarborenine D (100)



Scheme 12. Sequential Cyclobutane C−H Arylation and Olefination



Scheme 13. Synthesis of the Proposed Structure of Pipercyclobutanamide A (8)



The appropriate C−H functionalization precursor (**101**) was prepared using the methodology developed in the piperarborenine syntheses.[50] Methyl coumalate (**78**) was reacted in a telescoped sequence involving photochemical electrocyclization, hydrogenation, and EDC coupling to 8-aminoquinoline (**53a**)[5] to give **101** in 54% yield (Scheme 12). A monoolefination reaction was initially examined with iodostyrene **102** as the coupling partner, but the reaction surprisingly gave the tetrasubstituted all-*cis* cyclobutane **103** in 50% yield. X-ray crystallographic analysis confirmed that no epimerizations took place during the course of the reaction and the highly strained cyclobutane was successfully obtained. This is in direct contrast to the arylation chemistry, in which only small quantities of **96** could be produced. Taking this result into consideration, we

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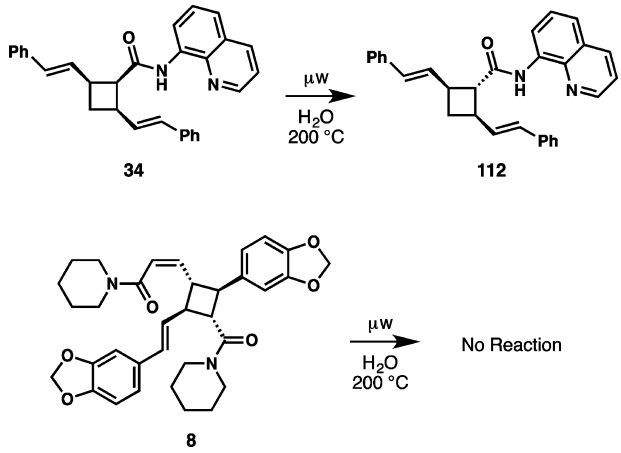
reversed the order of synthetic operations with a C−H monoarylation reaction performed first, followed by the olefination. While the HFIP solvent that was critical in the monoarylation of **80** was ineffective due to the intolerance of methylenedioxy aryl iodide **104**, the pivalic acid additive still proved beneficial and delivered **105** in 54% yield. Recalling the facile formation of all-*cis*-cyclobutane **103**, we directly olefinated monoarylated **105** with iodostyrene **106** to give the tetrasubstituted cyclobutane **107** in 59% yield, without needing to epimerize the C-3 ester stereocenter.

From cyclobutane **107**, two epimerization events were needed to obtain the relative stereochemistry found in pipercyclobutanamide A (**8**). This transformation was expected to occur easily, due to the thermodynamically favorable release of strain leading to the all-*trans* isomer, as well as previous experience during the synthesis of the proposed structure of piperarborenine D (**2**) (vide supra). Addition of sodium methoxide to a THF solution of **107** at room temperature rapidly epimerized the C-1 stereocenter, and warming the reaction mixture to 45 °C inverted the C-3 methyl ester stereocenter (Scheme 13). An aqueous solution of sodium hydroxide was added at the end of the reaction to give acid **108**. Treatment of the crude carboxylic acid with excess DIBAL transformed the aminoquinoline directing group into an aldehyde, providing the proper oxidation state required for pipercyclobutanamide A (**8**). The free carboxylic acid was intentionally used in the reaction to preserve this oxidation state, with the initially generated aluminum carboxylate protecting the functional group from further reduction. Reductions of secondary amides to aldehydes with DIBAL have scarcely been reported, and the success of this case is due to the chelating aminoquinoline amide and the pendant carboxylate.[51] This is supported by the complete failure of the reaction when more coordinating solvents, such as THF, were employed. The structure of pipercyclobutanamide A (**8**) was completed by peptide coupling of aldehyde **109** with piperidine (40−45% overall yield from **107**) and olefination following Ando's protocol for *cis*-selective unsaturated amide synthesis in 80% isolated yield.[52] Unfortunately, the ^{1}H and ^{13}C NMR data of **8** did not match the data reported for the natural product.[4c,53] Contemporaneous with our work, the Tang group also synthesized the proposed structure of pipercyclobutanamide A (**8**) and discovered that the data reported by the isolation chemists were identical with those of the [4 + 2] adduct chabamide (**25**), thereby revising its structure (Scheme 13).[19c]

While the proposed structure of pipercyclobutanamide A (**8**) proved to be incorrect, we were still interested in the possibility of vinylcyclobutane rearrangements to test the biogenetic hypothesis and give stereocontrolled access to the unsymmetrical cyclohexene derived natural products. To test this possibility, the symmetrical bis-olefinated cyclobutane **34** was suspended in water and heated to 200 °C for 5 min in a microwave reactor, the conditions developed for the conversion of sceptrin (**19**) to ageliferin (**20**) (Scheme 14). While the starting material cleanly transformed into a new compound, it was identified as epimer **112**. This result was further confirmed by treatment of **34** with potassium *tert*-butoxide to give the same compound. Curious if the electron-rich styrenes present in the piperine family would be more amenable to vinylcyclobutane rearrangement, we also subjected the proposed structure of pipercyclobutanamide A (**8**) to the microwave conditions. In this case, only starting material was recovered

Scheme 14. Attempted Vinylcyclobutane Rearrangements



and even the *cis*-olefin stereochemistry remained intact. Both of these compounds also failed to give any of the desired cyclohexene isomers when reacted with the radical cation salt tris(*p*-bromophenyl)aminium hexachloroantimonate.[54]

CONCLUSION

In conclusion, the use of C−H functionalization logic to tackle unaddressed problems in organic chemistry has provided an expedient and broadly applicable solution to the construction of stereochemically complex cyclobutanes.[55] In addition to the successful synthesis and structural revision of the piperarborenine natural products (**1**, **2**, **8**), a number of general discoveries were also made en route. During the investigations toward the dictazoles (**5**, **6**), a scalable, diastereocontrolled synthesis of 1,1-cyclobutanedicarboxylates was devised, the surprising reactivity of 8-isocyanoquinoines was unveiled, and a new, easily removable picolinimide directing group for the C−H functionalization chemistry was invented. The piperarborenines (**1**, **2**, **8**) led to the development of a new, one-step route to *cis*-1,3-cyclobutanedicarboxylates, divergent access to multiple cyclobutane stereoisomers through controlled epimerization reactions, and a reductive conversion of the 8-aminoquinoline amide directing group to an aldehyde under mild conditions. With this case study as additional support for the utility of C−H disconnections in synthesis, innumerable possibilities exist for creative scientists to imagine how the historically inert C−H bonds can be used as latent functional groups in synthesis planning, inevitably leading to the generation of new, useful methodologies and discoveries.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out under an argon atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Dry diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), acetonitrile (CH_3CN), toluene (PhMe), *N*,*N*-dimethylformamide (DMF), tetrahydrofuran (THF), methanol (MeOH), and triethylamine (Et_3N) were obtained by passing these previously degassed solvents through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent, as well as one of the following mixtures as a developing agent followed by heating of the TLC plate: anisaldehyde, phosphomolybdic acid, ceric ammonium molybdate, or

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potassium permanganate. E. Merck silica gel (60, particle size 0.043−0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25 or 0.5 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on 600, 500, and 400 MHz instruments and calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$ at 7.26 ppm for ^1H NMR and 77.16 ppm for ^{13}C NMR). The following abbreviations (or combinations thereof) are used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. High-resolution mass spectra (HRMS) were recorded on an LC/MSD TOF time-of-flight mass spectrometer by electrospray ionization time-of-flight reflectron experiments. IR spectra were recorded on a FTIR spectrometer. Melting points were recorded on a melting point apparatus and are uncorrected.

***N*-(Quinolin-8-yl)cyclobutanecarboxamide (28).** Cyclobutanecarbonyl chloride (2.47 g, 20.8 mmol, 1 equiv) in DCM (50 mL) was added dropwise to a vigorously stirred biphasic solution of 8-aminoquinoline (3.00 g, 20.8 mmol) in DCM/saturated aqueous sodium bicarbonate (50 mL/100 mL) at room temperature. The reaction mixture was stirred for 3 h, and the layers were separated, extracted with DCM (2 × 50 mL), washed with brine, and dried over sodium sulfate. After filtration and concentration, the product was filtered through a silica plug (3% Et_2O in DCM) to give **28** (4.58 g, 97%) as a colorless oil that slowly crystallizes upon standing: white crystalline solid (53−54 °C): R_f = 0.45 (silica gel, 3/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{14}H_{14}N_2O$ ($[M + H]^+$) 227.1184, found 227.1188; IR (film) ν_{max} 3351, 2942, 1680, 1521, 1484, 1323, 790 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.73 (br s, 1 H), 8.80 (dd, *J* = 7.6, 1.4 Hz, 1 H), 8.75 (dd, *J* = 4.2, 1.7 Hz, 1 H), 8.09 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.49 (t, *J* = 7.9 Hz, 1 H), 7.43 (dd, *J* = 8.3, 1.4 Hz, 1 H), 7.38 (dd, *J* = 8.2, 4.2 Hz, 1 H), 3.37 (p, *J* = 8.5 Hz, 1 H), 2.54−2.41 (m, 2 H), 2.35−2.19 (m, 2 H), 2.09−1.99 (m, 1 H), 1.99−1.89 (m, 1 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 173.7, 148.1, 138.4, 136.3, 134.6, 127.9, 127.4, 121.5, 121.3, 116.3, 41.4, 25.5, 18.2.

2,4-Diphenyl-*N*-(quinolin-8-yl)cyclobutane-1-carboxamide (29). **28** (226 mg, 1.00 mmol), $Pd(OAc)_2$ (2.25 mg, 0.01 mmol, 0.01 equiv), silver acetate (500 mg, 3.0 mmol, 3 equiv), and iodobenzene (334 μL, 3.0 mmol, 3 equiv) were placed in a sealed tube, and toluene (3.3 mL) was added under ambient conditions. The tube was sealed and placed in an 80 °C oil bath for 24 h. The reaction mixture was cooled to room temperature, diluted with DCM (5 mL), filtered through a pad of Celite, and concentrated. The resulting yellow solid was purified by silica gel chromatography (10−20% EtOAc in hexanes) to give **29** (368 mg, 97%) as a white crystalline solid (137−138 °C): R_f = 0.4 (silica gel, 3/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{26}H_{22}N_2O$ ($[M + H]^+$) 379.1810, found 379.1809; IR (film) ν_{max} br 3354, 3025, 1686, 1518, 1483, 1322, 1159, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.55 (s, 1 H), 8.73 (dd, *J* = 4.2, 1.7 Hz, 1 H), 8.33 (dd, *J* = 7.3, 1.7 Hz, 1 H), 8.01 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.39 (d, *J* = 7.3 Hz, 4 H), 7.35 (dd, *J* = 8.2, 4.2 Hz, 1 H), 7.32−7.27 (m, 2 H), 7.25 (t, *J* = 7.8 Hz, 4 H), 7.13−7.09 (m, 2 H), 4.19 (td, *J* = 8.2, 3.2 Hz, 1 H), 4.10 (dt, *J* = 11.7, 8.2 Hz, 2 H), 3.60 (td, *J* = 11.3, 10.1 Hz, 1 H), 2.77 (dtd, *J* = 10.1, 7.9, 3.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 168.9, 147.8, 140.7, 138.2, 136.1, 134.2, 128.1, 127.7, 127.2, 127.0, 126.1, 121.3, 121.0, 116.4, 54.6, 39.1, 29.9.

2,4-Bis(benzo[*d*][1,3]dioxol-5-yl)-*N*-(quinolin-8-yl)cyclobutane-1-carboxamide (31). **28** (50 mg, 0.221 mmol), $Pd(OAc)_2$ (2.5 mg, 0.011 mmol, 0.05 equiv), silver acetate (111 mg, 0.66 mmol, 3 equiv), and 3,4-methylenedioxyiodobenzene (164 mg, 0.66 mmol, 3 equiv) were placed in a sealed tube and toluene (740 μL) was added under ambient conditions. The tube was sealed and placed into an 80 °C oil bath for 5 h. The reaction mixture was cooled to room temperature, diluted with DCM (2 mL), filtered through a pad of Celite, and concentrated. The resulting orange solid was purified by silica gel chromatography (1/1/4 to 1/1/3 DCM/Et_2O/hexanes) to give **31** (96.5 mg, 98%) as a white crystalline solid (182−183 °C): R_f = 0.2 (silica gel, 3/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{28}H_{23}N_2O_5$ ($[M + H]^+$) 467.1607, found 467.1607; IR (film) ν_{max} br 3351, 2889, 1683, 1519, 1483, 1236, 1035, 931 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1 H), 8.72 (dd, *J* = 4.2, 1.7 Hz, 1 H), 8.39 (dd, *J* = 6.7, 2.3 Hz, 1 H), 8.03 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.39−7.28 (m, 3 H), 6.84 (d, *J* = 1.7 Hz, 2 H), 6.78 (ddd, *J* = 8.0, 1.8, 0.8 Hz, 2 H), 6.65 (d, *J* = 8.0 Hz, 2 H), 5.78 (dd, *J* = 9.2, 1.5 Hz, 4 H), 4.04 (td, *J* = 8.0, 3.3 Hz, 1 H), 3.97−3.87 (m, 2 H), 3.37 (q, *J* = 11.2 Hz, 1 H), 2.65 (dtd, *J* = 9.9, 7.8, 3.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 169.0, 147.9, 147.5, 145.9, 138.3, 136.2, 134.5, 134.3, 127.8, 127.3, 121.4, 121.1, 120.1, 116.5, 108.0, 107.8, 100.7, 54.8, 38.9, 30.7.

***N*-(Quinolin-8-yl)-2,4-bis(3,4,5-trimethoxyphenyl)cyclobutane-1-carboxamide (32).** This compound was prepared analogously to **31**, only employing 3,4,5-trimethoxyiodobenzene (195 mg), and purified by silica gel chromatography (2/2/3 to 2/2/1 DCM/Et_2O/hexanes) to give **32** (118.2 mg, 96%) as a pale yellow foam: R_f = 0.2 (silica gel, 1/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{32}H_{34}N_2O_7$ ($[M + H]^+$) 559.2444, found 559.2444; IR (film) ν_{max} br 3349, 2937, 1686, 1587, 1520, 1236, 1123, 1006, 826 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.56 (s, 1 H), 8.67 (dd, *J* = 4.3, 1.7 Hz, 1 H), 8.41 (dd, *J* = 7.4, 1.6 Hz, 1 H), 8.04 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.39−7.28 (m, 3 H), 6.51 (s, 4 H), 4.12 (td, *J* = 8.1, 3.2 Hz, 1 H), 3.96 (dt, *J* = 11.2, 8.0 Hz, 2 H), 3.69 (s, 12 H), 3.64 (s, 6 H), 3.36 (q, *J* = 11.1 Hz, 1 H), 2.75 (dtd, *J* = 9.7, 7.9, 3.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 169.1, 152.9, 147.8, 138.1, 136.5, 136.3, 136.2, 134.1, 127.7, 127.2, 121.4, 121.2, 116.3, 103.8, 60.6, 55.9, 54.3, 39.1, 31.1.

***N*-(Quinolin-8-yl)-2,4-bis(1-tosyl-1*H*-indol-3-yl)cyclobutane-1-carboxamide (33).** This compound was prepared analogously to **31**, only employing *N*-tosyl-3-iodoindole[56] (263 mg), and purified by silica gel chromatography (1/1/3 to 3/3/4 DCM/Et_2O/hexanes) to give **33** (156.1 mg, 92%) as light yellow crystals. Crystals suitable for X-ray diffraction were obtained from EtOAc: pale yellow crystals (185−187 °C); R_f = 0.1 (silica gel, 3/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{44}H_{36}N_4O_5S_2$ ($[M + H]^+$) 765.2205, found 765.2198; IR (film) ν_{max} br 3346, 2940, 1680, 1520, 1362, 1170, 1124, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1 H), 8.70 (dd, *J* = 4.3, 1.7 Hz, 1 H), 8.47 (dd, *J* = 7.1, 2.0 Hz, 1 H), 8.05 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.84−7.77 (m, 2 H), 7.73 (s, 2 H), 7.58−7.54 (m, 2 H), 7.52 (d, *J* = 8.4 Hz, 4 H), 7.44−7.33 (m, 3 H), 7.22−7.11 (m, 4 H), 6.82 (d, *J* = 8.0 Hz, 4 H), 4.28−4.10 (m, 3 H), 3.61−3.48 (m, 1 H), 2.99−2.87 (m, 1 H), 2.13 (s, 6 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 168.7, 148.2, 144.2, 138.1, 136.0, 135.2, 134.9, 134.2, 130.6, 129.6, 127.7, 127.1, 126.6, 125.0, 124.4, 123.0, 121.6, 121.4, 121.1, 119.3, 116.2, 113.6, 53.8, 33.1, 31.9, 21.4.

***N*-(Quinolin-8-yl)-2,4-di((*E*)-styryl)cyclobutane-1-carboxamide (34).** **28** (46 mg, 0.20 mmol), $Pd(OAc)_2$ (4.6 mg, 0.02 mmol, 0.10 equiv), silver acetate (100 mg, 0.60 mmol, 3 equiv), and iodostyrene (138 mg, 0.60 mmol, 3 equiv) were placed in a sealed tube, and toluene (1 mL) was added under ambient conditions. The tube was sealed and placed in an 80 °C oil bath for 12 h. The reaction mixture was cooled to room temperature, diluted with DCM (2 mL), filtered through a pad of Celite, and concentrated. The resulting orange solid was purified by silica gel chromatography (10% EtOAc in hexanes) to give **34** (66.2 mg, 77%) as pale yellow needles (128−129 °C): R_f = 0.45 (silica gel, 3/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{30}H_{26}N_2O$ ($[M + H]^+$) 431.2123, found 431.2125; IR (film) ν_{max} br 3349, 2934, 1677, 1519, 1483, 1322, 968, 748, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1 H), 8.87 (dd, *J* = 7.6, 1.4 Hz, 1 H), 8.61 (dd, *J* = 4.2, 1.7 Hz, 1 H), 8.07 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.52 (t, *J* = 7.9 Hz, 1 H), 7.45 (dd, *J* = 8.3, 1.4 Hz, 1 H), 7.38−7.31 (m, 5 H), 7.27−7.21 (m, 4 H), 7.19−7.12 (m, 2 H), 6.69 (dd, *J* = 15.8, 8.3 Hz, 2 H), 6.52 (d, *J* = 15.9 Hz, 2 H), 3.75 (td, *J* = 8.3, 3.0 Hz, 1 H), 3.48 (dqd, *J* = 10.4, 8.2, 0.9 Hz, 2 H), 2.87 (q, *J* = 10.6 Hz, 1 H), 2.53 (dtd, *J* = 10.9, 8.1, 2.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.3, 148.0, 138.5, 137.5, 136.3, 134.5, 131.2, 130.2, 128.4, 127.9, 127.4, 127.1, 126.4, 121.5, 121.5, 116.7, 53.2, 38.6, 34.0.

Dimethyl 5,5′-(2-(Quinolin-8-ylcarbamoyl)cyclobutane-1,3-diyl)-(2*E*,2′*E*,4*E*,4′*E*)-bis(4-methylpenta-2,4-dienoate) (35). **28** (90 mg, 0.40 mmol), $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 0.10 equiv), silver acetate (199 mg, 1.20 mmol, 3 equiv) and vinyl iodide[57] (301 mg, 1.20 mmol, 3 equiv) were placed in a sealed tube, and toluene (1.32 mL) was added under ambient conditions. The tube was sealed and placed in an 80 °C oil bath for 12 h. The reaction mixture was cooled to room temperature, diluted with DCM (3 mL), filtered

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through a pad of Celite, and concentrated. The resulting orange oil was purified by silica gel chromatography (15−30% EtOAc in hexanes) to give **35** (146.5 mg, 78%) as a pale yellow foam: R_f = 0.55 (silica gel, 1/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{28}H_{30}N_2O_5$ ([M + H]$^+$) 475.2233, found 475.2234; IR (film) ν_{max} br 3347, 2948, 1713, 1621, 1523, 1285, 1169 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1 H), 8.78 (dd, *J* = 7.5, 1.5 Hz, 1 H), 8.69 (dd, *J* = 4.2, 1.7 Hz, 1 H), 8.08 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.50 (dd, *J* = 8.3, 7.5 Hz, 1 H), 7.45 (dd, *J* = 8.3, 1.5 Hz, 1 H), 7.37 (dd, *J* = 8.3, 4.2 Hz, 1 H), 7.23 (dd, *J* = 15.7, 0.7 Hz, 2 H), 6.25 (d, *J* = 8.4 Hz, 2 H), 5.69 (d, *J* = 15.6 Hz, 2 H), 3.78−3.69 (m, 1 H), 3.64 (s, 6 H), 3.68−3.55 (m, 2 H), 2.63 (q, *J* = 10.4 Hz, 1 H), 2.51 (dtd, *J* = 10.8, 8.3, 2.9 Hz, 1 H), 1.77 (d, *J* = 1.2 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 169.6, 167.8, 149.4, 148.1, 141.5, 138.4, 136.5, 134.2, 133.7, 128.0, 127.5, 121.8, 121.7, 116.8, 116.1, 53.1, 51.5, 35.3, 34.4, 12.7.

***N*-(Quinolin-8-yl)-2,4-bis((triisopropylsilyl)ethynyl)cyclobutane-1-carboxamide (36).** **28** (200 mg, 0.884 mmol), $Pd(OAc)_2$ (10.0 mg, 0.045 mmol, 0.05 equiv), silver acetate (443 mg, 2.65 mmol, 3 equiv), lithium chloride (112 mg, 2.64 mmol, 3 equiv), and TIPS-bromoacetylene[32] (693 mg, 2.65 mmol, 3 equiv) were placed in a sealed tube, and toluene (1.76 mL) was added under ambient conditions. The tube was flushed with argon, sealed, and placed in a 100 °C oil bath for 12 h. The reaction mixture was cooled to room temperature, diluted with DCM (3 mL), filtered through a pad of Celite, and concentrated. The resulting orange oil was purified by silica gel chromatography (2.5−7% Et_2O in hexanes) to give **36** (430 mg, 83%) as a light yellow oil that crystallized upon standing: light yellow crystalline solid (61−63 °C); R_f = 0.7 (silica gel, 3/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{36}H_{54}N_2OSi_2$ ([M + H]$^+$) 587.3853, found 587.3857; IR (film) ν_{max} br 3355, 2942, 2864, 2159, 1698, 1524, 882, 675 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1 H), 8.90 (dd, *J* = 7.5, 1.6 Hz, 1 H), 8.77 (dd, *J* = 4.2, 1.7 Hz, 1 H), 8.13 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.53−7.44 (m, 2 H), 7.41 (dd, *J* = 8.2, 4.2 Hz, 1 H), 3.68 (td, *J* = 8.5, 3.5 Hz, 1 H), 3.41 (dt, *J* = 11.1, 8.4 Hz, 2 H), 3.06 (q, *J* = 11.0 Hz, 1 H), 2.70 (dtd, *J* = 10.5, 8.4, 3.0 Hz, 1 H), 0.85−0.75 (m, 42 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 167.5, 148.0, 138.8, 136.2, 135.0, 127.8, 127.5, 121.3, 121.1, 117.1, 106.7, 84.0, 52.8, 36.2, 26.6, 18.5, 11.2.

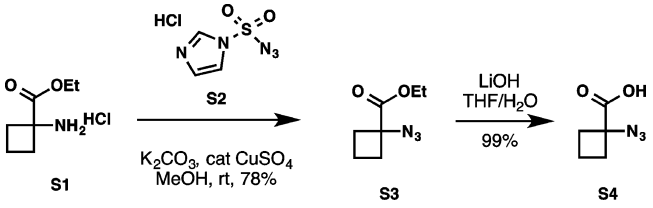
3-(Benzyloxy)cyclobutan-1-one (42). To benzyl vinyl ether (2.50 g. 18.6 mmol, 1 equiv) in dry diethyl ether (300 mL) at room temperature was added Zn−Cu (18.27 g, 279 mmol, 15 equiv), followed by trichloroacetyl chloride (5.30 mL, 46.5 mmol, 2.5 equiv) dropwise over 3 h. A saturated solution of ammonium chloride in methanol (250 mL) was added, and the mixture was refluxed for 30 min. The crude product was filtered through Celite and concentrated. The crude reaction product was partitioned between diethyl ether (200 mL) and water (200 mL), the layers were separated, and the aqueous layer was extracted with diethyl ether (2 × 75 mL). The combined organics were washed with brine (150 mL) and dried over Na_2SO_4. After filtration and concentration, the crude product was purified by column chromatography (10% Et_2O in hexanes) to give **42** (1.65 g, 50%) as a colorless oil with spectroscopic data that matched those previously reported.[58]

8-Isocyanoquinoline (39). Triethylamine (1.0 mL, 7.17 mmol, 2.5 equiv) was added to a solution of 8-formamidoquinoline (500 mg, 2.9 mmol) in DCM (4 mL) at room temperature in a two-neck flask equipped with a reflux condenser. A toluene solution of phosgene (1.9 M, 1.83 mL, 3.48 mmol, 1.2 equiv) was added dropwise, and the exothermic reaction was allowed to reflux gently. After the mixture was cooled to room temperature, ammonia gas was bubbled through the solution to quench any unreacted phosgene and then the mixture was purged with nitrogen. The black reaction mixture was diluted with DCM (4 mL) and filtered through Celite. The black filtrate was concentrated, and Et_2O (4 mL) was added. The soluble portion was filtered through Celite again, washing with Et_2O (3 × 3 mL). The resulting yellow solution was concentrated, giving an oily yellow solid. Trituration of this material with hexanes (3 × 2 mL) left the desired isonitrile **39** (285 mg, 64%) as a light yellow solid (>75 °C, decomp): R_f = 0.5 (silica gel, 1/1 hexanes/EtOAc) [reactive; spot is from the resulting formamide]; HRMS (*m*/*z*) N/A, unstable; IR (film) ν_{max} 3047, 2127, 1682, 1596, 1498, 1389, 826, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (dd, *J* = 4.2, 1.7 Hz, 1 H), 8.20 (dd, *J* = 8.4, 1.7 Hz, 1 H), 7.87 (dd, *J* = 8.3, 1.3 Hz, 1 H), 7.79 (dd, *J* = 7.5, 1.4 Hz, 1 H), 7.57−7.47 (m, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 152.0, 142.8, 136.4, 129.5, 128.8, 127.8, 125.9, 122.7, 77.5, 77.2, 76.8.

4-Methoxy-4*H*-imidazo[4,5,1-*ij*]quinolone (45b). Methanol (0.5 mL) was added to a solution of **39** (40 mg, 0.26 mmol) in DCM (0.5 mL) at room temperature. After 4 h, the mixture was concentrated and purified directly by column chromatography (25−50% EtOAc in hexanes) to give methanol adduct **45b** (25.3 mg, 52%) as a light yellow oil: R_f = 0.2 (silica gel, 1/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{11}H_{10}N_2O$ ([M + H]$^+$) 187.0871, found 187.0875; IR (film) ν_{max} br 3373, 2931, 1477, 1340, 1192, 1062, 803, 740 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.27 (dd, *J* = 15.3, 8.0 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 1H), 7.10 (dd, *J* = 9.8, 1.1 Hz, 1H), 6.66 (dd, *J* = 3.6, 1.1 Hz, 1H), 5.91 (dd, *J* = 9.8, 3.6 Hz, 1H), 3.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 141.6, 140.2, 130.9, 128.1, 123.1, 122.0, 121.0, 120.2, 117.5, 80.4, 50.3.

Ethyl 1-Azidocyclobutane-1-carboxylate (S3). Potassium carbonate (960 mg, 6.96 mmol, 2.5 equiv), copper sulfate (7 mg, 0.028 mmol, 0.01 equiv), and the diazo transfer agent **S2** (700 mg, 3.34 mmol, 1.2 equiv) were successively added to a solution of commercially available ethyl 1-amino-1-cyclobutanecarboxylate monohydrochloride (**S1**; 500 mg, 2.78 mmol) in methanol (14 mL) at room temperature. After 24 h, the mixture was concentrated, dissolved in EtOAc (20 mL), washed with 1 N aqueous HCl (10 mL) and brine, and dried over sodium sulfate. After concentration, the crude product was purified by column chromatography (25% Et_2O in hexanes) to give **S3** (324 mg, 78%) as a colorless oil with spectral data which matched those reported[59] (contained 20% of inconsequential methyl ester from concomitant transesterification during the reaction).

Scheme 15. Synthesis of Azido Acid S4



1-Azidocyclobutane-1-carboxylic Acid (S4; Scheme 15). Lithium hydroxide hydrate (131 mg, 3.12 mmol, 2 equiv) was added to a solution of azido ester **S3** (265 mg, 1.57 mmol) in THF/H_2O (10 mL, 3/1 v/v). The reaction mixture was stirred vigorously for 24 h and quenched with 3 N aqueous HCl (2 mL). The mixture was separated and extracted with EtOAc (3 × 5 mL), and the extract was washed with brine (10 mL) and dried over sodium sulfate. After concentration, azido acid **S4** (230 mg, 99%) was isolated as a colorless oil: R_f = 0.15 (silica gel, 3/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_5H_7N_3O_2$ ([M − H]$^-$) 140.0465, found 140.0464; IR (film) ν_{max} br 3001, 2100, 1706, 1416, 1248 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73−2.61 (m, 1H), 2.41−2.26 (m, 1H), 2.16−1.96 (m, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 178.6, 64.8, 31.2, 14.7.

1-Azido-*N*-(quinolin-8-yl)cyclobutane-1-carboxamide (46a; Scheme 16). 8-Aminoquinoline (260 mg, 1.8 mmol, 1.2 equiv) was added to a solution of **S4** (211 mg, 1.5 mmol) in DCM (15 mL) cooled to 0 °C, followed by T3P (50 wt % in EtOAc, 1.34 mL, 2.25 mmol, 1.5 equiv) and triethylamine (0.42 mL, 3 mmol, 2 equiv). The reaction mixture was warmed to room temperature and stirred for 24 h. Saturated sodium bicarbonate solution (10 mL) was added, and the biphasic reaction mixture was separated and extracted with DCM (2 × 10 mL), and the extract was washed with brine (10 mL) and dried over sodium sulfate. After filtration and concentration, the crude product was purified by silica gel chromatography (0−5% EtOAc in hexanes) to give **46a** (370 mg, 92%) as a colorless oil: R_f = 0.6 (silica gel, 3/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{14}H_{13}N_5O$ ([M +

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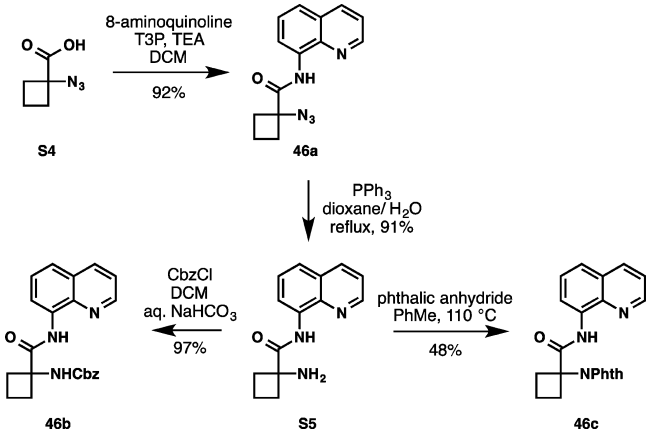
Scheme 16. Synthesis of Nitrogen-Containing Substrates for C−H Functionalization



H]$^+$) 268.1198, found 268.1201; IR (film) ν_{max} br 3328, 2107, 1681, 1523, 1485, 1257, 790 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.65 (br s, 1 H), 8.84 (dd, J = 4.2, 1.7 Hz, 1 H), 8.79 (dd, J = 6.7, 2.3 Hz, 1 H), 8.12 (dd, J = 8.3, 1.7 Hz, 1 H), 7.55−7.47 (m, 2 H), 7.42 (dd, J = 8.3, 4.2 Hz, 1 H), 2.91−2.77 (m, 2 H), 2.54−2.42 (m, 2 H), 2.32−2.17 (m, 1 H), 2.14−2.00 (m, 1 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 169.9, 148.6, 138.9, 136.3, 134.0, 128.0, 127.2, 122.1, 121.7, 116.6, 66.6, 31.5, 14.8.

1-Amino-*N*-(quinolin-8-yl)cyclobutane-1-carboxamide (S5; Scheme 16). Triphenylphosphine (367 mg, 1.4 mmol, 1.2 equiv) was added to a solution of **46a** (312 mg, 1.17 mmol) in dioxane/H_2O (11 mL, 10/1 v/v) at room temperature. A reflux condenser was attached to the flask, and the reaction mixture was placed in an oil bath preheated to 110 °C for 36 h. After it was cooled to room temperature, the reaction mixture was acidified with 1 N aqueous HCl (5 mL) and extracted with EtOAc (3 × 15 mL). The aqueous layer was basified with 3 N aqueous NaOH (5 mL), saturated with NaCl, extracted with EtOAc (3 × 25 mL), and dried over sodium sulfate. After filtration and concentration, the crude yellow oil was purified by silica gel chromatography (50−100% EtOAc in hexanes) to give **S5** (257 mg, 91%) as a colorless oil: R_f = 0.4 (silica gel, 1/1 hexanes/EtOAc); HRMS (m/z) calcd for $C_{14}H_{15}N_3O$ ([M + H]$^+$) 242.1293, found 242.1294; IR (film) ν_{max} br 3291, 2935, 1671, 1513, 1482, 1324, 790 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (dd, J = 7.6, 1.5 Hz, 1 H), 8.80 (dd, J = 4.2, 1.7 Hz, 1 H), 8.06 (dd, J = 8.3, 1.7 Hz, 1 H), 7.48 (t, J = 7.9 Hz, 1 H), 7.42 (dd, J = 8.2, 1.4 Hz, 1 H), 7.36 (dd, J = 8.3, 4.2 Hz, 1 H), 2.99−2.70 (m, 2 H), 2.20−1.84 (m, 6 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 175.0, 148.5, 139.1, 136.2, 134.7, 128.0, 127.3, 121.5, 121.4, 116.1, 60.0, 35.3, 14.3.

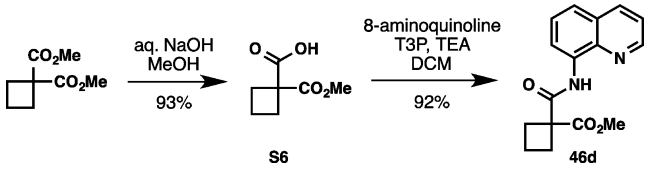
benzyl (1-(Quinolin-8-ylcarbamoyl)cyclobutyl)carbamate (46b; Scheme 16). CbzCl (88 μL, 0.62 mmol, 1.2 equiv) was added dropwise to a vigorously stirred biphasic solution of **S5** (124 mg, 0.52 mmol) in DCM/saturated aqueous sodium bicarbonate (7.5 mL, 2/1 v/v) at room temperature. The reaction mixture was stirred for 2.5 h, the phases were separated and extracted with DCM (2 × 5 mL), and the extract was washed with brine and dried over sodium sulfate. After filtration and concentration, the crude yellow foam was filtered through a plug of silica gel (50% EtOAc in hexanes) to give **46b** (188 mg, 97%) as a white foam: R_f = 0.15 (silica gel, 3/1 hexanes/EtOAc); HRMS (m/z) calcd for $C_{22}H_{21}N_3O$ ([M + H]$^+$) 376.1661, found 376.1663; IR (film) ν_{max} br 3326, 2951, 1688, 1525, 1486, 1256 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$; major rotamer) δ 10.68 (br s, 1 H), 8.83 (br d, J = 7.7 Hz, 1 H), 8.66 (s, 1 H), 8.08 (d, J = 8.0 Hz, 1 H), 7.50 (t, J = 7.9 Hz, 1 H), 7.45 (dd, J = 8.3, 1.5 Hz, 1 H), 7.39−7.29 (m, 3 H), 7.29−7.21 (m, 2 H), 7.13−6.79 (br m, 1 H), 6.15 (br s, 1 H), 5.14 (s, 2 H), 2.89 (app s, 2 H), 2.24−1.91 (m, 4 H); ^{13}C NMR ($CDCl_3$, 126 MHz; major rotamer) δ 172.0, 155.1, 148.2, 138.8, 136.1, 134.4, 128.5, 128.0, 127.9, 127.4, 127.3, 126.9, 121.6, 121.5, 116.4, 66.8, 60.4, 31.6, 15.4.

1-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)cyclobutane-1-carboxamide (46c; Scheme 16). Triethylamine (212 μL, 1.5 mmol, 3 equiv) was added to a solution of **S5** (122 mg, 0.51 mmol) in toluene (2.5 mL) at room temperature, followed by phthalic anhydride (150 mg, 1 mmol, 2 equiv). The reaction mixture was placed in an oil bath preheated to 110 °C for 20 h. After the mixture was cooled to room temperature, saturated sodium bicarbonate solution (1 mL) was added, the reaction mixture was extracted with EtOAc (3 × 3 mL), and the extract was washed with brine and dried over sodium sulfate. After filtration and concentration, the crude product was purified using column chromatography (50% EtOAc in hexanes) to give **46c** (90 mg, 48%) as colorless crystals (188−190 °C). (Note: the low yield likely due to crystallization of the product during chromatographic purification.): R_f = 0.15 (silica gel, 3/1 hexanes/EtOAc); HRMS (m/z) calcd for $C_{22}H_{17}N_3O_3$ ([M + H]$^+$) 372.1348, found 372.1350; IR (film) ν_{max} 3342, 1774, 1715, 1687, 1530, 1374, 719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.66 (br s, 1 H), 8.72 (dd, J = 6.7, 2.3 Hz, 1 H), 8.66 (dd, J = 4.3, 1.7 Hz, 1 H), 8.08 (dd, J = 8.3, 1.7 Hz, 1 H), 7.83 (dd, J = 5.5, 3.1 Hz, 2 H), 7.69 (dd, J = 5.5, 3.1 Hz, 2 H), 7.52−7.41 (m, 2 H), 7.36 (dd, J = 8.3, 4.2 Hz, 1 H), 3.19 (ddt, J = 13.5, 8.0, 2.5 Hz, 2 H), 3.07−2.94 (m, 2 H), 2.52−2.35 (m, 1 H), 2.22−2.09 (m, 1 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 169.7, 168.1, 148.4, 138.7, 136.2, 134.3, 134.1, 132.2, 127.8, 127.2, 123.3, 121.9, 121.6, 116.6, 62.0, 32.0, 18.0.

1-(Methoxycarbonyl)cyclobutane-1-carboxylic Acid (S6). Dimethyl cyclobutanedicarboxylate (3.50 g, 20.33 mmol) was dissolved in MeOH (150 mL) and cooled to 0 °C. An aqueous solution of NaOH (813 mg in 150 mL H_2O) was then added dropwise over 30 min. The reaction mixture was slowly warmed to room temperature and stirred for 12 h. The MeOH was removed in vacuo, and the resulting aqueous solution was washed with Et_2O (100 mL). The resulting aqueous phase was acidified with 3 N aqueous HCl (10 mL) and extracted with EtOAc (100 mL, 2 × 50 mL). The combined organics were washed with brine (100 mL), dried over sodium sulfate, and concentrated to give **S6** (3.00 g, 93%) as a colorless oil: R_f = 0.1 (silica gel, 3/1 hexanes/EtOAc); HRMS (m/z) calcd for $C_7H_{10}NaO_4$ ([M + H]$^+$) 181.0477, found 181.0478; IR (film) ν_{max} br 3504, 2956, 1705, 1281, 1202, 1138, 688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 1H), 2.59 (t, J = 8.1 Hz, 1H), 2.08−1.95 (m, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 177.9, 172.2, 100.1, 52.9, 52.6, 29.0, 16.3.

Methyl 1-(Quinolin-8-ylcarbamoyl)cyclobutane-1-carboxylate (46d; Scheme 17). 8-Aminoquinoline (260 mg, 1.8 mmol, 1.2

Scheme 17. Synthesis of Methyl Ester 46d



equiv) was added to a solution of **S6** (237 mg, 1.5 mmol) in DCM (15 mL) cooled to 0 °C, followed by T3P (50 wt % in EtOAc, 1.34 mL, 2.25 mmol, 1.5 equiv) and triethylamine (0.42 mL, 3 mmol). The reaction mixture was warmed to room temperature and stirred for 24 h. Saturated sodium bicarbonate solution (10 mL) was added, and the biphasic reaction mixture was separated, extracted with DCM (2 × 10 mL), washed with brine (10 mL), and dried over sodium sulfate. After filtration and concentration, the crude product was purified by silica gel chromatography (1/1/8 to 1/1/6 DCM/Et_2O/hexanes) to give **46d** (409 mg, 90%) as a pale yellow oil: R_f = 0.35 (silica gel, 3/1 hexanes/EtOAc); HRMS (m/z) calcd for $C_{16}H_{16}N_2O_3$ ([M + H]$^+$) 285.1239, found 285.1244; IR (film) ν_{max} br 3319, 2952, 1735, 1680, 1525, 1484, 1326, 825, 790 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.42 (br s, 1 H), 8.82 (dd, J = 4.2, 1.7 Hz, 1 H), 8.77 (dd, J = 7.2, 1.8 Hz, 1 H), 8.13 (dd, J = 8.3, 1.7 Hz, 1 H), 7.58−7.47 (m, 2 H), 7.43 (dd, J = 8.3, 4.2 Hz, 1 H), 3.83 (s, 3 H), 2.88−2.78 (m, 2 H), 2.77−2.68 (m, 2 H), 2.05 (p, J = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 101

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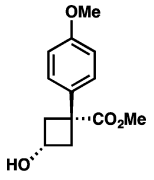
MHz) δ 173.7, 168.9, 148.5, 138.8, 136.3, 134.6, 128.0, 127.4, 121.8, 121.7, 116.6, 54.9, 53.0, 29.6, 16.3.

1-(1,3-Dioxoisoindolin-2-yl)-*N*-(quinolin-8-yl)-2,4-bis(1-tosyl-1*H*-indol-3-yl)cyclobutane-1-carboxamide (48c). **46c** (37.1 mg, 0.10 mmol), $Pd(OAc)_2$ (3.4 mg, 1.5 μmol, 0.15 equiv), silver acetate (50 mg, 0.30 mmol, 3 equiv), and *N*-tosyl-3-iodoindole (**47**; 119 mg, 0.30 mmol, 3 equiv) were placed in a sealed tube, and toluene (200 μL, 0.5 M) was added under ambient conditions. The tube was sealed and placed in an oil bath preheated to 130 °C for 24 h. The reaction mixture was cooled to room temperature, diluted with DCM (1 mL), filtered through a pad of Celite, and concentrated. The resulting dark red oil was purified by silica gel chromatography (1/1/6 to 1/1/3 DCM/Et_2O/hexanes) to give **48c** (12.9 mg, 14%) as colorless crystals (>175 °C, decomp): R_f = 0.4 (silica gel, 1/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{52}H_{39}N_5O_7S_2$ ($[M + H]^+$) 910.2369, found 910.2355; IR (film) ν_{max} 3334, 1777, 1720, 1682, 1527, 1364, 1170, 906, 719 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 10.26 (br s, 1 H), 8.73 (dd, *J* = 7.5, 1.4 Hz, 1 H), 8.02 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.96–7.86 (m, 6 H), 7.81 (td, *J* = 5.3, 2.1 Hz, 2 H), 7.67 (dd, *J* = 4.2, 1.7 Hz, 1 H), 7.64–7.58 (m, 2 H), 7.57–7.45 (m, 6 H), 7.28–7.18 (m, 4 H), 7.14 (dd, *J* = 8.3, 4.2 Hz, 1 H), 6.79–6.71 (m, 4 H), 4.91 (ddd, *J* = 10.8, 9.6, 1.1 Hz, 2 H), 3.21 (td, *J* = 11.2, 10.4, 6.7 Hz, 2 H), 2.09 (s, 6 H); ^{13}C NMR ($CDCl_3$, 151 MHz): 168.1, 165.4, 147.9, 144.2, 138.3, 135.9, 135.3, 134.7, 134.5, 133.6, 132.0, 131.2, 129.5, 127.7, 127.5, 126.8, 126.4, 124.3, 123.8, 123.0, 121.9, 121.5, 120.3, 120.2, 116.6, 113.6, 73.4, 39.1, 33.8, 21.5.

Methyl 1-(Quinolin-8-ylcarbamoyl)-2,4-bis(1-tosyl-1*H*-indol-3-yl)cyclobutane-1-carboxylate (48d). **46d** (30 mg, 0.106 mmol), $Pd(OAc)_2$ (3.6 mg, 1.6 μmol, 0.15 equiv), silver carbonate (44 mg, 0.16 mmol, 1.5 equiv), and *N*-tosyl-3-iodoindole (**47**; 119 mg, 0.30 mmol, 3 equiv) were placed in a sealed tube, and toluene (200 μL, 0.5 M) was added under ambient conditions. The tube was sealed and placed in an oil bath preheated to 90 °C for 24 h. The reaction mixture was cooled to room temperature, diluted with DCM (1 mL), filtered through a pad of Celite, and concentrated. The resulting yellow oil was purified by silica gel chromatography (30% EtOAc in hexanes) to give **48d** (18.3 mg, 21%) as a white crystalline solid, along with recovered **46d** (18.7 mg, 62%): white crystalline solid (150–155 °C); R_f = 0.5 (silica gel, 1/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{46}H_{38}N_4O_7S_2$ ($[M + H]^+$) 823.2260, found 823.2266; IR (film) ν_{max} 3294, 1730, 1673, 1529, 1359, 1170, 904, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1 H), 8.46 (d, *J* = 6.8 Hz, 1 H), 8.39 (dd, *J* = 4.4, 1.7 Hz, 1 H), 8.03 (d, *J* = 8.5 Hz, 1 H), 7.88–7.70 (m, 6 H), 7.48 (d, *J* = 8.1 Hz, 4 H), 7.47–7.37 (m, 2 H), 7.31–7.14 (m, 5 H), 6.77 (d, *J* = 7.9 Hz, 4 H), 4.47 (dd, *J* = 11.7, 8.1 Hz, 2 H), 4.05 (s, 3 H), 3.45 (q, *J* = 11.3 Hz, 1 H), 2.90 (q, *J* = 9.1 Hz, 1 H), 2.11 (s, 6 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 173.1, 164.6, 148.5, 144.4, 138.4, 135.9, 135.1, 134.9, 134.0, 130.8, 129.6, 127.8, 127.1, 126.7, 126.0, 124.6, 123.2, 121.7, 121.7, 120.3, 119.9, 116.6, 113.4, 67.2, 53.1, 36.6, 30.1, 21.5.

Methyl 3-Hydroxy-1-(4-methoxyphenyl)cyclobutane-1-carboxylate (S7).



4-Methoxyphenylacetic acid (**49**; 2.00 g, 12.0 mmol) was dissolved in dry THF (3 mL) and added dropwise to a solution of isopropylmagnesium chloride in THF (2 M, 13.2 mL, 26.4 mmol, 2.2 equiv) dropwise, keeping the internal temperature below 50 °C. The reaction mixture turned heterogeneous during the addition and was stirred for 30 min at room temperature. Epichlorohydrin (1.7 mL, 21.6 mmol, 1.8 equiv) was added dropwise, keeping the internal temperature below 35 °C, and the mixture was stirred at room temperature for 45 min. During the addition the solution homogenizes. A solution of isopropylmagnesium chloride (2 M in THF, 12 mL, 24 mmol, 2 equiv) was added to the reaction mixture, which was then warmed to 60 °C overnight (14 h). The reaction mixture was carefully quenched with 3 N aqueous HCl (20 mL), keeping the internal temperature below 35 °C. The resulting biphasic solution was separated and extracted with EtOAc (2 × 50 mL). The combined organics were washed with 1 N aqueous NaOH (2 × 25 mL), and the combined aqueous layer was acidified with 3 N aqueous HCl and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, and concentrated to give the crude hydroxy acid **50** (2.16 g) as a white solid that was used directly in the next reaction. To a solution of the crude hydroxy acid in MeOH (20 mL) was added concentrated sulfuric acid (54 μL, 1 mmol), and the mixture was warmed to 60 °C for 12 h. The reaction mixture was cooled to room temperature and neutralized with saturated sodium bicarbonate solution (2 mL), and the MeOH was removed in vacuo. The resulting mixture was diluted with EtOAc (50 mL), washed with brine (25 mL), dried over Na_2SO_4, and concentrated to give the crude methyl ester (2.16 g), which was used directly in the next step. This material could be further purified using silica gel chromatography (30–60% Et_2O in hexanes) for characterization to give the methyl ester **S7** as colorless crystals (mp 64–65 °C): R_f = 0.4 (silica gel, 1/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{13}H_{16}O_4$ ($[M + H]^+$) 237.1127, found 237.1131; IR (film) ν_{max} br 3419, 2950, 1727, 1511, 1250, 1130, 1031, 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.21 (m, 2 H), 6.90–6.83 (m, 2 H), 4.16 (apparent p, *J* = 6.9 Hz, 1 H), 3.79 (s, 3 H), 3.62 (s, 3 H), 2.97–2.82 (m, 2 H), 2.72–2.61 (m, 2 H), 2.56 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 176.4, 158.5, 133.3, 128.1, 113.9, 62.7, 55.4, 52.6, 44.0, 42.8.

Methyl 3-((*tert*-Butyldimethylsilyl)oxy)-1-(4-methoxyphenyl)cyclobutane-1-carboxylate (51). TBSCl (2.17 g, 14.4 mmol, 1.5 equiv) was added to a solution of crude **S7** (2.27 g, ca. 9.6 mmol) in dry DCM (35 mL) at room temperature, followed by imidazole (3.27 g, 48 mmol, 5 equiv). This mixture was stirred at room temperature for 30 min and quenched with MeOH (1 mL). The reaction mixture was diluted with DCM (50 mL), washed with 1 N aqueous HCl (50 mL) and brine (50 mL), and dried over Na_2SO_4. After filtration and concentration, the crude product was purified by column chromatography (0–20% Et_2O in hexanes) to give **51** (2.34 g, 56% for three steps) as colorless crystals (mp 63–65 °C): R_f = 0.6 (silica gel, 3/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{19}H_{30}O_4Si$ ($[M + H]^+$) 351.1992, found 351.1987; IR (film) ν_{max} 2952, 1732, 1512, 1251, 1145, 1053, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.29 (m, 2 H), 6.93–6.86 (m, 2 H), 4.10 (apparent p, *J* = 7.2 Hz, 1 H), 3.80 (s, 3 H), 3.61 (s, 3 H), 2.85 (ddt, *J* = 8.9, 6.9, 2.4 Hz, 2 H), 2.68 (ddt, *J* = 10.1, 7.5, 2.4 Hz, 2 H), 0.88 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 175.9, 175.8, 158.6, 133.3, 128.2, 113.9, 62.3, 55.3, 52.3, 43.6, 43.2, 25.9, 18.0, −4.7.

3-((*tert*-Butyldimethylsilyl)oxy)-1-(methoxycarbonyl)cyclobutane-1-carboxylic Acid (52). Sodium periodate (31.5 g, 147.3 mmol, 15 equiv) was added to a vigorously stirred biphasic solution of **51** (3.44 g, 9.82 mmol) in EtOAc/H_2O (390 mL/1.15 L) at 4 °C. Ruthenium oxide hydrate (148 mg, 0.98 mmol, 0.1 equiv) was added in a single portion, and the light yellow mixture was slowly warmed to room temperature and stirred for 14 h. The resulting black mixture was separated and extracted with EtOAc (2 × 200 mL). The combined organics were washed with a brine/saturated sodium sulfite solution (200 mL, 10/1 v/v), dried over Na_2SO_4 and concentrated. The crude product was filtered through a plug of silica gel (with EtOAc as eluent) to give **52** (1.97 g, 70%) as a semicrystalline waxy solid. (The yield of this reaction at different scales has varied between 62 and 70%; larger scales were generally higher yielding.): R_f = 0.5 (silica gel, EtOAc); HRMS (*m*/*z*) calcd for $C_{13}H_{24}O_5Si$ ($[M - H]^-$) 287.1320, found 287.1328; IR (film) ν_{max} br 3418, 2955, 1712, 1251, 1135, 1048, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.40 (apparent p, *J* = 7.3 Hz, 1 H), 3.78 (s, 3 H), 2.85 (ddd, *J* = 9.9, 7.1, 2.8 Hz, 2 H), 2.53 (ddd, *J* = 10.1, 7.5, 2.8 Hz, 2 H), 0.87 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 177.9, 171.4, 62.0, 53.0, 45.8, 41.1, 25.9, 18.0, −4.7.

Methyl 3-((*tert*-Butyldimethylsilyl)oxy)-1-(quinolin-8-ylcarbamoyl)cyclobutane-1-carboxylate (54a). 8-Aminoquinoline (180 mg, 1.25 mmol, 1.2 equiv) was added to a solution of **52** (300

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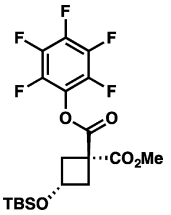
mg, 1.04 mmol) in DCM (5.2 mL) cooled to 0 °C, followed by EDC (210 mg, 1.35 mmol, 1.3 equiv). The reaction mixture was warmed to room temperature and stirred for 24 h. Saturated sodium bicarbonate solution (10 mL) was added, and the biphasic reaction mixture was separated, extracted with DCM (2 × 5 mL), washed with brine (5 mL), and dried over sodium sulfate. After filtration and concentration, the crude product was purified by silica gel chromatography (5% EtOAc in hexanes) to give **54a** (315 mg, 76%) as a pale yellow oil: R_f = 0.55 (silica gel, 3/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{22}H_{30}N_2O_4Si$ ([M + H]$^+$) 415.2053, found 415.2052; IR (film) ν_{max} br 3318, 2952, 1740, 1686, 1527, 1145, 1064, 825, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.63 (br s, 1 H), 8.84 (dd, *J* = 4.2, 1.7 Hz, 1 H), 8.75 (dd, *J* = 6.5, 2.5 Hz, 1 H), 8.15 (dd, *J* = 8.4, 1.7 Hz, 1 H), 7.58−7.50 (m, 2 H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1 H), 4.43 (p, *J* = 7.2 Hz, 1 H), 3.84 (s, 3 H), 3.09 (ddt, *J* = 9.2, 7.1, 2.3 Hz, 2 H), 2.64 (ddd, *J* = 9.9, 7.1, 2.9 Hz, 2 H), 0.88 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 173.1, 168.5, 148.6, 138.8, 136.4, 134.6, 128.1, 127.4, 122.0, 121.8, 116.7, 62.2, 53.1, 47.8, 41.7, 25.9, 18.1, −4.7.

Methyl 3-((*tert*-Butyldimethylsilyl)oxy)-1-(quinolin-8-ylcarbamoyl)-2,4-bis(1-tosyl-1*H*-indol-3-yl)cyclobutane-1-carboxylate (55a). **54a** (58.8 mg, 0.142 mmol), $Pd(OAc)_2$ (3.2 mg, 14.2 μmol, 0.10 equiv), silver acetate (71 mg, 0.425 mmol, 3 equiv), and *N*-tosyl-3-iodoindole (169 mg, 0.425 mmol, 3 equiv) were placed in a sealed tube, and toluene (280 μL, 0.5 M) was added under ambient conditions. The tube was sealed and placed in a 110 °C oil bath for 24 h. The reaction mixture was cooled to room temperature, diluted with DCM (1 mL), filtered through a pad of Celite, and concentrated. The resulting orange oil was purified by silica gel chromatography (1/1/8 to 1/1/4 DCM/Et_2O/hexanes) to give **55a** as a yellow foam (29.0 mg, 21% yield): R_f = 0.6 (silica gel, 1/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{52}H_{52}N_4O_8S_2Si$ ([M + H]$^+$) 953.3074, found 953.3076; IR (film) ν_{max} br 3314, 2927, 1736, 1676, 1369, 1174, 1126, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.59 (s, 1H), 8.79 (dd, *J* = 7.3, 1.7 Hz, 1H), 8.56 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.10 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.88 (d, *J* = 0.8 Hz, 2H), 7.88−7.84 (m, 1H), 7.76−7.69 (m, 2H), 7.60−7.47 (m, 7H), 7.35 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.26−7.20 (m, 5H), 6.75−6.69 (m, 4H), 5.51 (t, *J* = 8.2 Hz, 1H), 4.20 (dd, *J* = 8.1, 0.9 Hz, 2H), 4.04 (s, 3H), 2.04 (s, 6H), 0.74 (s, 8H), −0.14 (s, 5H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 172.7, 164.8, 148.5, 144.4, 138.6, 136.1, 135.2, 134.8, 134.4, 131.4, 129.6, 127.9, 127.5, 126.8, 126.4, 124.6, 123.2, 122.0, 121.7, 119.9, 118.0, 116.8, 113.6, 73.1, 60.4, 53.3, 48.2, 25.8, 21.4, 17.9, −4.4.

Methyl 3-((*tert*-Butyldimethylsilyl)oxy)-1-((2-(methylthio)phenyl)carbamoyl)cyclobutane-1-carboxylate (54b). 2-(Methylthio)aniline (40 μL, 0.32 mmol, 1.2 equiv) was added to a solution of **52** (77.1 mg, 0.267 mmol) in DCM (1.35 mL) cooled to 0 °C, followed by EDC (66.5 mg, 0.35 mmol, 1.3 equiv). The reaction mixture was warmed to room temperature and stirred for 24 h. Saturated sodium bicarbonate solution (1 mL) was added, and the biphasic reaction mixture was separated, extracted with DCM (2 × 1 mL), washed with brine (2 mL), and dried over sodium sulfate. After filtration and concentration, the crude product was purified by silica gel chromatography (5% EtOAc in hexanes) to give **54b** (92.1 mg, 84%) as a pale yellow oil: R_f = 0.6 (silica gel, 3/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{20}H_{31}NO_4SSi$ ([M + H]$^+$) 410.1821, found 410.1827; IR (film) ν_{max} br 3315, 2953, 1720, 1692, 1580, 1514, 1434, 1147, 1064, 836 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (br s, 1 H), 8.30 (d, *J* = 8.2 Hz, 1 H), 7.47 (dd, *J* = 7.9, 1.6 Hz, 1 H), 7.30 (t, *J* = 7.8 Hz, 1 H), 7.08 (t, *J* = 7.6 Hz, 1 H), 4.39 (p, *J* = 7.2 Hz, 1 H), 3.82 (s, 3 H), 3.00 (ddd, *J* = 9.9, 7.1, 3.0 Hz, 2 H), 2.58 (ddd, *J* = 12.7, 6.0, 2.5 Hz, 2 H), 2.37 (s, 3 H), 0.88 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 173.3, 168.1, 138.2, 132.8, 128.8, 126.1, 124.7, 120.8, 62.1, 53.1, 47.4, 41.7, 25.9, 18.7, 18.0, −4.8.

Methyl 3-((*tert*-Butyldimethylsilyl)oxy)-1-((2-(methylthio)phenyl)carbamoyl)-2,4-bis(1-tosyl-1*H*-indol-3-yl)cyclobutane-1-carboxylate (55b). **54b** (65 mg, 0.159 mmol), $Pd(OAc)_2$ (3.6 mg, 1.6 μmol, 0.10 equiv), silver carbonate (66 mg, 0.24 mmol, 1.5 equiv), and *N*-tosyl-3-iodoindole (144 mg, 0.48 mmol, 3 equiv) were placed in a sealed tube, and toluene (320 μL, 0.5 M) was added under ambient conditions. The tube was sealed and placed in a 110 °C oil bath for 24 h. The reaction mixture was cooled to room temperature, diluted with DCM (1 mL), filtered through a pad of Celite, and concentrated. The resulting dark red oil was purified by silica gel chromatography (20/5/75 DCM/Et_2O/hexanes) to give **55b** (77.3 mg, 51% yield) as a yellow foam: R_f = 0.6 (silica gel, 1/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{50}H_{53}N_3O_8S_3Si$ ([M + H]$^+$) 948.2842, found 948.2841; IR (film) ν_{max} br 3309, 2927, 1716, 1678, 1172, 735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (br s, 1 H), 8.10 (dd, *J* = 8.6, 1.4 Hz, 1 H), 7.95−7.89 (m, 2 H), 7.84 (d, *J* = 0.8 Hz, 2 H), 7.72−7.59 (m, 6 H), 7.35−7.21 (m, 6 H), 7.04 (td, *J* = 7.5, 1.4 Hz, 1 H), 6.91−6.83 (m, 4 H), 5.45 (t, *J* = 8.1 Hz, 1 H), 4.18 (dd, *J* = 8.1, 0.9 Hz, 2 H), 3.99 (s, 3 H), 2.23 (s, 6 H), 1.02 (s, 3 H), 0.75 (s, 9 H), −0.12 (s, 6 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 173.1, 164.1, 144.7, 138.5, 135.2, 134.7, 133.9, 131.1, 129.8, 129.2, 126.9, 126.3, 126.0, 124.7, 124.5, 123.2, 121.2, 119.9, 117.6, 113.5, 72.2, 59.7, 53.5, 48.3, 25.8, 21.6, 17.9, 16.9, −4.3.

1-Methyl 1-(Perfluorophenyl)(1*R*,3*R*)-3-((*tert*-butyldimethylsilyl)oxy)cyclobutane-1,1-dicarboxylate (S9).



Acid **52** (1.00 g, 3.47 mmol) was dissolved in dry DCM (17.5 mL) and cooled to 0 °C in an ice bath. Pentafluorophenol (958 mg, 5.2 mmol, 1.5 equiv), triethylamine (1.45 mL, 10.4 mmol, 3 equiv), and HATU (1.58 g, 4.16 mmol, 1.1 equiv) were added sequentially, and the reaction mixture was warmed to room temperature. After 15 h, the reaction mixture was diluted with DCM (15 mL) and quenched with 1 N aqueous HCl (15 mL). The biphasic mixture was separated, washed with brine (15 mL), and dried over Na_2SO_4. After filtration and concentration, the crude product was purified by column chromatography (25−50% DCM in hexanes) to give **S9** (1.30 g, 83%) as a colorless oil: R_f = 0.7 (silica gel, 3/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{19}H_{23}F_5O_5Si$ ([M + H]$^+$) 454.1313, found 454.1322; IR (film) ν_{max} 2956, 1789, 1749, 1518, 1244, 1054, 994, 835, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (apparent p, *J* = 7.5 Hz, 1 H), 3.81 (s, 3 H), 2.96 (m, 2 H), 2.65 (m, 2 H), 0.88 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 170.0, 168.4, 62.0, 53.2, 45.9, 41.2, 25.8, 18.0, −4.8.

Methyl 3-((*tert*-Butyldimethylsilyl)oxy)-1-(picolinoylcarbamoyl)cyclobutane-1-carboxylate (57). **S9** (1.27 g, 2.80 mmol) was dissolved in dry THF (14 mL) and cooled to 4 °C in a cold room. Picolinamide (678 mg, 5.6 mmol, 2 equiv) was added to the cooled reaction mixture, followed by potassium *tert*-butoxide solution in THF (2.0 M, 3.5 mL, 7 mmol, 2.5 equiv). After 30 min, the reaction was quenched with saturated aqueous ammonium chloride (3 mL). The biphasic mixture was diluted with EtOAc (30 mL), washed with brine (15 mL), and dried over Na_2SO_4. After filtration and concentration, the crude product was purified by column chromatography (10−25% EtOAc in hexanes) to give **57** (1.05 g, 95%) as colorless crystals (mp 83−85 °C): R_f = 0.25 (silica gel, 3/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{19}H_{28}N_2O_5Si$ ([M + H]$^+$) 393.1846, found 393.1845; IR (film) ν_{max} br 3324, 2952, 1750, 1725, 1698, 1478, 1267, 1062, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.78 (br s, 1 H), 8.61 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1 H), 8.18 (dt, *J* = 7.9, 1.1 Hz, 1 H), 7.89 (td, *J* = 7.7, 1.7 Hz, 1 H), 7.53 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1 H), 4.20 (tt, *J* = 8.0, 7.1 Hz, 1 H), 3.70 (s, 3 H), 2.90 (ddt, *J* = 9.7, 7.3, 2.6 Hz, 2 H), 2.61 (ddt, *J* = 12.6, 8.2, 2.8 Hz, 2 H), 0.83 (s, 9 H), −0.01 (s, 6 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 171.6, 170.9, 162.4, 148.5, 147.7, 138.0, 127.8, 123.3, 62.0, 52.8, 48.3, 40.5, 25.8, 18.0, −4.8.

Methyl 3-((*tert*-Butyldimethylsilyl)oxy)-1-(picolinoylcarbamoyl)-2,4-bis(1-tosyl-1*H*-indol-3-yl)cyclobutane-1-carboxylate (58). **57** (710 mg, 1.81 mmol), $Pd(OAc)_2$ (60.9 mg, 0.27 mmol, 0.15 equiv), silver pivalate (1.13 g, 5.41 mmol, 3 equiv), and *N*-tosyl-3-iodoindole (2.88 g, 7.24 mmol, 4 equiv) were placed in a sealed tube, and toluene (3.6 mL, 0.5 M) was added under ambient conditions. The tube was sealed and placed in a 120 °C oil bath for 24 h. The

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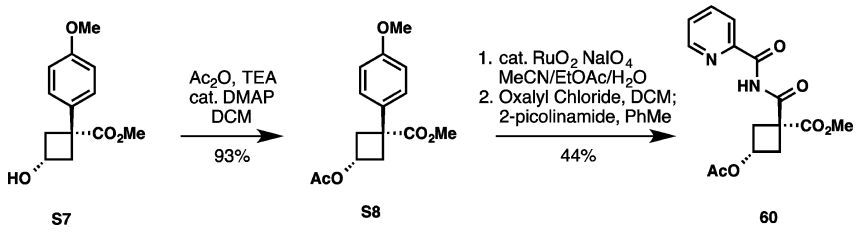
Scheme 18. Synthesis of Acetate 60



reaction mixture was cooled to room temperature, diluted with DCM (10 mL), filtered through a pad of Celite, and concentrated. The resulting dark red oil was purified by silica gel chromatography (1/1/6 to 1/1/2 DCM/Et_2O/hexanes) to give an orange solid which, upon washing three times with cold Et_2O (20 mL, 10 mL, 10 mL), gave a white powder (942 mg) containing a 5/1 mixture of **58** and Pd(**58**)$_2$ (55% combined yield), which was used directly in the next reaction. **58** could be separated from its palladium complex for characterization by silica gel chromatography (4/6 EtOAc/hexanes): colorless crystals (mp 197−200 °C); R_f = 0.5 (silica gel, 1/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{49}H_{50}N_4O_9S_2Si$ ([M + H]$^+$) 931.2867, found 931.2850; IR (film) ν_{max} 3301, 2954, 1757, 1738, 1473, 1368, 1173, 1126, 745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1 H), 7.92−7.84 (m, 3 H), 7.79 (d, *J* = 0.9 Hz, 2 H), 7.78−7.74 (m, 4 H), 7.72 (dd, *J* = 7.7, 1.7 Hz, 1 H), 7.67−7.62 (m, 2 H), 7.34 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1 H), 7.27−7.21 (m, 4 H), 7.15 (dd, *J* = 8.4, 0.9 Hz, 4 H), 5.34 (t, *J* = 8.3 Hz, 1 H), 4.21 (dd, *J* = 8.4, 0.9 Hz, 2 H), 3.95 (s, 3H), 2.23 (s, 6H), 0.72 (s, 9 H), −0.15 (s, 6 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.0, 165.6, 161.2, 148.2, 147.9, 144.7, 137.5, 135.3, 134.8, 131.0, 130.0, 127.3, 127.1, 126.1, 124.7, 123.2, 122.8, 119.9, 117.2, 113.6, 71.6, 59.9, 53.4, 48.5, 25.7, 21.6, 17.8, −4.4.

Methyl 3-((*tert*-Butyldimethylsilyl)oxy)-1-carbamoyl-2,4-bis-(1-tosyl-1*H*-indol-3-yl)cyclobutane-1-carboxylate (59). The mixture of **58** and Pd(**58**)$_2$ from the previous step (942 mg, 1.00 mmol) was added to a saturated ammonia solution of DCM/2-propanol (20 mL, 1/4 v/v) [saturated by bubbling ammonia gas through the solvent mixture for 5 min]. Scandium triflate (24.6 mg, 0.05 mmol, 0.05 equiv) was added, the flask was capped, and the reaction mixture was stirred at room temperature for 24 h. Nitrogen was bubbled though the reaction mixture to purge the excess ammonia, and the mixture was concentrated. Purification with silica gel chromatography (30% EtOAc in hexanes) gave **59** (794 mg, 53% for 2 steps) as a white foam: R_f = 0.15 (silica gel, 3/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{43}H_{48}N_3O_8S_2Si$ ([M + H]$^+$) 826.2652, found 826.2649; IR (film) ν_{max} 3472, 2954, 1733, 1679, 1447, 1366, 1173, 1123, 683 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.2 Hz, 2 H), 7.80 (d, *J* = 8.3 Hz, 4 H), 7.71 (s, 2 H), 7.60 (d, *J* = 7.7 Hz, 2 H), 7.30 (t, *J* = 7.3 Hz, 2 H), 7.24 (d, *J* = 7.3 Hz, 2 H), 7.20 (d, *J* = 8.2 Hz, 4 H), 6.24 (br s, 1 H), 5.26 (t, *J* = 8.0 Hz, 1 H), 4.99 (br s, 1 H), 4.06 (d, *J* = 8.2 Hz, 2 H), 3.90 (s, 3 H), 2.31 (s, 6 H), 0.72 (s, 9 H), −0.20 (s, 6 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 173.3, 167.8, 144.9, 135.4, 134.9, 131.1, 129.9, 127.1, 126.1, 124.7, 123.2, 119.8, 118.0, 113.8, 72.2, 58.3, 53.3, 47.9, 25.7, 21.6, 17.8, −4.4.

Methyl 3-acetoxy-1-(4-methoxyphenyl)cyclobutane-1-carboxylate (S8; Scheme 18). Triethylamine (450 μL, 3.23 mmol, 1.5 equiv) was added to a solution of **S7** (505 mg, 2.14 mmol) in DCM (20 mL) cooled to 0 °C in an ice bath, followed by acetic anhydride (300 μL, 3.23 mmol, 1.5 equiv) and DMAP (14 mg, 0.11 mmol, 0.05 equiv). The reaction was mixture was stirred at 0 °C for 2 h and then was quenched with saturated aqueous sodium bicarbonate (10 mL). The biphasic reaction mixture was separated, extracted with DCM (2 × 10 mL), washed with 1 N aqueous HCl (10 mL), washed with brine (20 mL), and dried over sodium sulfate. After filtration and concentration, the crude product was purified by silica gel chromatography (25% Et_2O in hexanes) to give **S7** (552 mg, 93%) as a colorless oil: R_f = 0.35 (silica gel, 3/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{15}H_{18}O_5$ ([M + H]$^+$) 279.1232, found 279.1231; IR (film) ν_{max} 2953, 1727, 1512, 1229, 1030, 832 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.27 (m, 2 H), 6.92−6.84 (m, 2 H), 4.86 (p, *J* = 7.2 Hz, 1 H), 3.80 (s, 3 H), 3.63 (s, 3 H), 3.04−2.91 (m, 2 H), 2.88−2.75 (m, 2 H), 2.03 (s, 3 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 175.5, 170.6, 158.8, 132.6, 128.1, 114.0, 64.5, 55.4, 52.6, 45.1, 39.7, 21.1.

Methyl 3-Acetoxy-1-(picolinoylcarbamoyl)cyclobutane-1-carboxylate (60; Scheme 18). Sodium periodate (3.8 g, 17.7 mmol, 10 equiv) was added to a vigorously stirred biphasic solution of **S8** (493 mg, 1.77 mmol) in EtOAc/MeCN/H_2O (9 mL/9 mL/30 mL) cooled to 0 °C in an ice bath. Ruthenium oxide hydrate (13.4 mg, 0.09 mmol, 0.05 equiv) was added in a single portion, and the light yellow mixture was vigorously stirred for 20 h, while being slowly warmed to room temperature. The resulting black mixture was separated and extracted with EtOAc (2 × 20 mL). The combined organics were washed with a brine/saturated sodium sulfite solution (200 mL, 10/1 v/v), dried over Na_2SO_4, and concentrated to give a crude acid that was used directly in the next reaction without further purification (^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (p, *J* = 7.6 Hz, 1H), 3.79 (s, 3H), 3.22−2.92 (m, 2H), 2.80−2.60 (m, 2H), 2.04 (s, 3H)). Oxalyl chloride (182 μL, 2.12 mmol, 1.2 equiv) was added dropwise to a solution of the acid (ca. 1.77 mmol) in DCM (10 mL) containing 1 drop of DMF. After the reaction mixture was stirred at room temperature for 4 h, toluene was added (5 mL) and the solvent concentrated to give the crude acid chloride. This material was dissolved in toluene, and 2-picolinamide (325 mg, 2.66 mmol, 1.5 equiv) was added, followed by 4 Å molecular sieves (1.7 g). The heterogeneous reaction mixture was heated to 90 °C for 16 h, and then the reaction mixture was filtered through Celite, concentrated, and purified by column chromatography (25−40% EtOAc in hexanes) to give **60** (251 mg, 44% for two steps) as colorless crystals (mp 138−139 °C): R_f = 0.25 (silica gel, 1/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{15}H_{16}N_2O_6$ ([M + H]$^+$) 321.1087, found 321.1095; IR (film) ν_{max} br 3319, 1735, 1726, 1698, 1481, 1234, 1044, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.70 (s, 1 H), 8.61 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1 H), 8.16 (dt, *J* = 7.9, 1.1 Hz, 1 H), 7.89 (td, *J* = 7.7, 1.7 Hz, 1 H), 7.53 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1 H), 4.91 (p, *J* = 7.7 Hz, 1 H), 3.71 (s, 3 H), 3.06 (ddt, *J* = 9.6, 7.7, 2.4 Hz, 2 H), 2.76 (ddt, *J* = 10.7, 7.8, 2.6 Hz, 2 H), 2.02 (s, 3 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.2, 170.4, 170.4, 162.6, 148.6, 147.5, 138.0, 127.9, 123.3, 63.7, 53.0, 49.4, 36.8, 20.9.

1-Amino-3-((*tert*-butyldimethylsilyl)oxy)-2,4-bis(1-tosyl-1*H*-indol-3-yl)cyclobutane-1-carbonitrile (62) and 2-((*tert*-Butyldimethylsilyl)oxy)-1,3-bis(1-tosyl-1*H*-indol-3-yl)-5,7-diazaspiro[3.4]octane-6,8-dione (63). **59** (400 mg, 0.484 mmol) was dissolved in THF (4.8 mL), and H_2O (1.6 mL) was added, followed by lithium hydroxide hydrate (102 mg, 2.43 mmol, 5 equiv). The biphasic reaction mixture was stirred vigorously for 12 h and quenched with 1 N aqueous HCl (3 mL). The layers were separated and extracted with EtOAc (4 × 5 mL), and the extract was washed with brine (10 mL), dried over sodium sulfate, filtered, and concentrated to give the carboxylic acid (388 mg, 99%) as a white foam ,which was dissolved in dry DCM (4.8 mL) and cooled to 0 °C. Triethylamine (0.27 mL, 1.94 mmol, 4 equiv) was added, followed by diphenylphosphoryl azide (0.42 mL, 1.94 mmol, 4 equiv). The reaction mixture was slowly warmed to room temperature and stirred for 24 h. The reaction mixture was then heated to 50 °C for 6 h and quenched with saturated aqueous sodium bicarbonate (5 mL). The layers were separated and extracted with DCM (2 × 3 mL). The combined organics were washed with brine (5 mL) and dried over sodium sulfate. After filtration and concentration, the crude product was purified by column chromatography (25−50% EtOAc in hexanes)

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to give aminonitrile **62** (257 mg, 69%) as a white foam and hydantoin **63** (91 mg, 23%) as a white solid.

62: white foam; R_f = 0.25 (silica gel, 3/1 hexanes/EtOAc); HRMS (m/z) calcd for $C_{41}H_{44}N_4O_5S_2SiNa$ ([M + Na]$^+$) 787.2420, found 787.2421; IR (film) ν_{max} 2928, 1597, 1447, 1368, 1174, 1129, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 8.02 (dt, J = 8.3, 0.9 Hz, 2 H), 7.85 (d, J = 8.4 Hz, 4 H), 7.80−7.79 (m, 2 H), 7.63 (ddd, J = 7.9, 1.3, 0.7 Hz, 2 H), 7.39−7.33 (m, 2 H), 7.31−7.25 (m, 2 H), 7.25−7.20 (m, 4 H), 4.57 (t, J = 8.3 Hz, 1 H), 3.66 (dd, J = 8.4, 0.9 Hz, 2 H), 2.33 (s, 6 H), 0.76 (s, 9 H), −0.12 (s, 6 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 145.1, 135.1, 135.1, 130.6, 130.0, 127.2, 125.4, 124.2, 123.6, 119.6, 119.4, 118.0, 114.0, 77.5, 77.2, 76.8, 69.6, 58.2, 52.2, 25.7, 21.7, 17.8, −4.4.

63: white solid (>180 °C, decomp); R_f = 0.4 (silica gel, 1/1 hexanes/EtOAc); HRMS (m/z) calcd for $C_{42}H_{44}N_4O_7S_2SiNa$ ([M + Na]$^+$) 831.2318, found 831.2332; IR (film) ν_{max} br 3358, 2928, 1727, 1367, 1173, 1127, 745 cm^{-1}; ^{1}H NMR (400 MHz, 1/1 MeOD/$CDCl_3$) δ 7.91 (d, J = 8.3 Hz, 2 H), 7.74 (d, J = 8.4 Hz, 4 H), 7.65 (d, J = 0.9 Hz, 2 H), 7.54 (ddd, J = 7.9, 1.2, 0.7 Hz, 2 H), 7.28 (ddd, J = 8.4, 7.3, 1.3 Hz, 2 H), 7.25−7.16 (m, 6 H), 5.02 (t, J = 8.1 Hz, 1 H), 3.88 (dd, J = 8.1, 1.0 Hz, 2 H), 2.30 (s, 6 H), 0.73 (s, 9 H), −0.11 (s, 6 H); ^{13}C NMR (1/1 MeOD/$CDCl_3$, 101 MHz) δ 173.5, 157.8, 145.8, 135.4, 135.3, 131.2, 130.4, 127.3, 125.5, 125.3, 124.0, 119.7, 117.7, 114.1, 68.9, 67.3, 50.3, 25.8, 21.6, 18.1, −4.2.

2-((*tert*-Butyldimethylsilyl)oxy)-5,7-dimethyl-1,3-bis(1-tosyl-1*H*-indol-3-yl)-5,7-diazaspiro[3.4]octane-6,8-dione (64). **63** (119 mg, 0.147 mmol) was dissolved in dry DMF (1.5 mL), and potassium carbonate (122 mg, 0.88 mmol, 6 equiv) was added, followed by methyl iodide (37 μL, 0.59 mmol, 4 equiv). The heterogeneous reaction mixture was warmed to 50 °C. After 2 h, the reaction mixture was quenched with saturated aqueous ammonium chloride (1 mL) and stirred for 30 min. The reaction mixture was concentrated and taken up in EtOAc (2 mL)/brine (2 mL). The biphasic mixture was separated and extracted with EtOAc (2 × 2 mL), and the extract was dried over sodium sulfate. After filtration and concentration, the crude product was purified by column chromatography (25% EtOAc in hexanes) to give **64** (98 mg, 80%) as a white foam: R_f = 0.6 (silica gel, 1/1 hexanes/EtOAc); HRMS (m/z) calcd for $C_{44}H_{48}N_4O_7S_2Si$ ([M + H]$^+$) 837.2812, found 837.2827; IR (film) ν_{max} 2929, 1768, 1711, 1446, 1368, 1173, 1126, 742 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 8.1 Hz, 2 H), 7.79 (d, J = 8.4 Hz, 4 H), 7.68 (d, J = 0.8 Hz, 2 H), 7.35−7.28 (m, 4 H), 7.25−7.19 (m, 6 H), 5.13 (t, J = 7.9 Hz, 1 H), 3.89 (d, J = 7.9 Hz, 2 H), 3.36 (s, 3 H), 2.42 (s, 3 H), 2.33 (s, 6 H), 0.76 (s, 9 H), −0.10 (s, 6 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 170.3, 155.8, 145.0, 135.3, 134.9, 130.5, 129.9, 127.1, 125.4, 125.1, 123.6, 118.5, 116.3, 114.0, 69.5, 68.9, 25.7, 25.3, 24.3, 21.7, 17.8, −4.4.

1-Amino-3-((*tert*-butyldimethylsilyl)oxy)-2,4-bis(1-tosyl-1*H*-indol-3-yl)cyclobutane-1-carboxamide (69). **62** (120 mg, 0.157 mmol) was dissolved in dioxane (500 μL), and H_2O (125 μL) was added, followed by Parkin's catalyst (13.5 mg, 0.031 mmol, 0.2 equiv). The reaction mixture was heated to 80 °C for 24 h. The reaction mixture was cooled to room temperature and diluted with EtOAc (1 mL). The layers were separated and extracted with EtOAc (3 × 1 mL), and the extract was washed with brine (2 mL) and dried over sodium sulfate. After filtration and concentration, the crude product was purified by column chromatography (15−25% EtOAc in hexanes) to give **69** (77 mg, 63%) as a pale yellow foam: R_f = 0.55 (silica gel, 1/1 hexanes/EtOAc); HRMS (m/z) calcd for $C_{41}H_{47}N_4O_6S_2Si$ ([M + H]$^+$) 783.2706, found 783.2707; IR (film) ν_{max} br 3453, br 3380, 2928, 1681, 1447, 1366, 1172, 1126 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.2 Hz, 2 H), 7.78 (d, J = 8.4 Hz, 4 H), 7.66 (s, 2 H), 7.62 (d, J = 7.3 Hz, 2 H), 7.29 (ddd, J = 8.4, 7.2, 1.3 Hz, 2 H), 7.25−7.17 (m, 6 H), 6.49 (br s, 1 H), 5.01 (t, J = 7.8 Hz, 1 H), 4.86 (br s, 1 H), 3.47 (d, J = 8.5 Hz, 2 H), 2.31 (s, 6 H), 0.72 (s, 9 H), −0.20 (s, 6 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 173.0, 144.8, 135.3, 134.9, 131.6, 129.8, 127.0, 125.1, 124.6, 123.2, 119.5, 118.5, 113.8, 69.6, 64.3, 54.7, 25.8, 21.6, 17.8, −4.4.

***N*-(2-((*tert*-Butyldimethylsilyl)oxy)-6-oxo-1,3-bis(1-tosyl-1*H*-indol-3-yl)-5,7-diazaspiro[3.4]octan-8-ylidene)-4-methylbenzenesulfonamide (66).** **69** (90 mg, 0.115 mmol) was dissolved in THF (2.3 mL), and tosyl isocyanate (21 μL, 0.138 mmol, 1.2 equiv) was added at room temperature. After the reaction mixture was stirred for 30 min, the reaction mixture was quenched with aqueous ammonium hydroxide (2 mL). The layers were separated and extracted with EtOAc (3 × 2 mL), and the extract was washed with brine (2 mL) and dried over sodium sulfate. After filtration and concentration, the crude **71** (91.1 mg) was obtained as a pale yellow foam and was used directly in the following reaction. Burgess reagent (7 mg, 0.03 mmol) was added to a heterogeneous solution of crude **71** (10 mg, 0.010 mmol) in DCM (200 μL). The reaction mixture was warmed to 50 °C for 2 h (mixture turns homogeneous after 15 min). After concentration, the crude product was purified directly by column chromatography (2% acetone in DCM) to give **66** (8.2 mg, 67%, two steps) as a white solid that is very sparingly soluble when purified, preventing NMR analysis. This compound was methylated to facilitate characterization. Colorless crystals serendipitously formed from slow evaporation of a dilute TLC sample in wet DCM to further confirm the structure: colorless crystals (>200 °C, decomp); R_f = 0.5 (silica gel, 1/1 hexanes/EtOAc); HRMS (m/z) calcd for $C_{49}H_{51}N_5O_8S_3Si$ ([M + H]$^+$) 962.2747, found 962.2734; IR (film) ν_{max} br 3532, br 3395, 2928, 1771, 1636, 1358, 1172, 670 cm^{-1};

***N*-(2-((*tert*-Butyldimethylsilyl)oxy)-5,7-dimethyl-6-oxo-1,3-bis(1-tosyl-1*H*-indol-3-yl)-5,7-diazaspiro[3.4]octan-8-ylidene)-4-methylbenzenesulfonamide (67).** Potassium carbonate (6.9 mg, 0.05 mmol, 6 equiv) was added to a solution of **66** (8.0 mg, 8.3 μmol) in DMF (100 μL), followed by methyl iodide (2.0 μL, 3.2 μmol, 4 equiv). The heterogeneous reaction mixture was stirred at room temperature for 30 min. The reaction mixture was quenched with saturated aqueous ammonium chloride (200 μL) and stirred for 30 min. The reaction mixture was concentrated and taken up in EtOAc (1 mL)/brine (1 mL). The mixture was separated and extracted with EtOAc (2 × 1 mL) and dried over sodium sulfate. After filtration and concentration, the crude product was purified by column chromatography (20% EtOAc in hexanes) to give **67** (7.8 mg, 95%) as a white foam. Alternate procedure: tosyl isocyanate (12 μL, 0.08 mmol, 1.25 equiv) was added to a solution of **62** (50 mg, 0.065 mmol) in THF (1.3 mL) at room temperature. The reaction mixture was concentrated after 15 min and dissolved in absolute ethanol (1.3 mL). This reaction mixture was heated to 70 °C for 14 h, and then the solvent was evaporated to give crude **66**. Potassium carbonate (54 mg, 0.39 mmol, 6 equiv) was added to a solution of crude **66** in DMF (650 μL), followed by methyl iodide (16.3 μL, 0.26 mmol, 4 equiv). The heterogeneous reaction mixture was warmed to 50 °C. After 2 h, the reaction mixture was quenched with saturated aqueous ammonium chloride (500 μL) and stirred for 30 min. The reaction mixture was concentrated and taken up in EtOAc (2 mL)/brine (2 mL). The mixture was separated and extracted with EtOAc (2 × 2 mL) and dried over sodium sulfate. After filtration and concentration, the crude product was purified by column chromatography (20% EtOAc in hexanes) to give **67** (47.2 mg, 73% over 2 steps) as a white foam: R_f = 0.6 (silica gel, 1/1 hexanes/EtOAc); HRMS (m/z) calcd for $C_{51}H_{55}N_5O_8S_3Si$ ([M + H]$^+$) 990.3060, found 990.3071; IR (film) ν_{max} 2927, 1764, 1627, 1447, 1370, 1173, 776, 669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.3 Hz, 2 H), 7.95 (d, J = 8.4 Hz, 2 H), 7.90 (d, J = 8.4 Hz, 4 H), 7.53 (d, J = 8.0 Hz, 2 H), 7.49 (s, 2 H), 7.32 (ddd, J = 8.4, 5.5, 2.9 Hz, 2 H), 7.25−7.17 (m, 8 H), 4.74 (t, J = 8.1 Hz, 1 H), 3.92 (dd, J = 8.2, 1.0 Hz, 2 H), 3.41 (s, 3 H), 3.30 (s, 3 H), 2.52 (s, 3 H), 2.33 (s, 6 H), 0.67 (s, 9 H), −0.36 (s, 6 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.9, 154.9, 145.2, 143.5, 139.8, 135.2, 134.7, 130.5, 130.1, 130.1, 127.4, 126.9, 125.2, 125.1, 123.6, 118.4, 115.4, 114.1, 69.5, 68.1, 48.2, 30.8, 26.1, 25.7, 21.7, 21.7, 17.8, −4.9.

3-(2-(Methylthio)phenyl)-6-(3,4,5-trimethoxyphenyl)-3-azabicyclo[3.1.1]heptane-2,4-dione (87). A flask containing **82** (1.60 g, 3.59 mmol) was evacuated and back-filled with argon. Toluene (12 mL) was added, followed by 3.59 mL of a 1.0 M solution of LiOtBu in hexanes (3.59 mmol, 1.0 equiv). The resulting suspension was warmed to 50 °C for 36 h. The reaction mixture was cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ (15 mL). The mixture was separated, washed with brine (20 mL), dried over

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sodium sulfate, and concentrated in vacuo. The resulting oil was purified by silica gel chromatography (12.5/12.5/75 to 15/15/70 DCM/Et_2O/hexanes) to give **87** (110 mg, 7%) as a crystalline solid (mp 200−205 °C). X-ray-quality crystals were obtained by crystallization from $CHCl_3/Et_2O$: R_f = 0.5 (silica gel, 3/1 hexanes:EtOAc); HRMS (*m*/*z*) calcd for $C_{22}H_{23}NO_5S$ ($[M + H]^+$) 414.1375, found 414.1380; IR (film) ν_{max} 2936, 1728, 1639, 1586, 1519, 1235, 1124, 814, 747; ^1H NMR (600 MHz, $CDCl_3$) δ 7.31 (ddd, *J* = 8.4, 7.2, 1.4 Hz, 1 H), 7.28 (dd, *J* = 8.0, 1.7 Hz, 1 H), 7.02 (ddd, *J* = 7.8, 7.1, 1.7 Hz, 1 H), 6.38 (d, *J* = 0.9 Hz, 2 H), 5.89 (dd, *J* = 7.8, 1.3 Hz, 1 H), 4.20 (tt, *J* = 6.0, 1.1 Hz, 1 H), 3.85 (s, 3 H), 3.79 (s, 6 H), 3.76 (t, *J* = 5.8 Hz, 2 H), 2.83 (d, *J* = 9.7 Hz, 1 H), 2.68 (dt, *J* = 9.6, 5.6 Hz, 1 H), 2.41 (s, 3 H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 173.8, 153.6, 138.1, 137.2, 133.5, 131.2, 129.9, 129.0, 127.0, 126.2, 103.1, 61.1, 56.3, 48.1, 47.1, 30.2, 15.7.

***N*-(Quinolin-8-yl)-2,4-bis((*E*)-styryl)cyclobutane-1-carboxamide (112).** **34** (221 mg, 0.513 mmol) was dissolved in dry THF (5 mL), and a toluene solution of potassium *tert*-butoxide was added (1.7M, 300 μL, 0.51 mmol, 1 equiv) at room temperature. The reaction mixture was warmed to 45 °C for 30 min, quenched with saturated aqueous sodium bicarbonate solution (3 mL), and extracted with EtOAc (2 × 5 mL), and the extract was washed with brine (5 mL) and dried over sodium sulfate. After filtration, concentration, and purification by a silica plug (DCM), epimer **112** (212 mg, 96%) was obtained as a white solid (mp 136−139 °C): R_f = 0.7 (silica gel, 3/1 hexanes/EtOAc); HRMS (*m*/*z*) calcd for $C_{30}H_{26}N_2O$ ($[M + H]^+$) 431.2123, found 431.2125; IR (film) ν_{max} br 3349, 2934, 1677, 1519, 1483, 1322, 968, 748, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1 H), 8.85 (dd, *J* = 7.6, 1.4 Hz, 1 H), 8.46 (dd, *J* = 4.2, 1.7 Hz, 1 H), 8.10 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.54 (t, *J* = 7.9 Hz, 1 H), 7.51−7.43 (m, 5 H), 7.39−7.31 (m, 5 H), 7.29−7.22 (m, 2 H), 6.62 (d, *J* = 15.9 Hz, 2 H), 6.46 (dd, *J* = 15.9, 7.2 Hz, 2 H), 3.43 (p, *J* = 8.5 Hz, 2 H), 3.14 (t, *J* = 9.4 Hz, 1 H), 2.53 (dt, *J* = 10.5, 7.8 Hz, 1 H), 2.03 (q, *J* = 10.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 171.4, 148.2, 138.4, 137.3, 136.2, 134.6, 132.1, 132.1, 130.6, 130.6, 128.6, 128.6, 127.9, 127.4, 127.4, 126.4, 126.4, 121.6, 121.5, 116.4, 54.1, 38.7, 38.7, 31.5.

Expermental data for compounds **1**, **2**, **80**−**86**, **89**−**91**, and **99**−**111** can be found in refs 50 and 53.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving relevant NMR spectra and CIF files giving crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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