2022

Catalytic Enantioselective Birch–Heck Sequence for the Synthesis of Phenanthridinone Derivatives with an All-Carbon Quaternary Stereocenter

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Citation

Sexton, M., Malachowski, W. P., Yap, G. P. A., Rachii, D., Feldman, G., Krasley, A. T., Chen, Z., Tran, M. A., Wiley, K., Matei, A., Petersen, S., and S. Tran Tien. 2022. "Catalytic Enantioselective Birch–Heck Sequence for the Synthesis of Phenanthridinone Derivatives with an All-Carbon Quaternary Stereocenter." *The Journal of Organic Chemistry* 87.2: 1154-1172.

Catalytic Enantioselective Birch-Heck Sequence for the Synthesis of Phenanthridinone Derivatives with an All-Carbon Quaternary Stereocenter

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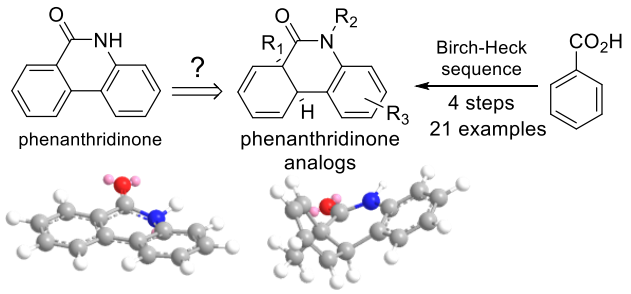
TOC Graphic



Abstract

Novel phenanthridinone analogs with an all-carbon quaternary stereocenter have been enantioselectively synthesized using the Birch-Heck sequence. Flat phenanthridinone structures have extensive bioactivity, but consequently also suffer from poor therapeutic selectivity. The addition of a quaternary center to the phenanthridinone skeleton has the potential to generate more complex analogs with improved selectivity. Unfortunately, no general synthetic pathway to such derivatives exists. Herein we report a four-step process that transforms inexpensive benzoic acid into twenty-two different quaternary carbon containing phenanthridinone analogs with a variety of substituents on all three rings: alkyl groups at the quaternary center; methyl, methoxymethyl or para-methoxybenzyl on the amide nitrogen; and halogen and methyl substituents on the aryl ring. Good to very good enantioselectivity was demonstrated in the key intramolecular desymmetrizing Mizoroki-Heck reaction. Transformations of the Heck reaction products into molecules with potentially greater therapeutic relevance were also accomplished.

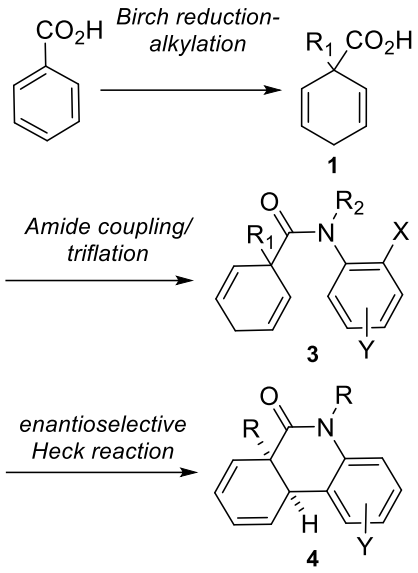
Introduction

Drug development efforts are constantly seeking new synthetic tools to allow more efficient access to complex molecules that can enhance the potency and selectivity of new therapies. Synthetic transformations that create sp^3 carbons and quaternary stereocenters are particularly relevant based on recent surveys of the most successful drugs over the past three decades[1-3], which demonstrated that small molecule drugs with greater three-dimensional structure were more likely to succeed in clinical trials and be approved. Two reasons have been advanced to explain the better pharmaceutical profile of sp^3 rich and chiral molecules: improved solubility[1,4] and less promiscuous binding behavior[2]. Unfortunately, the

current synthetic tools to efficiently construct molecules with chiral sp^3 carbons are deficient. In particular, the enantioselective synthesis of quaternary stereocenters has long been recognized as one of the most significant challenges[5-8] due to the steric congestion around the sp^3 carbon and the task of controlling the absolute stereochemistry. And yet these same quaternary carbon-containing structures have demonstrated greater potency and enhanced selectivity in drug development[9].

In this report, we describe a technique for accomplishing the enantioselective synthesis of phenanthridinone derivatives with a quaternary stereocenter in an expedient and general manner. Although one earlier report of the synthesis of a phenanthridinone derivative with a quaternary center exists[10], it was not an enantioselective process and was more limited in scope. Phenanthridinone is emblematic of many bioactive structures, with its flat sp^2-rich molecular architecture and broad bioactivity. In fact, a PubChem/PubMed search for its core tricyclic architecture returns over 360 molecules that show bioactivity[11]. Reports of bioactivity for phenanthridinone or its derivatives have included anti-cancer[12-19], anti-bacterial[20], anti-viral[21], anti-plasmodial[22], and anti-inflammatory agents[23], along with treatments for hyperlipidaemia[24] and ischemic stroke[25]. The reported protein targets for phenanthridinone derivative anti-cancer activity include poly-adenosyl ribosyl polymerase (PARP)[18], BET bromodomain[16], topoisomerase 1B[12], tyrosyl-DNA phosphodiesterase[12], CDK11[19], progesterone receptor[14] and Auroroa kinase[15]. With such a privileged structure with regards to bioactivity, it can often become a starting point for many therapy programs but will also likely fail to advance due to its promiscuity, which contributes to poor pharmacokinetic properties and potential side effects. In contrast, phenanthridinone derivatives that incorporated sp^3 carbon centers and had more three-dimensionality to their architecture might be capable of greater potency and selectivity by, in theory, uniquely accessing regions of one biomolecule while undermining the affinity for a range of other biomolecules[1,2,9,18]. An analysis of reported crystal structures of phenanthridinone with human tankyrase 2[26], PARP-14[18] and BRD2 bromodomain[27] demonstrated the potential for such structural embellishment as there was considerable unoccupied space both above and below the flat tricyclic structure. Unfortunately, a general synthetic pathway to phenanthridinone derivatives with an all-carbon quaternary stereocenter has never been reported and therefore analysis of such molecules has been limited. More generally, the absence of efficient synthetic tools for the enantioselective generation of quaternary carbons has meant chemical libraries in the pharmaceutical industry have a preponderance of flat sp^2 structures.

To help address this deficiency, we report the development of an efficient synthetic tool to generate phenanthridinone derivatives with all-carbon quaternary stereocenters. The process involves a Birch reduction-alkylation followed by coupling of an aminophenol derivative, triflation of the phenol and desymmetrizing enantioselective intramolecular Mizoroki-Heck reaction (**Scheme 1**). The intramolecular Heck reaction has a rich history of valuable asymmetric transformations[28] and desymmetrization reactions have been powerful tools for the enantioselective synthesis of complex molecules[7,29-31]. The related desymmetrization work of Shibasaki[32] with 1,4-cyclohexadienes was particularly inspirational. The sequence reported herein demonstrates further utility of the desymmetrizing intramolecular Heck reactions in the asymmetric synthesis of complex quaternary carbon containing tricyclic structures. In an efficient, four-step synthetic process, inexpensive benzoic acid is transformed into potentially powerful analogs of the highly bioactive phenanthridinone structure.



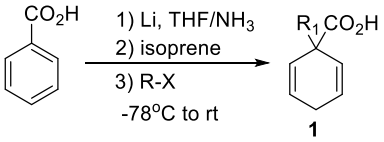
Scheme 1. Birch-Heck sequence to phenanthridinone derivatives

Results and Discussion

Synthesis of the Heck Substrates

The synthesis of quaternary carbon-containing phenanthridinone derivatives began with the Birch reduction-alkylation of benzoic acid (**Table 1**). Fourteen different alkylating agents were used to demonstrate a range of alkyl size and functionality at the quaternary center. Although benzoic acid is a classic Birch reaction substrate, seven of the fourteen examples were previously unreported. The reaction yields of 1,4-cyclohexadiene product **1** were consistently high and the products were pure enough for subsequent use without chromatographic purification. In certain cases (R_1= -CH_2CN, -CH_2CO_2Et, -CH_2Ph, -CH_2(3-CN)Ph, -CH_2-naphthyl), an alkyl chloride is the best choice for the alkylating agent because the alkyl iodide and bromide derivatives resulted in recovered benzoic acid starting material. We believe this occurs because the enolate reacts with the iodine or bromine as the electrophile instead of the carbon of the alkyl halide. Subsequent elimination of H-I or H-Br from the halo-cyclohexadiene returns the cyclohexadiene to benzoic acid. In these aberrant side reactions, the halide is the preferred electrophile because the alkyl carbanion byproduct generated in the process is less basic and more stable than the dianion generated from the reduction of the ammonium benzoate.

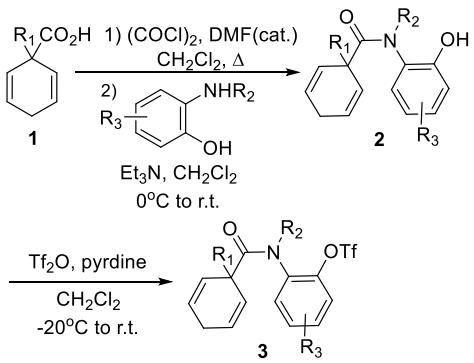
Table 1. Birch reduction-alkylation reaction.



entry	R_1	X	yield (%)	compd
1	Me	I	98	1a
2	Et	Br	100	1b
3	i-Pr	I	97	1c
4	$-CH_2CH=CH_2$	Br	95	1d
5	i-Bu	I	94	1e
6	$-CH_2(c-C_3H_5)$	Br	96	1f
7	$-CH_2CH_2CH=CH_2$	Br	89	1g
8	$-CH_2OCH_3$	Cl	90	1h
9	$-CH_2CN$	Cl	80	1i
10	$-CH_2CO_2Et$	Cl	99	1j
11	$-c-C_6H_{10}$	I	96	1k
12	$-CH_2Ph$	Cl	94	1l
13	$-CH_2Ph(3-CN)$	Cl	92	1m
14	$-CH_2-(1)$-naphthyl	Cl	90	1n

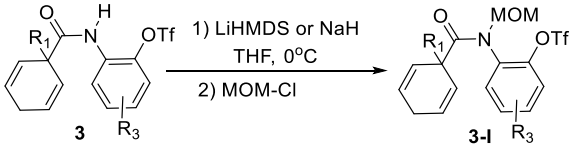
Conversion of the carboxylic acid products **1** to amides **2** used standard acid chloride formation with $(COCl)_2$/ DMF (cat.) followed by reaction with the appropriate primary or secondary amine (**Table 2**). Again, amide products were pure enough after aqueous washes to allow use in the subsequent triflation reaction without chromatographic purification. Triflation with pyridine and triflic anhydride provided the substrates **3** for the Heck reaction. The yields for the two-step sequence ranged from 47-84% with the triflation process being the most inconsistent. Secondary amide products (**3a-d**, **3f**, **3o**, **3s**) were protected as the methoxymethyl tertiary amides (**Table 3**) by treatment with base and alkylation with methoxymethyl chloride or bromide (MOM-Cl/Br) in 56-86% yields. The tertiary amides were all purified chromatographically prior to the Heck reaction, and all demonstrated the presence of atropisomers in NMR analysis which necessitated conducting experiments at 100ºC in DMSO-d_6. At lower temperatures, broad peaks and complex spectra were routinely seen. Coalescence of peaks only occurred at the higher temperatures and supported the need for higher temperatures in the subsequent Heck reaction to foster chiral induction from the chiral catalyst instead of differences in atropisomer populations and reactivity[33-35].

Table 2. Amide and triflate formation



entry	R_1	R_2	R_3	yield (%, 2 steps)	compd
1	Me, 1a	H	H	57	3a
2	Me, 1a	H	4-F	82	3b
3	Me, 1a	H	4-Me	62	3c
4	Me, 1a	H	5-Cl	59	3d
5	Me, 1a	Me	H	56	3e
6	Et, 1b	H	H	74	3f
7	Et, 1b	Me	H	68	3g
8	i-Pr, 1c	Me	H	81	3h
9*	i-Pr, 1c	PMB	H	42	3i
10	-$CH_2CH=CH_2$, 1d	Me	H	79	3j
11	i-Bu, 1e	Me	H	59	3k
12	-CH_2(c-C_3H_5), 1f	Me	H	67	3l
13	-$CH_2CH_2CH=CH_2$, 1g	Me	H	79	3m
14	-CH_2OCH_3, 1h	Me	H	47	3n
15	-CH_2CN, 1i	H	H	48	3o
16	-CH_2CN, 1i	Me	H	61	3p
17	-CH_2CO_2Et, 1j	Me	H	84	3q
18	-c-C_6H_{10}, 1k	Me	H	54	3r
19	-CH_2Ph, 1l	H	H	66	3s
20	-CH_2Ph, 1l	Me	H	84	3t
21	-CH_2Ph(3-CN), 1m	Me	H	68	3u
22	-CH_2-(1)-naphthyl, 1n	Me	H	62	3v

Table 3. Amide protection

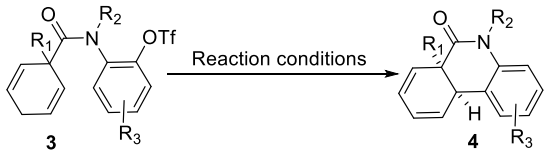


entry	R_1	R_3	yield (%)	compd
1	Me, 3a	H	86	3a-I
2	Me, 3b	4-F	82	3b-I
3	Me, 3c	4-Me	67	3c-I
4	Me, 3d	5-Cl	61	3d-I
5	Et, 3f	H	86	3f-I
6	-CH_2CN, 3n	H	60	3o-I
7	-CH_2Ph, 3r	H	56	3s-I

atalytic Enantioselective Desymmetrizing Heck reaction

The optimal conditions for the enantioselective desymmetrizing Heck reaction were informed by our previous studies with a related system[36] and further optimized through additional screening of Pd source, ligands, solvents and additives (**Table 4** and **SI-1**). In the end, $Pd(OAc)_2$ was found to be the optimal palladium source and (R)-BINAP was determined to be the best chiral ligand with the broadest utility (entry 1). DMF was again confirmed as the optimal solvent. Entries 2 and 3 explored conditions that had proven reliable or optimal in our prior work with a different substrate[36] but failed to afford optimal enantioselectivity with the current tertiary amide substrates **3**. Entry 4 demonstrated that a secondary amide was incompatible with these conditions. The benefits of BINAP over DM-BINAP in terms of yield and enantioselectivity were discovered with entry 5. Entry 6 and 7 attempted to enhance Heck reaction enantioselectivity at lower temperatures and found the optimal enantioselectivity at 80ºC. $Pd(TFA)_2$ was used in place of $Pd(OAc)_2$ in entry 8 but failed to enhance either yield or enantioselectivity. The optimized conditions were applied to the ethyl derivative (R_1=Et) and found to be sluggish (entry 9). Interestingly, n acetate intermediate **4g-OAc** (**Figure 1**) was detected by GC-MS and TLC analysis in the course of the ~48 h reaction and subsequently isolated and characterized to confirm its identity. We postulated that the allylic acetate intermediate was the result of nucleophilic addition of acetate anion, from $Pd(OAc)_2$ catalyst, to the allylic Pd complex intermediate, which is the result of chain walking by the Pd catalyst[37-40]. LaRock has reported the isolation of allylic acetate products in similar achiral intramolecular Heck reactions with cyclohexadiene substrates[37]. Similar to LaRock, we believe the acetate adds to the face opposite the aryl group and the presumed face of Pd-allylic complexation. In our reactions, the Pd catalyst would convert the allylic acetate intermediate to the desired 1,3-diene over several hours. There was no elimination reaction seen when **4g-OAc** was subjected to Cy_2NMe at 80ºC (data not shown), so Pd is necessary for conversion of the allylic acetate intermediate to the 1,3-diene product. Further evidence for the presence of the Pd-allyl complex was discovered from a side reaction with the butenyl substituted derivative (**3m**, R_1= -$CH_2CH_2CH{=}CH_2$) detailed below.

Table 4. Heck reaction optimization



entry	R_1	R_2	X	Pd source (mol %)	ligand (mol%)	additive (eq.)	solvent	temp (ºC)	yield (%)	e.r.
1	Me-	Me	OTf	$Pd(OAc)_2$ (10)	(R)-BINAP (12)	Cy_2NMe (2.0), LiOAc (2.0)	DMF	80	72 (1 day)	12:1
2	Me-	Me	I	$Pd(OAc)_2$ (10)	(R)-DM-BINAP (12)	Ag_2CO_3 (2.0)	1,4-dioxane	23	77	1.6:1
3	Me-	Me	OTf	$Pd(OAc)_2$ (20)	(R)-DM-BINAP (24)	Cy_2NMe (2.0)	DMF	100	74	6:1
4	Me-	H	OTf	$Pd(OAc)_2$ (20)	(R)-DM-BINAP (24)	Cy_2NMe (2.0)	DMF	100	no rxn.	--
5	Me-	Me	OTf	$Pd(OAc)_2$ (20)	(S)-BINAP (24)	Cy_2NMe (2.0)	DMF	100	93	8:1
6	Me-	Me	OTf	$Pd(OAc)_2$ (20)	(S)-BINAP (24)	Cy_2NMe (2.0)	DMF	80	96	12:1
7	Me-	Me	OTf	$Pd(OAc)_2$ (20)	(S)-BINAP (24)	Cy_2NMe (2.0)	DMF	60	no rxn.	--
8	Me-	Me	OTf	$Pd(TFA)_2$ (20)	(S)-BINAP (24)	Cy_2NMe (2.0)	DMF	80	89	11:1
9	Et-	Me	OTf	$Pd(OAc)_2$ (20)	(R)-BINAP (24)	Cy_2NMe (2.0)	DMF	80	51 (2 days)	8:1

10	Et-	Me	OTf	$Pd(OAc)_2$ (20)	(R)-BINAP (24)	Cy_2NMe (2.0), LiOAc (2.0)	DMF	80	86	10:1
11	Et-	Me	OTf	$Pd(OAc)_2$ (10)	(R)-BINAP (12)	Cy_2NMe (2.0), LiOAc (2.0)	DMF	80	62	11:1
12	Et-	Me	OTf	$Pd(OAc)_2$ (10)	(R)-BINAP (12)	Cy_2NMe (2.0), LiOAc (2.0)	DMF	60	40, **4**; 60 **4-OAc**	--
13	Et-	Me	OTf	$Pd(OAc)_2$ (4)	(R)-BINAP (7)	Cy_2NMe (2.0), LiOAc (2.0)	DMF	80	62 (4 days)	11:1
14	Et-	Me	OTf	$Pd(OAc)_2$ (10)	(R)-(+)-Cl-MeO-BIPHEP (12)	Cy_2NMe (2.0), LiOAc (2.0)	DMF	80	no rxn.	--
15	Et-	Me	OTf	$Pd(OAc)_2$ (10)	(R)-QUINAP (12)	Cy_2NMe (2.0), LiOAc (2.0)	DMF	80	no rxn.	--

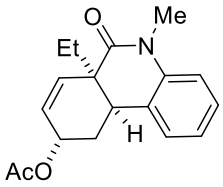


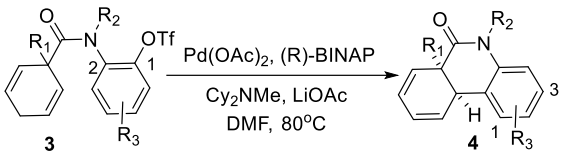
Figure 1. Acetate intermediate **4g-OAc** detected and isolated

As it appeared the allylic acetate intermediate was the preferred pathway to the desired 1,3-diene product, we added LiOAc to the reaction to increase the amount of acetate present and to hopefully accelerate the formation of **4g-OAc** (entry 10). To our pleasure, this not only accelerated the formation of **4g-OAc**, but also facilitated the formation of 1,3-diene product and improved the reaction enantioselectivity (cf. entry 9 versus 10). In practice, it was not easy to obtain high yields of the acetate intermediate during the course of the reaction as it was usually quickly converted to the 1,3-diene product. LiOAc was determined the optimal reagent as NaOAc, KOAc, and nBu_4NOAc were all slower and yielded incomplete reactions (**Table SI-1**). LiBr failed to promote the reaction, so both components of the LiOAc salt are critical. Running the reaction with $PdCl_2$ catalyst also took considerably longer (**Table SI-1**). LaRock demonstrated that a variety of nucleophiles could add into the resting state Pd-allyl catalyst complex, albeit with the key additive tetra-n-butylammonium chloride (TBAC)[37]. However, neither diethyl malonate nor aniline coupled with the Pd-allyl complex in any detectable amount (**Table SI-1**). Lower catalyst loading (10 mol%) was possible but lead to a lower chemical yield (entry 11). Dropping the reaction temperature to 60ºC caused the reaction to stall, even with the extra LiOAc added (entry 12). Lowering the catalyst loading further (4 mol%) afforded an identical yield and similar enantioselectivity, but the reaction took 4 days (entry 13). Several alternative ligands were tried, but no reaction was seen (entry 14 and 15, and **Table SI-1**).

An analysis of the enantioselective desymmetrizing intramolecular Heck reaction substrate scope (**Table 5**) demonstrated compatibility with variations at the quaternary center (R_1), the amide nitrogen (R_2) and the aryl triflate (R_3). At the quaternary center (R_1), a range of alkyl groups was permitted, including methyl (**3a-I**, **3e**), ethyl (**3f-I**, **3g**), isopropyl (**3h**), isobutyl (**3k**), cyclopropylmethyl (**3l**), and cyclohexyl (**3r**). The more sterically demanding alkyl groups, such as isopropyl, isobutyl and cyclohexyl, afforded slightly lower enantioselectivities (5-7:1) versus the typical enantiomeric ratios around 10:1. Functionalized side chains were also permitted, including alkene (**3j**, **3m**), ether (**3n**), nitrile (**3o-I**, **3p**), and ester (**3q**); only the ester had lower enantioselectivity (7:1). Interestingly, the nitrile derivatives, **3o-I** and **3p**, afforded lower yields (same enantioselectivity) with LiOAc added to the reaction. Large aryl

groups (**3s-I**, **3t**, **3u**, **3v**) were also permitted and afforded generally good yields and enantioselectivities. Aryl triflate substitution (R_3) was also permitted as evidenced by the success of the 4-F (**3b-I**), 4-Me (**3c-I**) and 5-Cl (**3d-I**) derivatives, although the chloro analog had lower enantioselectivity. This does not appear to be the result of competing oxidative addition to the C-Cl bond, but the exact reason for the poor outcome is not clear. Catalyst loadings ranged from 10-20 mole percent with higher loadings necessary for the larger R_1 groups and for the reaction to be completed in 48 hrs.

Table 5. Enantioselective Heck reaction



3 **4**

entry	R_1	R_2	R_3	yield (%)	e.r.	compd
1	Me, 3a-I	MOM	H	72	11:1	4a
2	Me, 3b-I	MOM	4-F	78	11:1	4b
3	Me, 3c-I	MOM	4-Me	67	16:1	4c
4	Me, 3d-I	MOM	5-Cl	54[a]	6:1	4d
5	Me, 3e	Me	H	96	12:1	4e
6	Et, 3f-I	MOM	H	90	12:1	4f
7	Et, 3g	Me	H	62	10:1	4g
8	i-Pr, 3h	Me	H	82	7:1	4h
9	iPr, 3i	PMB	H	41	5:1	4i
10	-$CH_2CH{=}CH_2$, 3j	Me	H	100	10:1	4j
11	i-Bu, 3k	Me	H	83	7:1	4k
12	-CH_2(c-C_3H_5), 3l	Me	H	65	9:1	4l
13	-$CH_2CH_2CH{=}CH_2$, 3m	Me	H	55[b]	8:1	4m
14	-CH_2OCH_3, 3n	Me	H	88	20:1	4n
15	-CH_2CN, 3o-I	MOM	H	73[a]	10:1	4o
16	-CH_2CN, 3p	Me	H	97[a]	9:1	4p
17	-CH_2CO_2Et, 3q	Me	H	86	7:1	4q
18	-c-C_6H_{11}, 3r	Me	H	57	6:1	4r
19	-CH_2Ph, 3s-I	MOM	H	82	12:1	4s
20	-CH_2Ph, 3t	Me	H	83	11:1	4t
21	-CH_2Ph(3-CN), 3u	Me	H	59	11:1	4u
22	-CH_2-(1)-naphthyl, 3v	Me	H	65	8:1	4v

Typical conditions: 10-20 mol% $Pd(OAc)_2$, 12-24 mol% (R)-BINAP, Cy_2NMe (2 eq.), LiOAc (2 eq.), DMF (0.1-0.25 mmol triflate/mL)
[a]Note: better yields and/or e.r. obtained without LiOAc.
[b]16% cyclized product also obtained

As noted earlier, the butenyl derivative (**3m**) provided additional evidence for the presence of the Pd-allyl complex in the form of a serendipitous cycloisomerization side reaction between the Pd-allyl complex and

the side chain alkene. A tetracyclic side product **4m-C** was isolated, and a crystal structure was obtained to prove the structure (**Figure 2**, Supporting Information). Not surprisingly, this side product was formed in greater yield when the reaction was run in the absence of LiOAc. Besides confirming the presence of the Pd-allyl complex, the crystal structure also provided evidence for the preferred absolute stereochemical outcome of the enantioselective Heck reaction. The stereochemical assignment for R_1 for all substrates is thus tentatively assigned in an analogous manner.

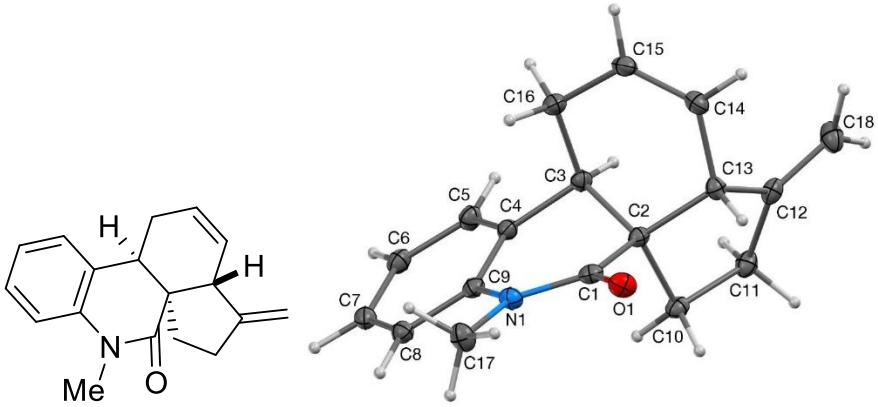


Figure 2. Cyclized side product **4l-C**.

Tertiary amides were the only successful substrate for the Heck reaction and R_2 groups methyl, methoxymethyl (MOM), and para-methoxybenzyl (PMB) were utilized. The methoxymethyl (MOM) protection of the amide nitrogen was deemed more likely to allow subsequent conversion of the tertiary amide to a secondary amide (vide infra), which potentially provides a critical hydrogen bond donor for interactions with target proteins and nucleic acids. The larger PMB group as another potentially cleavable group but also to determine if the nitrogen group might influence the enantioselectivity of the Heck reaction. It did, but unfortunately it resulted in a slight decrease in enantioselectivity (**Table 5**, entry 9). Tertiary amides are much more commonly used in intramolecular Heck reactions, although there are exceptions[41,42]. In our case, we believe the failure of secondary amides is the result of an intramolecular reaction: a six-member ring chelation between the amide oxygen and palladium after the oxidative addition, which creates a stable Pd complex resistant to catalysis. Circumstantial evidence for this intramolecular phenomenon was achieved by adding one equivalent of acetanilide, Ph-NHAc, to the entry 5 reaction (**Table 5**) and finding no difference in the outcome. Therefore, the presence of a secondary amide in the reaction has no effect, except when part of the actual substrate.

With a focus on elaborating the Heck substrate into potentially more viable drug molecules, the 1,3-diene products **4** were subjected to a variety of further transformations. Attempts at cleavage of the N-Me amide to afford a secondary amide proved unsuccessful under a selection of conditions, including $AlCl_3$[43,44], $Cu(acac)_2$/NFSI[45], and trimethylsilyl iodide (TMS-I). However, removal of the MOM amide protecting group was achieved with TMS-I[46], either as a reagent or generated in situ (**Table 6**). As expected, and confirmed by molecular modeling, the cis ring junction of the 1,3-diene Heck products **4** have a convex shape in sharp contrast with phenanthridinone's planar structure (**Figure 3**). We conducted two reactions to create analogs that mimic phenanthridinone's planarity, while retaining the quaternary center (R_1). Alkene isomerization of the 1,3-diene (**4e**) to a planar 1,4-diene (**6e**) was achieved under either basic (t-BuOK/t-BuOH) or transition metal catalyzed ($RuCl_3$) conditions (**Scheme 2**). Additionally, oxidation of the 1,3-diene **4a** with CuI (cat.)/t-BuOOH afforded the 2,5-cyclohexadienone **7a** (**Scheme 3**). Given the

recent renewed interest in covalent drugs[47-49], this potential conjugate addition substrate could prove a valuable structure.

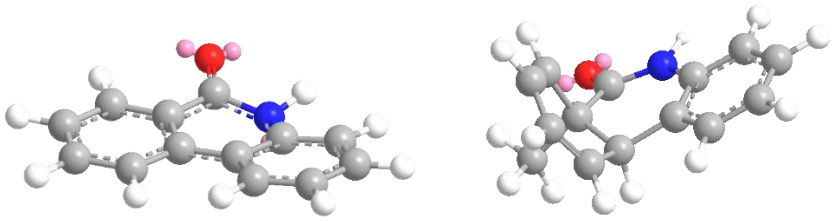
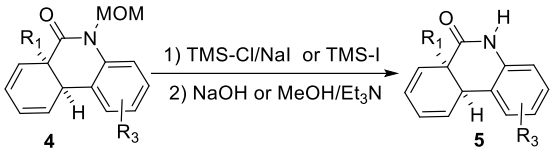
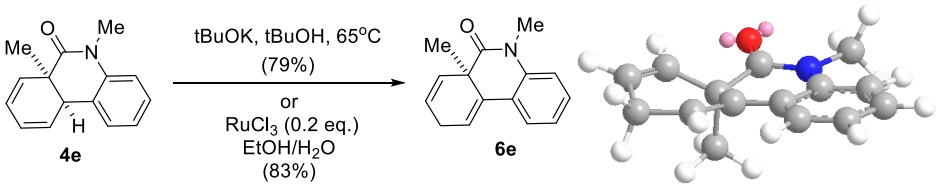


Figure 3. Minimized structures of phenanthridinone (left) versus 1,3-diene Heck product **5a**.

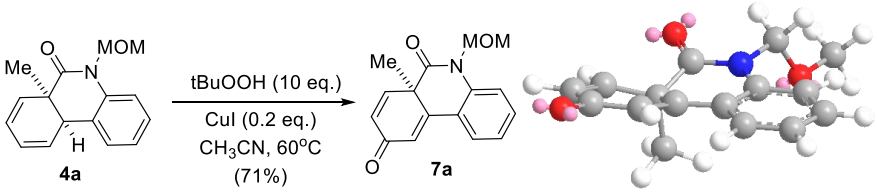
Table 6. MOM group deprotection



entry	R_1	R_3	yield (%)	compd
1	Me, 4a	H	81	5a
2	-CH_2Ph, 4s	H	58	5s



Scheme 2. Alkene isomerization



Scheme 3. Dienone synthesis

In conclusion, a new efficient enantioselective synthetic pathway to create phenanthridinone structures with a quaternary center has been achieved and represents the first example of such a transformation of the broadly bioactive phenanthridinone skeleton. The synthetic pathway involves a Birch reduction-alkylation, amide coupling and an enantioselective desymmetrizing intramolecular Heck reaction. A wide range of substrates were demonstrated to work in good yield and with good to very good enantioselectivity. Subsequent transformations of the resulting 1,3-diene Heck products illustrate the potential to transform these molecules into potential new drugs. Indeed, a variety of phenanthridinone

derivatives have already been synthesized with the methods described here and tested for cytotoxicity. Results of these biological studies will be reported in due course.

Experimental Section

General Procedures

All reactants and reagents were commercially available and were used without further purification unless otherwise indicated. Anhydrous tetrahydrofuran (THF) was obtained by distillation from benzophenone-sodium under argon. Copper(I) iodide was purified by boiling CuI with saturated aqueous KI or NaI for 30 minutes, diluting with H_2O, then sequentially washing with water (H_2O), ethanol (EtOH), ethyl acetate (EtOAc), diethyl ether (Et_2O), and pentane. The greyish-white solid was dried in vacuo for 24h at 110°C[50]. All reactions were carried out under an inert atmosphere of argon in flame-dried glassware unless otherwise indicated. Concentrated refers to the removal of solvent with a rotary evaporator at normal water aspirator pressure. Concentrated under high vacuum refers to removal of solvent with a direct-drive rotary vane vacuum pump. Thin layer chromatography (TLC) was performed using silica gel 60 Å precoated aluminum backed plates (0.25 mm thickness) with fluorescent indicator. Developed TLC plates were visualized with UV light (254 nm) and $KMnO_4$ spray. Flash column chromatography was conducted with the indicated solvent system using normal phase silica gel 60 Å, 230-400 mesh. Yields refer to chromatographically and spectroscopically pure (> 95%) compounds, except as otherwise indicated.

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in δ values (ppm) relative to an internal reference (0.05% v/v) of tetramethylsilane (TMS) for ^1H NMR or the solvent signal, chloroform ($CDCl_3$) or DMSO-d_6, for ^{13}C NMR. Peak splitting patterns in the ^1H NMR are reported as follows: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ddd, doublet of doublets of doublets; dt, doublet of triplets; dq, doublet of quartets; m, multiplet. ^{13}C NMR experiments were conducted with the attached proton test (APT) pulse sequence. ^{13}C multiplicities are reported as δ_u (up) for methyl and methine, and δ_d (down) for methylene and quaternary carbons.

GC-MS analyses were performed with an Agilent 6890 GC and a Hewlett-Packard 5973 EI-MS detector fitted with a 30 m x 0.25 mm column filled with crosslinked 5% PH ME siloxane (0.25 μm film thickness); gas pressure 7.63 psi He. Analysis of samples involved either heating from 70 to 250°C (10°C / min), then hold at 250°C for 5 min. (method A) or heating from 175 to 250°C (25°C/min), then hold at 250°C for 2 min. (method B). Melting points were measured on a Stanford Research Systems MPA160 melting point apparatus and are uncorrected. HPLC analysis was conducted using an Agilent 1100 fitted with a DAD at 254 nm using a CHIRACEL OD-H 4.6 mm x 250 mm, 5 μm column, run with the specified conditions. HRMS were collected at the University of Delaware using a Q-Exactive Orbitrap with an ESI source in positive mode or a Waters GCT Premier equipped with a LIFDI (liquid field desorption ionization). Optical rotations were conducted on a Perkin Elmer 341 polarimeter at Haverford College at 589 nm and 20.0°C.

Birch reduction/alkylation

General procedure

A flame dried 3-necked round bottom flask with a stir bar, connected to a Dewar condenser, under argon, was charged with benzoic acid (1.0 eq) which was dissolved in THF (0.43 mL/mmol) and cooled to -78˚C. Ammonia (7 mL/mmol) was distilled into the flask and lithium (4.0 eq) was added in small pieces until a dark blue color was maintained for 30 minutes. Isoprene was added dropwise to quench the excess

lithium and produce a bright yellow opaque solution. Alkylating agent (2.0 eq) was added slowly dropwise. When the addition was complete the reaction was maintained at -78˚C while the color faded to white/off-white over 1h. The reaction was then warmed to room temperature and the ammonia was allowed to evaporate. Once evaporated the reaction was quenched with water, and washed with diethyl ether. The aqueous layer was acidified with 6N HCl (until pH ~1), and then extracted with diethyl ether. The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated in vacuo.

1-Methylcyclohexa-2,5-diene-1-carboxylic acid (1a). Using the general procedure described above with benzoic acid (5.14 g, 42.1 mmol) and iodomethane (5.25 mL, 84.2 mmol) afforded **1a** (5.70 g, 41.3 mmol) in 98% yield as a white solid, mp = 31.2 – 33.4ºC. NMR spectral data were in accordance with the literature[51].

1-Ethylcyclohexa-2,5-diene-1-carboxylic acid (1b). Using the general procedure described above with benzoic acid (3.03 g, 24.6 mmol) and bromoethane (3.70 mL, 49.6 mmol) provided **1b** (3.74 g, 24.6 mmol) in 100% yield as a white solid. NMR spectral data were in accordance with the literature[52].

1-Isopropylcyclohexa-2,5-diene-1-carboxylic acid (1c). Using the general procedure described above with benzoic acid (5.33 g, 43.6 mmol) and 2-iodopropane (8.71 mL, 87.3 mmol) afforded isopropyl diene acid **1c** (7.07 g, 42.5 mmol) in 97% yield as a white solid, mp=74-76ºC.
^{1}H NMR (400 MHz, $CDCl_3$) δ 12.0-10.5 (br s, 1H), 5.96 (dt, *J* = 10.4, 3.3 Hz, 2H), 5.74 (dt, *J* = 10.6, 2.0 Hz, 2H), 2.74 – 2.55 (m, 2H), 2.13 (dt, *J* = 13.7, 6.9 Hz, 1H), 0.87 (d, *J* = 6.9 Hz, 6H).
^{13}C{^{1}H}[53] NMR (101 MHz, $CDCl_3$) δ_u 127.0, 125.3, 35.7, 17.4; δ_d 179.9, 51.8, 26.5.
GC (method A) *t*R = 6.684 min. **EI-MS** *m/z* (%): 123.0 (M-43+, 100), 119.0 (1), 115.0 (1), 105.0 (38), 96.0 (1), 91.0 (10), 79.0 (82), 74.0 (1), 65.0 (4), 55.0 (1), 51.1 (7).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{10}H_{15}O_2$ 167.1072; found 167.1063.

1-Allylcyclohexa-2,5-diene-1-carboxylic acid (1d). Using the general procedure described above with benzoic acid (1.00 g, 8.20 mmol) and allyl bromide (1.55 mL, 17.9 mmol) afforded **1d** (1.27 g, 7.8 mmol) in 95% yield as a pale yellow oil. NMR spectral data were in accordance with the literature[52,53].

1-Isobutylcyclohexa-2,5-diene-1-carboxylic acid (1e). Using the general procedure described above with benzoic acid (2.06 g, 16.9 mmol) and 1-iodo-2-methylpropane (3.60 mL, 31.3 mmol) afforded 1e (2.87 g, 15.9 mmol) in 94% yield as an orange oil. NMR spectral data were in accordance with the literature[54].

1-(Cyclopropylmethyl)cyclohexa-2,5-diene-1-carboxylic acid (1f). Using the general procedure described above with benzoic acid (2.00 g, 16.4 mmol) and (bromomethyl)cyclopropane (2.38 mL, 24.6 mmol) afforded **1f** (2.81 g, 15.8 mmol) in 96% yield as a yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93-5.77 (m, 4H), 2.67 (s, 2H), 1.67 (d, *J* = 6.9 Hz, 2H), 0.76 – 0.65 (m, 1H), 0.47 – 0.40 (m, 2H), 0.08 (q, *J* = 5.0 Hz, 2H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) d_u 127.2, 125.5, 6.5; d_d 181.2, 48.3, 45.3, 26.1, 4.5.
GC (method A) *t*R = 7.83 min. **EI-MS** *m/z* (%): 178.0 (M+, 9), 177.1 (39), 123.0 (36), 91.0 (47), 79.0 (78), 55.1 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{11}H_{15}O_2$ 179.1072; found 179.1061.

1-(But-3-en-1-yl)cyclohexa-2,5-diene-1-carboxylic acid (1g). Using the general procedure described above with benzoic acid (3.19 g, 26.1 mmol) and 4-bromobutene (5.29 mL, 52.2 mmol) provided **1g** (4.12 g, 23.1 mmol) in 89% yield as a dark yellow free flowing oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (dtd, 2H, *J* = 10.6, 3.4, 1.8 Hz), 5.86 – 5.71 (m, 3H), 5.00 (dq, 1H, *J* = 17.1, 1.7 Hz), 4.94 (dq, 1H, *J* = 10.2, 1.5 Hz), 2.66 (dtt, 2H, *J* = 4.3, 3.3, 2.1 Hz), 2.00 (dddd, 2H, *J* = 12.7, 6.4, 3.2, 1.6 Hz), 1.84 – 1.75 (m, 2H).

$^{13}C\{^1H\}$[53] NMR (101 MHz, $CDCl_3$) δ_u 138.1, 133.8, 130.2, 128.5, 126.5, 126.4; δ_d 181.0, 114.7, 47.6, 38.4, 28.6, 26.2.
GC (method A) *t*R = 7.67 min. **EI MS**, m/z: 177 (1), 160 (3), 133 (11), 123 (5), 115 (1), 105 (6), 91 (100), 79 (20), 65 (6), 55 (11).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{11}H_{15}O_2$ 179.1072; found 179.1062.

1-(Methoxymethyl)cyclohexa-2,5-diene-1-carboxylic acid (1h). Using the general procedure described above with benzoic acid (3.02 g, 24.76 mmol) and chloromethyl methyl ether (3.76 mL, 49.5 mmol) provided **1h** (3.74 g, 22.2 mmol) in 90% yield as a white solid. m.p.= 66.9-70.5˚C.
^1H NMR (400 MHz, $CDCl_3$) δ 6.01 – 5.93 (m, 2H), 5.84 (dt, 2H, *J* = 10.5, 2.0 Hz), 3.52 (s, 2H), 3.37 (s, 3H), 2.71 (m, 2H).
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ_u 127.2, 124.4, 59.5; δ_d 178.2, 78.7, 49.2, 26.3 ppm.
GC (method A) *t*R = 6.53 min. **EI MS**, m/z (%): 138 (5), 136 (5), 122 (15), 106 (100), 91 (47), 77 (42), 65 (9), 51 (10).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_9H_{13}O_3$ 169.0865; found 169.0853.

1-(Cyanomethyl)cyclohexa-2,5-diene-1-carboxylic acid (1i). Using the general procedure described above with benzoic acid (2.20 g, 18.0 mmol) and chloroacetonitrile (2.28 mL, 36.0 mmol) afforded **1i** (2.33 g, 14.3 mmol) in 80% yield as a tan solid, m.p. = 98.3-102.3˚C. Spectral data were in accordance with the literature[55].

1-(2-Ethoxy-2-oxoethyl)cyclohexa-2,5-diene-1-carboxylic acid (1j). Using the general procedure described above with benzoic acid (2.00 g, 16.4 mmol) and ethyl 2-chloroacetate (3.51 mL, 32.8 mmol) afforded **1j** (3.41 g, 16.2 mmol) in 99% yield as a pale yellow liquid that solidified to white crystals on cooling, m.p.=63.5-66ºC.
^1H NMR (400 MHz, $CDCl_3$) δ 11.47 (br s, 1H) 5.94 (dt, *J* = 10.1, 3.1 Hz, 2H), 5.82 (d, *J* = 10.4 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.74 (s, 2H), 2.71 – 2.66 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H).
$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ_u 126.9, 125.8, 14.1 d_d 179.9, 170.3, 60.7, 45.6, 44.3, 26.0.
GC (method A) *tR* = 9.84 min. **EI MS**, m/z (%): 165 (6, M-CO_2H), 137 (5), 119 (13), 105 (8), 91 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{11}H_{15}O_4$ 211.0970; found 211.0958.

[1,1'-Bi(cyclohexane)]-2,5-diene-1-carboxylic acid (1k). Using the general procedure described above with benzoic acid (3.09 g, 25.3 mmol) and iodocyclohexane (6.56 mL, 50.7 mmol) provided **1k** (5.00 g, 24.2 mmol) in 96% yield as an off-white solid, m.p.= 120.5-125.5˚C.
^1H NMR (400 MHz, $CDCl_3$) δ 5.93 (dtd, *J* = 10.6, 3.3, 1.6 Hz, 2H), 5.74 (ddt, 2H, *J* = 19.6, 10.6, 2.0 Hz), 2.62 (tdd, 2H, *J* = 5.4, 3.4, 2.1 Hz), 1.77 – 1.70 (m, 3H), 1.63 (d, 3H, *J* =12.6 Hz), 1.22 (qt, 2H, *J* = 12.9, 3.3 Hz), 1.12 – 0.95 (m, 3H).
$^{13}C\{^1H\}$ NMR (101 MHz, CDCl3) δ_u 126.7, 125.7, 45.9; δ_d 180.6, 51.8, 27.6, 26.6, 26.5, 26.3.
GC (method A) *tR* = 10.44 min. **EI MS**, m/z (%): 206 (1), 160 (4), 131 (1), 124 (100), 117 (6), 105 (8), 91 (8), 79 (18), 65 (2), 5 (20).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{13}H_{19}O_2$ 207.1385; found 207.1374.

1-Benzylcyclohexa-2,5-diene-1-carboxylic acid (1l). Using the general procedure described above with benzoic acid (2.33 g, 19.1 mmol) and benzyl chloride (4.38 mL, 38.1 mmol) afforded 1l (3.83 g, 17.9 mmol) in 94% yield as a white crystalline solid, m.p. = 71.9-75.0˚C. Spectral data were in accordance with a prior literature report[52].

1-(3-Cyanobenzyl)cyclohexa-2,5-diene-1-carboxylic acid (1m). Using the general procedure described above with benzoic acid (1.01 g, 8.24 mmol) and 3-cyanobenzyl chloride (1.87 g, 12.4 mmol) afforded **1m** (1.80 g, 7.52 mmol) in 92% yield as a white crystalline solid, m.p.= 142.4-144.1ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.43 (s, 1H), 7.41 – 7.32 (m, 2H), 5.89 (dt, *J* = 10.4, 3.3 Hz, 2H), 5.77 (dt, *J* = 10.4, 1.9 Hz, 2H), 3.05 (s, 2H), 2.61 – 2.49 (m, 1H), 2.31 – 2.26 (m, 1H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 135.2, 134.1, 130.4, 128.5, 127.5, 125.5; δ_d 179.1, 137.8, 119.0, 111.8, 48.8, 44.9, 25.9.
GC (method A) *tR* = 14.93 min. **EI MS**, m/z (%): 194 (15), 193 (100, M-CO_2H), 178 (5), 165 (22).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{15}H_{14}NO_2$ 240.1025; found 240.1019.

1-(Naphthalen-1-ylmethyl)cyclohexa-2,5-diene-1-carboxylic acid (1n). Using the general procedure described above with benzoic acid (2.28 g, 18.7 mmol) and 1-(chloromethyl)napthalene (5.60 mL, 37.4 mmol) provided **1n** (4.43 g, 16.8 mmol) in 90% yield as a light-yellow solid. m.p.=130.5-133.8ºC.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (ddd, 1H, *J* = 7.2, 2.8, 1.6 Hz), 7.82 (dd, 1H, *J* = 7.8, 1.8 Hz), 7.76 – 7.70 (m, 1H), 7.46 (tdt, 2H, *J* = 10.6, 6.8, 3.5 Hz), 7.39 – 7.34 (m, 2H), 5.87 (dt, 2H, *J* = 10.5, 1.9 Hz), 5.79 (dt, 2H, *J* = 10.3, 3.2 Hz), 3.56 (s, 2H), 2.54 (dd, 1H, *J* = 13.0, 1.8 Hz), 2.36 (dd, 1H, *J* = 13.1, 1.8 Hz).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 128.6, 128.6, 127.5, 126.8, 126.2, 125.5, 125.3, 125.1, 124.8; δ_d, 179.8, 133.7, 133.1, 132.7, 49.3, 41.7, 26.0.
GC (method A) *tR* = 13.44 min. **EI MS**, m/z (%): 218 (100), 202 (35), 189 (8), 163 (2), 152 (2), 141 (13), 115 (8), 108 (8), 91 (4), 65 (3).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{18}H_{17}O_2$ 265.1229; found 265.1214.

Benzamide synthesis general procedure:

In a round bottom flask with a stir bar, oxalyl chloride (2.2 eq) was dissolved in CH_2Cl_2 and a catalytic amount of DMF (1.4 μL/mmol) was added. The Birch product (1.0 mmol) was dissolved in DCM and added dropwise to the flask. The reaction was refluxed under argon for an hour until it turned deep yellow. Once completed, as judged by GC-MS analysis, the reaction was concentrated under vacuum to remove excess oxalyl chloride.

In a round bottom flask with a stir bar, purified 2-aminophenol or 2-(methylamino)phenol (1.5 eq) was dissolved in DCM and cooled to 0°C. Triethylamine (2.5 eq) was added dropwise followed shortly thereafter by the addition of the acid chloride in DCM. The mixture was allowed to warm to room temperature and react overnight. The reaction mixture was diluted with DCM and washed with saturated $NaHCO_3$, 1N HCl, brine and then dried with Na_2SO_4. The crude product was concentrated under vacuum and either purified by column chromatography or, if pure enough, taken on without further purification.

Triflation general procedure

A flame-dried flask with a stir bar was charged with benzamide phenol (1.0 eq) in DCM (2.5 mL/mmoL). Pyridine (2.0 eq) was added and the solution was stirred at -20˚C for 10 minutes. Tf_2O (3.0 eq) was added in a dropwise manner and the reaction was allowed to warm to room temperature. When determined to be complete by GC-MS and/or TLC, the reaction mixture was partitioned between 1N HCl and DCM. The organic layer was separated and washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude products were purified by column chromatography. For tertiary amides, NMR analyses were conducted in DMSO-d_6 at 100˚C to allow equilibration of the atropisomers that formed in the reaction.

2-(1-Methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (3a). Using the general procedure detailed above, diene acid **1a** (0.962g, 6.97 mmol) reacted with 2-aminophenol (1.35 g, 12.4 mmol) to afford 1.14 g (71% yield) of the amide intermediate. Triflation of 1.14 g (4.98 mmol) of the amide afforded crude product which was purified by column chromatography (silica, 9:1 hexanes:EtOAc) to afford pure **3a** (1.43 g, 3.96 mmol) as a yellow oil in 80% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.02 (br s, 1H), 7.40 – 7.31 (m, 1H), 7.28 (d, *J* = 1.3 Hz, 1H), 7.13 (ddd, *J* = 8.4, 7.5, 1.6 Hz, 1H), 6.00 (dt, *J* = 10.3, 3.4 Hz, 2H), 5.76 (dt, *J* = 10.4, 2.0 Hz, 2H), 2.90 – 2.71 (m, 2H), 1.41 (s, 3H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 129.0, 128.9, 126.6, 124.7, 123.0, 121.2 (d, $^5J_{C\text{-}F}$=1.0 Hz), 24.9; δ_d 173.1, 138.8, 131.0, 118.5 (q, $^1J_{C\text{-}F}$=322 Hz), 46.2, 25.9.
^{19}F NMR (376 MHz, $CDCl_3$) δ -73.24.
GC t_R= 1.97 min. **EI MS**, m/z (%): 361.1 (3, M+), 346.1 (3), 268.9 (21), 93.0 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{15}H_{15}NO_4F_3S$ 362.0674; found 362.0668.

4-Fluoro-2-(1-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (3b).
Using the general procedure detailed above, diene acid **1a** (1.21 g, 8.76 mmol) reacted with 4-fluoro-2-aminophenol (1.67 g, 13.1 mmol) to afford 2.14 g (99% yield) of the amide intermediate. Triflation of 2.14 g (8.66 mmol) of the amide afforded crude product which was purified by column chromatography (silica, 20:1 hexanes:EtOAc) to afford pure **3b** (2.71 g, 7.15 mmol) as a clear, colorless oil in 83% yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 10.5, 3.1 Hz, 1H), 8.08 (s, 1H), 7.23 (dd, *J* = 9.2, 5.0 Hz, 1H), 6.81 (ddd, *J* = 9.2, 7.2, 3.1 Hz, 1H), 6.01 (dt, *J* = 10.3, 3.4 Hz, 2H), 5.74 (dt, *J* = 10.4, 2.0 Hz, 2H), 2.81 (dtt, *J* = 5.5, 3.7, 2.2 Hz, 2H), 1.41 (s, 3H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 128.6, 126.9, 122.3 ($^3J_{C\text{-}F}$=10 Hz), 110.9 (d, $^2J_{C\text{-}F}$=24 Hz), 109.6 (d, $^2J_{C\text{-}F}$=30 Hz) 24.8; δ_d 173.1, 161.7 (d, $^1J_{C\text{-}F}$=249 Hz), 133.9, 132.6, 118.5 (q, $^1J_{C\text{-}F}$=321 Hz), 46.4, 25.8.
^{19}F NMR (376 MHz, $CDCl_3$) δ -73.17 (3H), -109.12 (1H).
GC (method B) t_R=1.83 min. **EI MS**, m/z (%): 379 (M+, 2), 364 (1), 287 (8), 154 (6), 126 (15), 93 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{15}H_{14}O_4NF_4S$ 380.0580; found 380.0565.

4-Methyl-2-(1-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (3c).
Using the general procedure detailed above, diene acid **1a** (0.945 g, 6.84 mmol) reacted with 2-amino-4-methylphenol (1.04 g, 8.46 mmol) to afford 1.36 g (84% yield) of the amide intermediate. Triflation of 1.36 g (5.63 mmol) of the amide afforded crude product which was purified by column chromatography (silica, 88:12 hexanes: EtOAc) to afford pure **3c** (1.91 g, 5.08 mmol) as an off-white solid in 74% yield, m.p.=39.9-42.2°C.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 1.9 Hz, 1H), 7.96 (s, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 6.96 – 6.89 (m, 1H), 6.00 (dt, *J* = 10.3, 3.4 Hz, 2H), 5.76 (dt, *J* = 10.4, 2.0 Hz, 2H), 2.84 – 2.76 (m, 2H), 2.36 (s, 3H), 1.41 (s, 3H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 128.9, 126.6, 125.3, 123.4, 120.8 (d, $^5J_{C\text{-}F}$=1.0 Hz), 24.9, 21.3. δ_d 173.2, 139.4, 136.8, 130.5, 118.5 (q, $^1J_{C\text{-}F}$=322 Hz), 46.2, 25.9.
^{19}F NMR (376 MHz, $CDCl_3$) δ -73.22.
GC (method B) t_R=2.23 min. **EI MS**, m/z (%): 375.2 (M+, 3), 360.1 (3), 283.1 (13), 150.0 (17), 122.1 (34), 93.1 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{16}H_{17}O_4NF_3S$ 376.0830; found 376.0822.

5-Chloro-2-(1-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (3d).
Using the general procedure detailed above, diene acid **1a** (0.945 g, 6.84 mmol) reacted with 2-amino-5-chlorophenol (1.21 g, 8.43 mmol) to afford 1.80 g (100% yield) of the amide intermediate. Triflation of 1.80 g (6.84 mmol) of the amide afforded crude product which was purified by column chromatography (silica, 88:12 hexanes: EtOAc) to afford pure **3d** (1.59 g, 4.04 mmol) as a brown solid in 59% yield, m.p.=35.3-38.4°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.9 Hz, 1H), 7.98 (s, 1H), 7.34 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.28 (d, *J* = 2.3 Hz, 1H), 6.00 (dt, *J* = 10.3, 3.4 Hz, 2H), 5.74 (dt, *J* = 10.4, 2.0 Hz, 2H), 2.80 (ddq, *J* = 5.5, 3.7, 2.1 Hz, 2H), 1.41 (s, 3H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 129.2, 128.7, 126.8, 123.5, 121.6 (d, $^5J_{C\text{-}F}$=1.0 Hz), 24.8; δ_d 173.1, 138.3, 129.8, 118.4 (q, $^1J_{C\text{-}F}$=322 Hz), 46.2, 25.8.
^{19}F NMR (376 MHz, $CDCl_3$) δ -73.06.
GC (method B) t_R=2.35 min. **EI MS**, m/z (%): 395.1 (M+, 1), 380.1 (1), 303.0 (8), 142.0 (9), 93.1 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calculated for $C_{15}H_{14}O_4NClF_3S$ 396.0284; found 396.0276.

2-(N,1-Dimethylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (3e). Using the general procedure detailed above, diene acid **1a** (2.82 g, 20.4 mmol) reacted with 2-(methylamino)phenol (3.01 g, 24.5 mmol) to afford 4.33 g (87% yield) of the amide intermediate. Triflation of 4.33 g (17.8 mmol) of the amide afforded crude product which was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford pure **3e** (4.29 g, 11.4 mmol) in 64% yield as an orange oil that crystalized on standing, m.p.=64-68ºC.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54 – 7.36 (m, 4H), 5.65 (d, *J* = 11.4 Hz, 4H), 3.25 (s, 3H), 2.47 (dd, *J* = 80, 24 Hz, 2H), 1.26 (s, 2H).
^{13}C{^{1}H} NMR (101 MHz, DMSO- d_6) δ_u 131.3, 129.8, 129.7, 129.6, 124.0, 39.6, 29.2; δ_d 173.3, 145.6, 137.9, 118.7 (q, $^1J_{C\text{-}F}$ = 322 Hz), 45.7, 25.9.
^{19}F NMR (376 MHz, DMSO-d_6) δ -73.64.
GC (method A) t_R =12.80 min.; (method B) t_R =2.05 min. **EI-MS** m/z (%): 375.1 (M+, 2), 360.1 (1), 284.0 (42), 252.9 (1), 218.0 (5), 149.0 (42), 134.0 (64), 93.0 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{16}H_{17}O_4NF_3S$ 376.0830; found 376.0814.

2-(1-Ethylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (3f). Using the general procedure detailed above, diene acid **1b** (0.760 g, 5.00 mmol) reacted with 2-aminophenol (0.720 g, 6.60 mmol) to afford 1.13 g (93% yield) of the amide intermediate. Triflation of 1.13 g (4.65 mmol) of the amide afforded crude product which was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford pure **3f** (1.39 g, 3.71 mmol) in 80% yield as a light orange oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.02 (s, 1H), 7.41 – 7.31 (m, 1H), 7.31 – 7.22 (m, 1H), 7.13 (ddd, *J* = 8.4, 7.5, 1.6 Hz, 1H), 6.10 (ddd, *J* = 8.6, 5.1, 2.5 Hz, 2H), 5.68 (dt, *J* = 10.4, 2.0 Hz, 2H), 2.91 – 2.61 (m, 2H), 1.87 (q, *J* = 7.5 Hz, 2H), 0.85 (t, *J* = 7.5 Hz, 3H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 129.0, 128.3, 127.2, 124.7, 123.3, 123.1, 121.18, 121.17, 120.1, 116.9, 8.7; δ_d 172.9, 138.9, 131.0, 118.6 (q, $^1J_{C\text{-}F}$=322 Hz) 50.7, 29.6, 26.2.
^{19}F NMR (376 MHz, $CDCl_3$) δ -73.26.
GC (method B) t_R =2.26 min. **EI-MS** m/z (%): 375.0 (M+, 5), 346.0 (8), 268.9 (20), 107.0 (69), 79.0 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{16}H_{17}O_4NF_3S$ 376.0830; found 376.0815.

2-(1-Ethyl-N-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (3g). Using the general procedure detailed above, diene acid **1b** (1.20 g, 7.89 mmol) reacted with 2-(methylamino)phenol (1.37 g, 11.1 mmol) to afford 2.57 g (>100% yield) of the amide intermediate. Triflation of 2.57 g (7.89 mmol) of the amide afforded crude product which was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford pure **3g** (2.10 g, 5.40 mmol) in 68% yield as an orange-brown oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (d, *J* = 10.1 Hz, 3H), 7.37 (d, *J* = 7.5 Hz, 1H), 5.65 (t, *J* = 9.0 Hz, 2H), 5.48 (d, *J* = 9.9 Hz, 2H), 3.22 (s, 3H), 2.51 (d, *J* = 24 Hz, 1H), 2.33 (d, *J* = 24 Hz, 1H), 1.71 (q, *J* = 7.4 Hz, 2H), 0.73 (t, *J* = 7.4 Hz, 3H).
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ_u 131.5, 129.8, 129.6, 127.9, 125.4, 121.6, 39.6, 8.3; δ_d 173.3, 145.7, 138.0, 118.7 (q, $^1J_{C\text{-}F}$ = 322 Hz), 50.0, 33.0, 26.3.
^{19}F NMR (376 MHz, DMSO-d_6) δ -73.61.
GC (method A) t_R =13.01 min.; (method B) t_R =2.33 min. **EI-MS** m/z (%): 389.0 (M+, 1), 360.0 (3), 284.0 (45), 107.1 (47), 79.1 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{17}H_{19}O_4NF_3S$ 390.987; found 390.0968.

2-(1-Isopropyl-N-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (3h). Using the general procedure detailed above, diene acid **1c** (1.30 g, 7.79 mmol) reacted with 2-(methylamino)phenol (1.60 g, 13.0 mmol) to afford 1.90 g (90% yield) of the amide intermediate. Triflation of 1.54 g (5.67 mmol) of the amide afforded crude product which was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford pure **3h** (2.05 g, 5.09 mmol) in 90% yield as an red-brown oil.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 – 7.35 (m, 4H), 5.59 (s, 2H), 5.41 (d, *J* = 10.2 Hz, 2H), 3.25 (s, 3H), 2.37 (tt, *J* = 14.0, 7.9 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 6H).
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ_u 131.5, 130.0, 129.7, 126.7, 125.8, 121.7, 39.9, 35.9, 17.7; δ_d 173.7, 145.7, 137.9, 118.6 (q, $^1J_{C\text{-}F}$ = 321 Hz), 53.8, 26.6.
^{19}F NMR (376 MHz, DMSO-d_6) δ -73.65.
GC (method A) t_R =13.93 min.; (method B) t_R =2.46 min. **EI-MS** m/z (%): 403.2 (M+, 5), 360.1 (52), 284.1 (71), 105.1 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{18}H_{21}O_4NF_3S$ 404.1143; found 404.1129.

2-(1-isopropyl-N-(4-methoxybenzyl)cyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (**3i**). Using the general procedure detailed above, diene acid **1c** (0.448 g, 1.87 mmol) reacted with 2-((4-methoxybenzyl)amino)phenol[56] (0.654g, 2.85 mmol) to afford 0.426 g (60% yield) of the amide intermediate. Triflation of 0.394 g (1.04 mmol) of the amide afforded crude product which was purified by column chromatography (silica, 9:1 hexanes: EtOAc) to afford pure **3i** (0.374 g, 0.734 mmol) in 71% yield as a light-yellow oil.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.47 (td, *J* = 7.9, 7.5, 1.7 Hz, 1H), 7.39 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.23 (td, *J* = 7.7, 1.4 Hz, 1H), 7.12 – 7.04 (m, 2H), 6.91 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.83 (d, *J* = 7.9 Hz, 2H), 5.47 (s, 2H), 5.38 (d, *J* = 10.0 Hz, 2H), 3.74 (s, 3H), 2.51 (s, 2H), 2.50-2.40 (m, 1H), 2.37 (d, *J* = 24 Hz, 1H), 2.13 (d, *J* = 24 Hz, 1H), 0.77 (d, *J* = 8 Hz, 6H).
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ_u 133.3, 130.5, 130.3, 128.5, 125.7, 125.6, 121.1, 114.4, 55.7, 36.1, 17.6; δ_d 173.7, 159.4, 146.1, 134.8, 129.4, 118.6 (q, $^1J_{C\text{-}F}$ = 321 Hz), 54.3, 54.0, 26.5.
^{19}F NMR (376 MHz, DMSO-d_6) δ -73.69.
GC (method A) t_R =19.51 min. **EI-MS** m/z (%): 509.2 (M+, 1), 389.0 (5), 121.0 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{25}H_{27}O_5NF_3S$ 510.1562; found 510.1540.

2-(1-Allyl-N-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (3j). Using the general procedure detailed above, diene acid **1d** (1.45 g, 9.29 mmol) reacted with 2-(methylamino)phenol (1.38 g, 11.2 mmol) to afford 1.53 g (61% yield) of the amide intermediate after column chromatography (silica, 4:1 hexanes: EtOAc). Triflation of 1.09 g (4.05 mmol) of the amide afforded crude product which was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to

afford pure **3j** (1.31 g, 3.27 mmol) in 81% yield as a clear colorless oil that became a white crystalline solid on cooling, m.p.=35.0-36.5ºC.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 – 7.37 (m, 4H), 5.74 – 5.59 (m, 3H), 5.54 (d, *J* = 10.4 Hz, 2H), 5.02 – 4.92 (m, 2H), 3.24 (s, 3H), 2.54 – 2.30 (m, 4H).
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ_u 134.8, 131.4, 129.9, 129.7, 127.9, 125.2, 121.7 (d, $^5J_{C-F}$=1.0 Hz), 39.7; δ_d 172.8, 145.6, 118.6 (q, $^1J_{C-F=}$322 Hz), 117.6, 117.0, 49.4, 45.2, 26.2.
^{19}F NMR (376 MHz, DMSO-d_6) δ -73.62.
GC (method A) t_R =13.53 min.; (method B) t_R =2.50 min. **EI-MS** m/z (%): 401.1 (M+, 2), 360.0 (30), 284.0 (40), 19.0 (65), 105.0 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{18}H_{19}O_4NF_3S$ 402.0987; found 402.0982.

2-(1-Isobutyl-N-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (3k). Using the general procedure detailed above, diene acid **1e** (1.07 g, 5.93 mmol) reacted with 2-(methylamino)phenol (1.18 g, 5.93 mmol) to afford 1.68 g (99% yield) of the amide intermediate. Triflation of 1.11 g (3.88 mmol) of the amide afforded crude product which was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford pure **3k** (0.972 g, 2.33 mmol) in 60% yield as a light-yellow oil.
^{1}H NMR (400 MHz, DMSO-d_6): 7.50-7.36 (m, 4H), 5.55 (dd, *J* = 30.4, 10.0 Hz, 4H), 3.18 (s, 3H), 2.51 (d, 1H, *J* = 24.0 Hz), 2.30 (d, 1H, *J* = 24.0 Hz), 1.59 (m, 3H), 0.83 (d, 6H, *J* = 6.4 Hz) ppm.
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ_u 131.5, 129.9, 129.7, 128.8, 124.8, 121.7, 39.8, 24.9, 24.2; δ_d 173.5, 145.6, 138.0, 118.6 (d, $^1J_{C-F}$= 322 Hz), 49.9, 49.7, 26.2.
^{19}F NMR (376 MHz, DMSO-d_6) δ -73.62.
GC (method A) t_R= 13.89 min. **EI MS**, m/z (%): 417 (1), 360 (4), 284 (58), 253 (1), 218 (4), 150 (6), 134 (70), 91 (41), 57 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{19}H_{23}O_4NF_3S$ 418.1300; found 418.1291.

2-(1-(Cyclopropylmethyl)-N-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (3l). Using the general procedure detailed above, diene acid **1f** (1.02 g, 5.73 mmol) reacted with 2-(methylamino)phenol (0.85 g, 6.88 mmol) to afford 1.58 g (98% yield) of the amide intermediate. Triflation of 0.914 g (3.23 mmol) of the amide afforded crude product which was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford pure **3l** (0.905 g, 2.18 mmol) in 68% yield as a pale-yellow oil.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 – 7.43 (m, 3H), 7.43 – 7.29 (m, 1H), 5.61 (s, 4H), 3.22 (s, 3H), 2.66 – 2.19 (m, 4H), 1.64 (d, *J* = 6.6 Hz, 2H), 0.74 – 0.55 (m, 1H), 0.34 (ddd, *J* = 8.1, 5.7, 4.0 Hz, 2H), 0.09 – -0.06 (m, 2H).
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ_u 131.4, 129.9, 129.7, 128.78, 124.7, 121.7, 120.2, 117.0, 39.7, 6.7; δ_d 173.3, 145.7, 118.6 (d, $^1J_{C-F}$= 322 Hz), 50.3, 46.1, 26.2, 5.1.
^{19}F NMR (376 MHz, DMSO-d_6) δ -73.63.
GC (method B) t_R= 2.94 min. **EI MS**, m/z (%): 415 (M+, 11), 414.1 (24), 360.0 (37), 284.0 (68), 149.0 (55), 105.0 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{19}H_{21}O_4NF_3S$ 416.1143; found 416.1131.

2-(1-(But-3-en-1-yl)-N-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (3m). Using the general procedure detailed above, diene acid **1g** (1.16 g, 6.51 mmol) reacted with 2-(methylamino)phenol (1.04 g, 8.46 mmol) to afford 1.82 g (99% yield) of the amide intermediate. Triflation of 0.927 g (3.27 mmol) of the amide afforded crude product which was purified by column

chromatography (silica, 4:1 hexanes: EtOAc) to afford pure **3m** (1.09 g, 2.62 mmol) in 80% yield as an orange solid, m.p. = 51.7-52.9˚C.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 – 7.45 (m, 3H), 7.40 (d, 1H, *J* = 7.2 Hz), 5.80 (ddt, 1H, *J* = 17.0, 10.4, 6.4 Hz), 5.68 (d, 2H, *J* = 9.8 Hz), 5.54 (d, 2H, *J* = 10.3 Hz), 4.96 (dd, 1H, *J* = 17.2, 1.6 Hz), 4.90 (dd, 1H, *J* = 10.2, 1.2 Hz), 3.24 (s, 3H), 2.55 (d, 1H, *J* = 23.3 Hz), 2.36 (d, 1H, *J* = 23.3 Hz), 1.96 – 1.84 (m, 2H), 1.80 – 1.76 (m, 2H) ppm.
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ_u 139.4, 131.4, 129.9, 129.7, 127.8, 125.5, 121.7, 39.6; δ_d 170.1, 145.6, 137.9, 118.6 (q, $^1J_{C\text{-}F}$ = 322 Hz), 114.5, 49.4, 39.7, 28.3, 26.2.
^{19}F NMR (376 MHz, DMSO-d_6) δ -73.60.
GC (method A) t_R = 14.49 min. **EI MS**, m/z (%): 414 (1, M-1+), 360 (3), 324 (3), 284 (25) 266 (1), 218 (3), 149 (22), 122 (16), 91 (100), 55 (9).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{19}H_{21}O_4NF_3S$ 416.1143; found 416.1130.

2-(1-(Methoxymethyl)-N-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (3n). Using the general procedure detailed above, diene acid **1h** (1.16 g, 6.51 mmol) reacted with 2-(methylamino)phenol (2.07 g, 12.3 mmol) to afford 3.04 g (90% yield) of the amide intermediate. Triflation of 2.14 g (7.85 mmol) of the amide afforded crude product which was purified by column chromatography (silica, 7:3 hexanes: EtOAc) to afford pure **3n** (1.66 g, 4.09 mmol) in 52% yield as a white solid, m.p. = 55.7-58.0˚C.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 – 7.39 (m, 3H), 7.37 (d, 1H, *J* = 7.9 Hz), 5.61 (d, 2H, *J* = 8.0 Hz), 5.54 (d, 2H, *J* = 8.0 Hz), 3.46 (s, 2H), 3.20 (s, 3H), 3.18 (s, 3H), 2.49 (d, 1H, *J* = 23.6 Hz), 2.30 (d, 1H, *J* = 23.6 Hz).
^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ_u 131.6, 130.0, 129.6, 126.3, 126.0, 121.7, 59.3, 39.6; δ_d 171.9, 145.7, 137.4, 118.6 (d, $^1J_{C\text{-}F}$ = 326 Hz), 79.7, 51.0, 26.3.
^{19}F NMR (376 MHz, DMSO-d_6) δ -73.58.
GC (method A) t_R= 13.42 min. **EI MS**, m/z (%): 405 (10), 375 (8), 360 (39), 314 (3), 284 (11), 268 (6), 242 (1), 227 (5), 210 (22), 182 (1), 166 (1), 149 (89), 122 (25), 105 (100), 77 (24), 51 (4).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{17}H_{19}O_5NF_3S$ 406.0936; found 406.0920.

2-(1-(Cyanomethyl)cyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (3o). Using the general procedure detailed above, diene acid **1i** (2.14 g, 13.1 mmol) reacted with 2-aminophenol (2.29 g, 21.0 mmol) to afford 2.81 g (84% yield) of the amide intermediate. Triflation of 2.23 g (8.77 mmol) of the amide afforded crude product which was purified by column chromatography (silica, 7:3 hexanes: EtOAc) to afford pure **3o** (1.94 g, 5.03 mmol) in 57% yield as a light-yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, 1H, *J* = 8.3, 1.6 Hz), 7.94 (s, 1H), 7.39 (ddd, 1H, *J* = 8.8, 7.4, 1.5 Hz), 7.28 (dd, 1H, *J* = 8.3, 1.5 Hz), 7.19 (ddd, 1H, *J* = 8.4, 7.4, 1.6 Hz), 6.28 (dt, *J* = 10.4, 3.4 Hz, 2H), 5.79 (dt, 2H, *J* = 10.4, 2.1 Hz), 2.95 – 2.90 (m, 2H), 2.89 (s, 2H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 130.8, 129.2, 125.6, 124.2, 123.3, 121.5; δ_d 169.9, 139.0, 130.3, 118.5 (q, $^1J_{C\text{-}F}$=322 Hz), 117.3, 48.0, 26.9, 26.0.
^{19}F NMR (376 MHz, $CDCl_3$) δ -73.17.
GC (method A) t_R= 14.91 min. **EI MS**, m/z (%): 386 (0.1, M+), 269 (2), 241 (3), 196 (2), 135 (15), 119 (31), 92 (100), 78 (14), 52 (7).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{16}H_{14}O_4N_2F_3S$ 387.0626; found 387.0608.

2-(1-(cyanomethyl)-N-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (3p). Using the general procedure detailed above, diene acid **1i** (1.01 g, 6.18 mmol) reacted with 2-(methylamino)phenol (0.989 g, 8.03 mmol) to afford 1.59 g (96% yield) of the amide intermediate.

Triflation of 0.983 g (3.66 mmol) of the amide afforded crude product which was purified by column chromatography (silica, 7:3 hexanes: EtOAc) to afford pure **3p** (0.943 g, 2.36 mmol) in 64% yield as a light yellow oil.
^{1}H NMR (400 MHz, DMSO-d^{6}): 7.48 (dtt, *J* = 13.0, 8.3, 4.3 Hz, 3H), 7.42-7.36 (m, 1H), 5.85 (s, 2H), 5.66 (d, 2H, *J* =9.4 Hz), 3.23 (s, 3H), 2.77 (s, 2H), 2.62 (d, 1H, J=22.9 Hz), 2.35 (d, 1H, *J* = 22.2 Hz) ppm.
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6): d_u 131.5, 130.3, 129.8, 128.1, 125.1, 121.8, 39.8; d_d 170.7, 145.4, 133.8, 118.6 (q, $^{1}J_{C\text{-}F}$=321 Hz), 118.1, 47.7, 30.1, 26.2.
^{19}F NMR (376 MHz, DMSO-d^{6}) δ -73.49.
GC (method A) t_R= 15.16 min. **EI MS**, m/z (%): 400 (1), 360 (1), 331 (1), 282 (11), 218 (19), 149 (100), 134 (40).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{17}H_{16}O_4N_2F_3S$ 401.0783; found 401.0774.

Ethyl 2-(1-(methyl(2-(((trifluoromethyl)sulfonyl)oxy)phenyl)carbamoyl)cyclohexa-2,5-dien-1-yl)acetate (3q). Using the general procedure detailed above, diene acid **1j** (0.525 g, 2.49 mmol) reacted with 2-(methylamino)phenol (0.420 g, 3.41 mmol) to afford 1.09 g (>100% yield) of the amide intermediate. Triflation of 0.788 g (2.49 mmol) of the amide afforded crude product which was purified by column chromatography (silica, 2:1 heptanes: EtOAc) to afford pure **3q** (0.940 g, 2.10 mmol) in 84% yield as an orange oil.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54-7.44 (m, 3H), 7.40 (d, *J* = 7.9 Hz, 1H), 5.75 (d, *J* = 9.6 Hz, 2H), 5.63 (d, *J* = 10.8 Hz, 2H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.22 (s, 3H), 2.61 (s, 2H), 2.58 – 2.20 (m, 2H), 1.17 (t, *J* = 7.1 Hz, 3H).
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ_u 131.7, 130.1, 129.6, 127.5, 125.4, 125.0, 121.7, 46.5, 39.9, 14.4. δ_d 172.2, 170.3, 145.7, 118.6 (q, $^{1}J_{C\text{-}F}$=322 Hz), 59.9, 26.0.
^{19}F NMR (376 MHz, DMSO-d_6) δ -73.54.
GC (method B) t_R= 3.22 min. **EI MS**, m/z (%): 402.1 (12, M-OEt+), 360.1 (3), 331 (1), 284.0 (6), 218.1 (8), 165.1 (46), 149.1 (46), 91.1 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{19}H_{21}O_6NF_3S$ 448.1042; found 448.1041.

2-(N-Methyl-[1,1'-bi(cyclohexane)]-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (3r). Using the general procedure detailed above, diene acid **1k** (1.48 g, 7.16 mmol) reacted with 2-(methylamino)phenol (1.15 g, 9.31 mmol) to afford 2.16 g (97% yield) of the amide intermediate. Triflation of 1.38 g (4.42 mmol) of the amide afforded crude product which was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford pure **3r** (1.10 g, 2.10 mmol) in 56% yield as a white solid, m.p. = 45.2-48.3˚C.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50-7.35 (m, 4H), 5.55 (d, 2H, *J* = 8.5 Hz), 5.38 (d, 2H, *J* = 9.8 Hz), 3.16 (s, 3H), 2.41 (d, 1H, *J* = 23.6 Hz), 2.26 (d, 1H, *J* = 22.7 Hz), 1.98 (t, 1H, *J* = 12.0 Hz), 1.62 (dd, 5H, *J* = 32.7, 11.1 Hz), 1.18 (q, 2H, *J* =25.5, 12.8 Hz), 1.00 (q, 1H, *J* = 25.2, 12.4 Hz), 0.86 (q, 2H, *J* = 24.4, 12.0 Hz).
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ_u 131.5, 130.0, 129.6, 127.2, 125.5, 121.7 (d, $^{5}J_{C\text{-}F}$=1 Hz), 46.9, 40.0; δ_d 173.6, 145.7, 137.9, 118.6 (d, $^{1}J_{C\text{-}F}$ = 322 Hz), 53.8, 27.7, 26.9, 26.7, 26.5.
^{19}F NMR (376 MHz, DMSO-d_6) δ -73.65.
GC (method A) t_R= 17.24 min. **EI MS**, m/z (%): 443 (3) 360 (77), 284 (89), 227 (5), 210 (5), 160 (38), 122 (27), 105 (71), 83 (100), 55 (37).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{21}H_{25}O_4NF_3S$ 444.1456; found 444.1458.

1-Benzyl-N-(2-hydroxyphenyl)cyclohexa-2,5-diene-1-carboxamide (3s). Using the general procedure detailed above, diene acid **1l** (2.35 g, 11.0 mmol) reacted with 2-aminophenol (1.92 g, 17.6 mmol) to afford 3.31 g (99% yield) of the amide intermediate. Triflation of 2.74 g (8.98 mmol) of the amide afforded crude product which was purified by column chromatography (silica, 9:1 hexanes: EtOAc) to afford pure **3s** (2.64 g, 6.04 mmol) in 67% yield as a light-yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.97 (s, 1H), 7.42 – 7.33 (m, 1H), 7.26 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.24 – 7.19 (m, 2H), 7.19 – 7.15 (m, 3H), 7.15 – 7.10 (m, 1H), 5.99 (dt, *J* = 10.4, 3.3 Hz, 2H), 5.78 (dt, *J* = 10.4, 2.0 Hz, 2H), 3.19 (s, 2H), 2.76 – 2.63 (m, 1H), 2.51 (dtt, *J* = 23.5, 3.6, 1.9 Hz, 1H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 130.7, 129.0, 128.2, 127.8, 127.1, 126.3, 124.9, 123.2, 121.3 (d, $^{5}J_{C\text{-}F}$ = 1 Hz); δ_d 172.4, 139.0, 137.2, 130.8, 118.4 (q, $^{1}J_{C\text{-}F}$ = 321 Hz), 51.2, 43.5, 26.0.
^{19}F NMR (376 MHz, $CDCl_3$) δ -73.30.
GC (method A) t_R= 17.27 min. **EI MS**, m/z (%): 437 (9), 346 (28), 270 (2), 213 (7), 196 (19), 168 (17), 135 (15), 108 (7), 91 (100), 65 (7).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{21}H_{19}O_4NF_3S$ 438.0987; found 438.0986.

2-(1-Benzyl-N-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (3t). Using the general procedure detailed above, diene acid **1l** (2.01 g, 9.37 mmol) reacted with 2-(methylamino)phenol (1.85 g, 15.0 mmol) to afford 3.17 g (>100% yield) of the amide intermediate. Triflation of 2.31 g (7.22 mmol) of the amide afforded crude product which was purified by column chromatography (silica, 1% Et_3N in 4:1 hexanes: EtOAc) to afford pure **3t** (2.74 g, 6.04 mmol) in 84% yield as a yellow oil.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.47 – 7.32 (m, 4H), 7.17 – 7.10 (m, 3H), 7.05 (dd, 2H, *J* = 7.6, 1.8 Hz), 5.55-5.46 (m, 4H), 3.20 (s, 3H), 3.01 (s, 2H), 2.14 (d, 1H, *J* = 23.2 Hz), 1.97 (d, 1H, *J* = 23.2 Hz).
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ_u 131.4, 130.0, 129.6, 127.9, 127.6, 126.2, 125.4, 121.7, 40.0; δ_d 173.1, 145.6, 137.7, 118.6 (d, $^{1}J_{C\text{-}F}$=322 Hz), 50.9, 46.5, 39.9, 25.9.
^{19}F NMR (376 MHz, DMSO-d_6) δ -73.61.
GC (method A) t_R= 17.82 min. **EI MS**, m/z (%): 451 (1), 360 (30), 284 (14), 227 (6), 210 (45), 168 (14), 149 (38), 122 (10), 105 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{22}H_{21}O_4NF_3S$ 452.1143; found 452.1141.

2-(1-(3-Cyanobenzyl)-N-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate, 3u. Using the general procedure detailed above, diene acid **1m** (0.513 g, 2.15 mmol) reacted with 2-(methylamino)phenol (0.391 g, 3.17 mmol) to afford 0.700 g (97% yield) of the amide intermediate. Triflation of 0.693 g (2.01 mmol) of the amide afforded crude product which was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford pure **3u** (0.672 g, 1.41 mmol) in 70% yield as a colorless oil.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60-7.30 (m, 8H), 5.58 (s, 4H), 3.25 (s, 3H), 3.10 (s, 2H), 2.23-2.07 (m, 1H), 2.02-1.88 (m, 1H).
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ_u 136.5, 134.9, 131.4, 130.1, 130.0, 129.7, 127.9, 128.7, 127.3, 126.1, 121.7, 40.0; δ_d 172.7, 145.5, 139.5, 137.6, 120.2, 118.6 (d, $^{1}J_{C\text{-}F}$=322 Hz), 111.0 50.8, 45.4, 39.8, 25.9.
^{19}F NMR (376 MHz, DMSO-d_6) δ -73.60.
GC (method A) t_R= 21.03 min. (method B) t_R= 2.16 min. EI MS, m/z (%): 360 (70, M-(3-CN-Bn)+), 284 (24), 194 (44), 149 (75), 116 (100), 105 (100).
HRMS (LIFDI oa-TOF) m/z: $[M]^+$ calcd for $C_{23}H_{19}O_4N_2F_3S$ 476.1018; found 476.1030.

2-(N-Methyl-1-(naphthalen-1-ylmethyl)cyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate, 3v. Using the general procedure detailed above, diene acid **1n** (1.04 g, 3.93 mmol) reacted with 2-(methylamino)phenol (0.629 g, 5.11 mmol) to afford 1.48 g (>100% yield) of the amide intermediate. Triflation of 0.963 g (2.61 mmol) of the amide afforded crude product which was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford pure **3v** (0.811 g, 1.62 mmol) in 62% yield as a yellow viscous oil.
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 – 7.96 (m, 1H), 7.80 (dd, 1H, *J* = 6.7, 4.0 Hz), 7.70 (d, 1H, *J* = 7.4 Hz), 7.46 – 7.28 (m, 8H), 5.59 (d, 2H, *J* = 9.9 Hz), 5.33 (d, 4H, *J* = 9.9 Hz), 3.57 (s, 2H), 3.22 (s, 3H), 2.06 (d, 1H, *J* = 23.2 Hz), 1.80 (dp, 1H, *J* = 23.3, 2.4 Hz).
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ_u 131.4, 130.0, 129.6, 129.4, 128.7, 128.0, 127.1, 125.5, 125.4, 125.3, 125.2, 125.1, 121.7 (d, $^{5}J_{C\text{-}F}$ = 1 Hz), 40.0; δ_d 173.4, 145.7, 137.8, 134.1, 133.8, 133.7, 118.7 (q, $^{1}J_{C\text{-}F}$ = 322 Hz), 51.5, 41.5, 25.8.
^{19}F NMR (376 MHz, DMSO-d_6) δ -73.58.
GC (method A) t_R= 17.72 min. (Note: product behaves poorly on GC-MS.) **EI MS**, m/z (%): 210 (45), 141 (33), 115 (11), 105 (100), 77 (32).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{26}H_{23}O_4NF_3S$ 502.1300; found 502.1288.

General procedure and data for methoxymethyl (MOM) group protection of amide N

General procedure A:
Secondary amide (1.0 eq.) was dissolved in THF (0.07 mL/mmol amide) and cooled to 0ºC. LiHMDS (1.0 M in hexanes, 1.2 eq.) was added dropwise, and the solution stirred for 10 min. Chloro- or bromomethyl methyl ether (5.0 eq.) was added dropwise to the reaction solution and the reaction was left stirring while slowly warming to r.t. After 3 h, the reaction was quenched with a few drops (5 drops/mmol base) of saturated NH_4Cl and stirred for 5 min. The liquid was decanted from the white precipitate and the precipitate was washed with diethyl ether and EtOAc. The combined organic layer and washes were dried with Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography.

General procedure B:
NaH (60% dispersion in mineral oil, 1.1 eq) was added to a flame dried round bottom flask under argon, suspended in THF (5 mL/mmol amide) and the resulting mixture cooled to 0ºC. The secondary amide substrate (1.0 eq.) was added dropwise as a THF solution (1 mL/mmol amide) to the NaH/THF mixture, and the reaction stirred for 1h. Chloromethyl methyl ether (2.0 eq.) was added dropwise and the reaction was stirred at 0ºC for several minutes. The ice bath was removed, and the mixture stirred overnight at r.t. The reaction was quenched with saturated NH_4Cl, diluted with EtOAc, washed with H_2O (six times), dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography.

2-(N-(Methoxymethyl)-1-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (3a-I). Using general procedure A, secondary amide **3a** (0.32 g, 0.89 mmol) was alkylated with chloromethyl methyl ether (0.135 mL, 1.78 mmol, 2.0 eq.). The crude product was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford **3a-I** (0.31 g, 0.77 mmol) in 86% yield as a light-yellow oil.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 – 7.26 (m, 4H), 5.60 (dd, *J* = 24.7, 8.8 Hz, 4H), 4.89 (s, 2H), 3.22 (s, 3H), 2.64 – 2.17 (m, 2H), 1.24 (s, 3H).
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ_u 132.8, 130.3, 129.8, 129.1, 123.9, 121.3 (d, $^{5}J_{C\text{-}F}$ = 1 Hz), 56.2, 29.3; δ_d 174.3, 146.0, 134.8, 118.6, (q, $^{1}J_{C\text{-}F}$ = 322 Hz), 81.1, 46.2, 25.8.

^{19}F NMR (376 MHz, DMSO-d_6) δ -73.68.
GC (method B) t_R= 2.28 min. **EI MS**, m/z (%): 405.2 (0.1, M+), 373.1 (8), 314.1 (8), 282.0 (9), 253.0 (41), 120.1 (45), 93.1 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{16}H_{18}O_2N$ 256.1338; found 256.1330.

4-Fluoro-2-(N-(methoxymethyl)-1-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (3b-I). Using general procedure A, secondary amide **3b** (0.655 g, 1.73 mmol) was alkylated with chloromethyl methyl ether (1.40 mL, 18.4 mmol, 10 eq.). The crude product was purified by column chromatography (silica, 20:1 hexanes: EtOAc) to afford **3b-I** (0.600 g, 1.42 mmol) in 82% yield as a clear, colorless oil, along with 0.080 g (12%) recovered starting material, **3b**.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (dd, J = 8.6, 4.8 Hz, 1H), 7.38 – 7.24 (m, 2H), 5.69 – 5.55 (m, 4H), 4.89 (s, 2H), 3.20 (s, 3H), 2.65 – 2.22 (m, 4H), 1.23 (s, 3H).
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ_u 129.7, 124.0, 123.0 (d, $^3J_{C\text{-}F}$=10.1 Hz), 120.2, 119.4 (d, $^2J_{C\text{-}F}$=25.3 Hz), 117.0 (d, $^2J_{C\text{-}F}$=24.2 Hz), 56.3, 29.2; δ_d 174.2, 160.9 (d, $^1J_{C\text{-}F}$ = 248 Hz), 159.6, 142.4, 136.6 (d, $^3J_{C\text{-}F}$=11.1 Hz), 118.6 (q, $^1J_{C\text{-}F}$ = 321 Hz), 80.9, 46.2, 25.8.
^{19}F NMR (376 MHz, DMSO-d_6) δ -73.51, -111.94 (m).
GC (method B) t_R= 2.04 min. **EI MS**, m/z (%): 423.1 (1, M+), 391.1 (2), 332.1 (5), 300.0 (6), 271.0 (20), 138.0 (31), 93.1 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{17}H_{18}O_5NF_4S$ 424.0842; found 424.0830.

2-(N-Methoxymethyl)-1-methylcyclohexa-2,5-diene-1-carboxamido)-4-methylphenyl trifluoromethanesulfonate (**3c-I**). Using general procedure A, secondary amide **3c** (0.724 g, 1.93 mmol) was alkylated with chloromethyl methyl ether (0.800 mL, 9.65 mmol, 5 eq.). The crude product was purified by column chromatography (silica, 10:1 hexanes: EtOAc) to afford **3c-I** (0.539 g, 1.28 mmol) in 67% yield as a clear, colorless oil.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.30 – 7.20 (m, 3H), 5.65 – 5.50 (m, 4H), 4.90 (br s, 2H), 3.22 (s, 3H), 2.55 – 2.45 (m, 2H), 2.32 (s, 3H), 2.32-2.20 (m, 2H), 1.23 (s, 3H).
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ_u 133.1, 130.5, 129.8, 123.7, 120.9 (d, $^5J_{C\text{-}F}$=1 Hz), 56.3, 29.3, 20.6; δ_d 174.3, 144.0, 139.1, 134.4, 118.60 (q, $^1J_{C\text{-}F}$=322 Hz), 81.0, 46.2, 25.8.
^{19}F NMR (376 MHz, DMSO-d_6) δ -73.72.
GC (method B) t_R= 2.44 min. **EI MS**, m/z (%): 388 (1, M-OCH_3+), 387 (3), 328 (2), 296 (4), 267 (30). 178 (52), 134 (72), 93 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{18}H_{21}O_5NF_3S$ 420.1093; found 420.1082.

5-Chloro-2-(N-(methoxymethyl)-1-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (**3d-I)**.). Using general procedure A, secondary amide **3d** (1.034 g, 2.61 mmol) was alkylated with chloromethyl methyl ether (0.992 mL, 13.1 mmol, 5 eq.) to afford **3d-I** (0.790 g, 1.80 mmol) in 69% yield as a white solid, m.p.=62.9-67.2ºC.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53 (s, 2H), 7.45 (s, 1H), 5.63 (s, 4H), 4.88 (br s, 2H), 3.21 (s, 3H), 2.64 – 2.52 (m, 1H), 2.41-2.30 (m, 1H), 1.24 (s, 3H).
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ_u 133.9, 129.7, 129.4, 124.2, 121.5, 56.3, 29.2, δ_d 174.2, 145.9, 134.1, 133.8, 118.5 (q, $^1J_{C\text{-}F}$=322 Hz), 80.9, 46.1, 25.8.
^{19}F NMR (376 MHz, DMSO-d_6) δ -73.38.
GC (method B) t_R= 2.54 min. **EI MS**, m/z (%): 407 (2, M-32+), 316 (3), 287 (25), 154 (27), 93 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{17}H_{18}O_5NClF_3S$440.0546; found 440.0543.

2-(1-Ethyl-N-(methoxymethyl)cyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (3f-I). Using general procedure A, secondary amide **3f** (0.627 g, 1.67 mmol) was alkylated with chloromethyl methyl ether. The crude product was purified by column chromatography (silica, 8:1 hexanes: EtOAc) to afford **3f-I** (0.600 g, 1.43 mmol) in 86% yield as a clear, colorless oil, along with 0.31 g (5%) recovered starting material, **3f**.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 – 7.30 (m, 4H), 5.74 – 5.59 (m, 2H), 5.51 (d, *J* = 10.5 Hz, 2H), 4.92 (s, 2H), 3.26 (s, 3H), 2.54-2.49 (m, 2H), 1.72 (q, *J* = 7.4 Hz, 2H), 0.74 (t, *J* = 7.4 Hz, 3H).
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ_u 132.9, 130.3, 129.1, 127.9, 125.4, 121.3, 56.4, 8.3; δ_d 174.2, 146.0, 134.9, 81.0, 33.1, 26.2.
^{19}F NMR (376 MHz, DMSO-d_6) δ -73.66.
GC (method B) t_R= 2.54 min. **EI MS**, m/z (%): 387.1 (7, M-OCH_3+), 314.0 (11), 282.0 (17), 253.0 (55), 107.0 (62), 79.0 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{18}H_{21}O_5NF_3S$ 420.1093; found 420.1077.

2-(1-(cyanomethyl)-N-(methoxymethyl)cyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (3o-I). Using general procedure B, secondary amide **3o** (1.52 g, 3.94 mmol) was alkylated with chloromethyl methyl ether. The crude product was purified by column chromatography (silica, 7:3 hexanes: EtOAc) to afford **3o-I** (1.02 g, 2.37 mmol) in 60% yield as a cloudy yellow oil.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 – 7.39 (m, 4H), 5.81 (s, 2H), 5.67 (d, 2H, *J* = 9.8 Hz), 4.88 (s, 2H), 3.24 (s, 3H), 2.79 (s, 2H), 2.60 (d, 1H, *J* = 23.4 Hz), 2.30 (d, 1H, *J* = 23.5 Hz).
^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ_u 133.1, 130.8, 129.2, 127.9, 125.3, 121.4, 118.6 (d, *J* = 322 Hz), 117.9, 56.5; δ_d 171.8, 145.9, 133.9, 118.6 (q, $^{1}J_{C-F}$ = 322 Hz), 81.2, 48.2, 30.1, 26.2.
^{19}F NMR (376 MHz, DMSO-d_6) δ -73.55 (s).
GC (method A) t_R= 15.70 min. **EI MS**, m/z (%): 399.1 (1, M-OCH_3+), 270 (1), 253 (38), 196 (1), 164 (13), 149 (1), 134 (15), 117 (73), 91 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{18}H_{18}O_5N_2F_3S$ 431.0889; found 431.0869.

2-(1-Benzyl-N-(methoxymethyl)cyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (3s-I). Using general procedure B, secondary amide **3s** (1.55 g, 3.53 mmol) was alkylated with chloromethyl methyl ether. The crude product was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford **3s-I** (0.956 g, 1.99 mmol) in 56% yield as a white amorphous solid.
^{1}H NMR (400 MHz, DMSO) δ 7.52 – 7.46 (m, 1H), 7.41 – 7.29 (m, 3H), 7.13 (td, 3H, *J* = 5.8, 2.8 Hz), 7.06 – 7.04 (m, 2H), 5.55 (d, 2H, *J* = 10.0 Hz), 5.46 (d, 2H, *J* = 10.0 Hz), 4.90 (s, 1H), 3.23 (s, 3H), 3.02 (s, 2H), 2.11 (d, 1H, *J* = 23.5 Hz), 1.95 (d, 1H, *J* = 23.0 Hz).
^{13}C{^{1}H} NMR (101 MHz, DMSO) δ_u 132.9, 131.5, 130.4, 129.1, 128.0, 127.6, 126.3, 125.4, 121.3, 56.5; δ_d 174.0, 146.0, 137.5, 81.2, 46.5, 25.8.
^{19}F NMR (376 MHz, DMSO) δ -73.63 (s).
GC (method A) t_R= 17.81 min. **EI MS**, m/z (%): 481 (0.1, M+), 449 (3), 389 (2), 358 (7), 314 (2), 282 (5), 253 (15), 196 (3), 168 (23), 134 (1), 105 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{23}H_{23}O_5NF_3S$ 482.1249; found 482.1224.

Mizoroki-Heck General Procedure and Data
A flame dried vial or round-bottom flask under argon was charged with $Pd(OAc)_2$ (0.1-0.2 eq) and (R or racemic) BINAP (0.12-0.24 eq) and DMF (0.05-0.15 mmol triflate/mL) was added. The resulting mixture was stirred for 30-60 minutes to foster active catalyst formation. Cy_2NMe (2.0 eq) was added, and the

resulting solution was stirred for 5-10 minutes. Finally, the aryl triflate diene (1.0 eq) in DMF (~0.1 mmol triflate/mL) was added, followed by LiOAc (2.0 eq.). The vial or flask was stirred at 80˚C in a pie reactor or oil bath until the reaction was determined to be complete by GC-MS analysis, typically 24-48 hrs. GC-MS analysis was optimal because the reactant and the product have quite similar thin-layer chromatographic properties. On completion the reaction mixture was filtered through a silica gel/celite plug to remove Pd catalyst and the plug washed with EtOAc. The resulting organic solution was either subjected to aqueous washes and purified by column chromatography or concentrated in vacuo and immediately subjected to column purification. When aqueous washes were used, the EtOAc organic solution was washed with 1 N HCl (twice) and brine, dried with Na_2SO_4, filtered and concentrated.

(6aR,10aR)-5-(Methoxymethyl)-6a-methyl-6a,10a-dihydrophenanthridin-6(5H)-one (4a). Using the general procedure detailed above with diene triflate **3a-I** (0.173 g, 0.426 mmol) was subjected to the Heck reaction with 10 mol% Pd/15 mol% (R)-BINAP. The crude product was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford **4a** (0.079 g, 0.309 mmol) with an enantiomeric ratio of 11:1 (83% e.e.) in 72% yield as a white solid, m.p.= 134.8-137.2ºC.
$[\alpha]_D^{20}$ = +312 (c 0.74, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 4H), 7.21 (s, 1H), 7.12 (d, *J* = 8.5 Hz, 1H), 6.13 (dd, *J* = 9.4, 5.1 Hz, 1H), 6.07 – 5.98 (m, 1H), 5.94 – 5.87 (m, 1H), 5.63 – 5.56 (m, 2H), 5.10 (d, *J* = 10.7 Hz, 1H), 3.50 (s, 1H), 3.34 (s, 3H), 1.28 (s, 3H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 131.6, 128.8, 128.7, 128.0, 125.3, 124.5, 124.0, 115.6, 56.1, 44.5, 23.3. δ_d 174.8, 137.6, 126.3, 73.7, 40.9.
GC (method B) t_R= 2.13 min. **EI MS**, m/z (%): 255 (37, M+), 223 (24), 210 (100), 192 (97).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{16}H_{18}O_2N$ 256.1338; found 256.1330.
HPLC: Chiralcel OD-H, n-hexane/isopropanol=97.5:2.5, flow rate=1 mL/min, I=254 nm, t_{R1} =9.67 min. (major), t_{R2} = 14.48 min. (minor).

(6aR,10aR)-3-Fluoro-5-(methoxymethyl)-6a-methyl-6a,10a-dihydrophenanthridin-6(5H)-one (4b). Using the general procedure detailed above with diene triflate **3b-I** (0.110 g, 0.260 mmol) was subjected to Heck reaction with 10 mol% Pd/12 mol% (R)-BINAP. The crude product was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford **4a** (0.050 g, 0.18 mmol) with an enantiomeric ratio of 11:1 (83% e.e.) in 70% yield as a white solid, m.p.=85-86ºC.
$[\alpha]_D^{20}$ = +183 (c 0.31, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (dd, *J* = 8.3, 6.2 Hz, 1H), 6.97 (dd, *J* = 10.8, 2.4 Hz, 1H), 6.73 (td, *J* = 8.2, 2.5 Hz, 1H), 6.05 (dd, *J* = 9.3, 5.1 Hz, 1H), 5.99 – 5.92 (m, 1H), 5.81 (d, *J* = 9.3 Hz, 1H), 5.49 (dd, *J* = 10.0, 4.0 Hz, 2H), 4.98 (d, *J* = 10.7 Hz, 1H), 3.41 (s, 1H), 3.26 (s, 3H), 1.21 (s, 3H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 131.4, 129.7 (d, $^3J_{C\text{-}F}$=9.1 Hz), 128.7 (d, $^1J_{C\text{-}F}$=245 Hz), 125.5, 124.6, 110.4 (d, $^2J_{C\text{-}F}$=21 Hz), 103.6 (d, $^2J_{C\text{-}F}$=27 Hz), 56.1, 43.8, 23.2; δ_d 174.6, 162.5 (d, $^1J_{C\text{-}F}$=245 Hz) 161.3, 139.0 (d, $^3J_{C\text{-}F}$=11 Hz), 139.0, 121.89, 121.86, 73.9, 40.9.
GC (method B) t_R= 2.07 min. **EI MS**, m/z (%): 273 (28, M+), 241 (29), 228 (81), 210 (100).
^{19}F NMR (376 MHz, DMSO-d_6) δ -113.40, -113.42, -113.43, -113.44, -113.45, -113.47.
HRMS (ESI-Orbitrap) m/z; $[M+H]^+$ calcd for $C_{16}H_{17}ON_2F$ 274.1243; found 274.1232.
HPLC: Chiralcel OD-H, n-hexane/isopropanol=97.5:2.5, flow rate=1 mL/min, I=254 nm, t_{R1} =8.52 min. (major), t_{R2} = 11.34 min. (minor).

(6aR,10aR)-5-(Methoxymethyl)-3,6a-dimethyl-6a,10a-dihydrophenanthridin-6(5H)-one (4c). Using the general procedure detailed above with diene triflate **3a-I** (0.553 g, 1.32 mmol) was subjected to Heck reaction with 10 mol% Pd/12 mol% (R)-BINAP. The crude product was purified by column

chromatography (silica, 15:1 hexanes: EtOAc) to afford **4a** (0.239 g, 0.89 mmol) with an enantiomeric ratio of 16:1 (88% e.e.) in 67% yield as a white solid, m.p.=119.2-124.4ºC.
$[\alpha]_D^{20}$ = +262 (*c* 0.87, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 7.5 Hz, 2H), 6.92 (d, *J* = 8.3 Hz, 1H), 6.11 (dd, *J* = 9.4, 5.1 Hz, 1H), 6.05 – 5.97 (m, 1H), 5.89 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.62 – 5.54 (m, 2H), 5.10 (d, *J* = 10.7 Hz, 1H), 3.45 (s, 1H), 3.35 (s, 3H), 2.37 (s, 3H), 1.28 (s, 3H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 131.6, 129.2, 128.5, 125.2, 124.7, 124.5, 116.2, 56.2, 44.1, 23.3, 21.5. δ_d 175.0, 137.9, 137.5, 123.3, 73.7, 40.9.
GC (method B) t_R= 2.36 min. **EI MS**, m/z (%): 269 (40, M+), 254 (10), 237 (25), 224 (100), 206 (75).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{17}H_{20}O_2N$ 270.1494; found 270.1485.
HPLC: Chiralcel OD-H, n-hexane/isopropanol=97.5:2.5, flow rate=1 mL/min, I=254 nm, t_{R1} =7.89 min. (major), t_{R2} = 10.08 min. (minor).

(6aR,10aR)-2-Chloro-5-(methoxymethyl)-6a-methyl-6a,10a-dihydrophenanthridin-6(5H)-one (4d). Using the general procedure detailed above with diene triflate **3d-I** (0.140 g, 0.32 mmol) was subjected to Heck reaction with 10 mol% Pd/12 mol% (R)-BINAP. The crude product was purified by column chromatography (silica, 85:15 hexanes: EtOAc) to afford **4d** (0.050 g, 0.17 mmol) with an enantiomeric ratio of 6:1 (70% e.e.) in 54% yield as a yellow oil.
$[\alpha]_D^{20}$ = +141 (*c* 0.4, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.18 (m, 3H), 6.16 – 6.01 (m, 2H), 5.88 (dd, *J* = 12, 1.0 Hz, 1H), 5.61 – 5.51 (m, 2H), 5.08 (d, *J* = 10.7 Hz, 1H), 3.46 (t, *J* = 2.9 Hz, 1H), 3.33 (s, 3H), 1.29 (s, 3H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 131.4, 128.5, 127.9, 127.8, 125.8, 124.7, 117.0, 56.1, 44.2, 23.1; δ_d 174.5, 136.3, 129.0, 128.2, 73.8, 40.8, 29.7.
GC (method B) t_R= 2.72 min. **EI MS**, m/z (%): 291 (12, M+, Cl^{37} isotope), 289 (36, M+, Cl^{35} isotope), 244 (100), 226 (65).
HRMS (LIFDI oa-TOF) m/z: $[M]^+$ calcd for $C_{16}H_{16}O_2NCl$ 289.0870 found 289.0879.
HPLC: Chiralcel OD-H, n-hexane/isopropanol=97.5:2.5, flow rate=1 mL/min, I=254 nm, t_{R1} =12.88 min. (major), t_{R2} = 15.72 min. (minor).

(6aR,10aR)-5,6a-Dimethyl-6a,10a-dihydrophenanthridin-6(5H)-one (4e). Using the general procedure detailed above with diene triflate **3a-I** (2.05 g, 5.46 mmol) was subjected to Heck reaction with 10 mol% Pd/12 mol% (R)-BINAP. The crude product was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford **4a** (0.890 g, 3.96 mmol) with an enantiomeric ratio of 12:1 (85% e.e.) in 72% yield as a yellow oil.
$[\alpha]_D^{20}$ = +146 (*c* 0.95, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (td, *J* = 8.0, 1.5 Hz, 1H), 7.23 (d, *J* = 7.4 Hz, 1H), 7.08 (td, *J* = 7.4, 0.9 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.14 – 5.99 (m, 2H), 5.93 – 5.86 (m, 1H), 5.58 (dd, *J* = 9.3, 2.8 Hz, 1H), 3.48 (t, *J* = 2.7 Hz, 1H), 3.35 (s, 3H), 1.23 (s, 3H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 131.8, 128.6, 127.8, 125.2, 124.2, 123.3, 123.3, 114.3, 44.3, 29.9, 23.3. δ_d 173.4, 139.0, 126.6, 40.8.
GC (method B) t_R= 1.92 min. **EI MS**, m/z (%): 225 (50, M+), 224 (74), 210 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{15}H_{16}ON$ 226.1232; found 226.1222.
HPLC: Chiralcel OD-H, n-hexane/isopropanol=97.5:2.5, flow rate=1 mL/min, I=254 nm, t_{R1} =10.70 min. (major), t_{R2} = 12.02 min. (minor).

(6aR,10aR)-6a-Ethyl-5-(methoxymethyl)-6a,10a-dihydrophenanthridin-6(5H)-one (4f). Using the general procedure detailed above with diene triflate **3f-I** (0.160 g, 0.382 mmol) was subjected to Heck

reaction with 10 mol% Pd/12 mol% (R)-BINAP. The crude product was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford **4f** (0.092 g, 0.34 mmol) with an enantiomeric ratio of 12:1 (85% e.e.) in 90% yield as a colorless oil.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +157 (*c* 0.35, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.18 (m, 3H), 7.11 (dd, *J* = 7.0, 1.5 Hz, 1H), 6.18 (dd, *J* = 9.5, 5.1 Hz, 1H), 6.04 – 5.98 (m, 1H), 5.95 (d, *J* = 9.5 Hz, 1H), 5.63 (d, *J* = 10.7 Hz, 1H), 5.55 (dd, *J* = 9.3, 2.3 Hz, 1H), 5.05 (d, *J* = 10.7 Hz, 1H), 3.67 (s, 1H), 3.34 (s, 3H), 1.72 – 1.64 (m, 1H), 1.52 (dd, *J* = 13.9, 7.3 Hz, 1H), 0.91 (t, *J* = 7.5 Hz, 3H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 129.8, 128.9, 128.6, 128.0, 125.2, 125.2, 124.0, 115.5, 56.2, 41.3, 9.1; δ_d 174.4, 137.8, 126.2, 73.8, 45.2, 27.9.
GC (method B) t_R= 2.39 min. **EI MS**, m/z (%): 269 (34, M+), 237 (27), 224 (100), 208 (95), 196 (68), 178 (93).
HRMS (LIFDI oa-TOF) m/z: $[M]^+$ calcd for $C_{17}H_{19}O_2N$ 269.1416; found 269.1415.
HPLC: Chiralcel OD-H, n-hexane/isopropanol=97.5:2.5, flow rate=1 mL/min, I=254 nm, t_{R1} =10.71 min. (major), t_{R2} = 20.55 min. (minor).

(6aR,10aR)-6a-ethyl-5-methyl-6a,10a-dihydrophenanthridin-6(5H)-one (4g). Using the general procedure detailed above with diene triflate **3g** (0.092 g, 0.24 mmol) was subjected to Heck reaction with 10 mol% Pd/12 mol% (R)-BINAP. The crude product was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford **4g** (0.049 g, 0.21 mmol) with an enantiomeric ratio of 10:1 (82% e.e.) in 86% yield as a pale-yellow oil.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +198 (*c* 0.75, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 1H), 7.26 – 7.16 (m, 1H), 7.13 – 7.02 (m, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 6.15 (dd, *J* = 9.5, 5.1 Hz, 1H), 6.03-5.97 (m, 1H), 5.93 (d , *J* = 8.0 Hz, 1H), 5.54 (dd, *J* = 9.3, 2.5 Hz, 1H), 3.66 (s, 1H), 3.34 (s, 3H), 1.63 (dd, *J* = 13.8, 7.4 Hz, 1H), 1.45 (dd, *J* = 13.9, 7.3 Hz, 1H), 0.87 (t, *J* = 7.5 Hz, 3H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 130.1, 128.7, 128.6, 127.8, 125.1, 124.9, 123.3, 114.2, 41.0, 29.8, 9.2; δ_d 173.1, 139.1, 126.5, 45.1, 28.0.
GC (method B) t_R= 2.17 min. **EI MS**, m/z (%): 239 (22, M+), 238 (27), 210 (100).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{16}H_{18}ON$ 240.1388; found 240.1379.
HPLC: Chiralcel OD-H, n-hexane/isopropanol=99.0:1.0, flow rate=1 mL/min, I=254 nm, t_{R1} =13.72 min. (major), t_{R2} = 16.35 min. (minor).

(6aR,9S,10aR)-6a-ethyl-5-methyl-6-oxo-5,6,6a,9,10,10a-hexahydrophenanthridin-9-yl acetate (4g-OAc). Using the general procedure detailed above with diene triflate **3g** was subjected to Heck reaction with 10 mol% Pd/12 mol% (R)-BINAP. The allylic acetate was isolated by column chromatography (silica, 4:1 hexanes: EtOAc) to afford **4g-OAc**.
^{1}H NMR (400 MHz, $CDCl_3$) 7.28 (ddd, *J* = 7.7, 5.5, 1.6 Hz, 1H), 7.21 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 6.26 (d, *J* = 10.0 Hz, 1H), 6.02 (dd, *J* = 10.1, 5.0 Hz, 1H), 5.21 (td, *J* = 4.7, 1.9 Hz, 1H), 3.35 (s, 3H), 3.06 (dd, *J* = 12.8, 4.0 Hz, 1H), 2.11 (s, 3H), 2.00 – 1.81 (m, 2H), 1.64 (dt, *J* = 14.8, 7.4 Hz, 1H), 1.46 (dq, *J* = 14.5, 7.5 Hz, 1H), 0.92 – 0.83 (t, *J* = 8 Hz, 3H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 135.6, 128.7, 127.8, 125.2, 123.5, 114.5, 65.4, 36.0, 33.1, 29.6, 21.4, 8.1; δ_d 172.3, 170.5, 138.8, 127.4, 46.4, 33.1, 28.4.
GC (method B) t_R= 3.10 min. **EI MS**, m/z (%): 299 (10, M+), 256 (4), 238 (8), 210 (100).

(6aR,10aR)-6a-isopropyl-5-methyl-6a,10a-dihydrophenanthridin-6(5H)-one (4h). Using the general procedure detailed above with diene triflate **3h** (0.091 g, 0.23 mmol) was subjected to Heck reaction with

15 mol% Pd/18 mol% (R)-BINAP for 21 hrs. The crude product was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford **4h** (0.047 g, 0.19 mmol) with an enantiomeric ratio of 7:1 (75% e.e.) in 82% yield as a clear, colorless oil.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +270 (*c* 0.5, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (td, *J* = 8.0, 1.6 Hz, 1H), 7.20 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.07 (td, *J* = 7.4, 1.0 Hz, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 6.20 (dd, *J* = 9.5, 5.0 Hz, 1H), 6.04 – 5.94 (m, 2H), 5.54 – 5.45 (m, 1H), 3.80 (s, 1H), 3.36 (s, 3H), 1.79 – 1.66 (m, 1H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 129.2, 128.5, 127.8, 127.2, 125.39, 125.38, 125.2, 123.3, 114.2, 41.1, 29.9, 29.8, 18.5, 18.0; δ_d 172.6, 139.4, 126.9, 48.5.
GC (method A) t_R= 13.46 min. **EI MS**, m/z (%): 253 (14, M+), 210 (100), 195 (24).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{17}H_{20}ON$ 254.1545; found 254.1541.
HPLC: Chiralcel OD-H, n-hexane/isopropanol=97.5:2.5, flow rate=1 mL/min, I=254 nm, t_{R1} =9.21 min. (major), t_{R2} = 11.02 min. (minor).

(6aR,10aR)-6a-isopropyl-5-(4-methoxybenzyl)-6a,10a-dihydrophenanthridin-6(5H)-one (4i). Using the general procedure detailed above with diene triflate **3i** (0.080 g, 0.16 mmol) was subjected to Heck reaction with 1o mol% Pd/15 mol% (R)-BINAP for 21 hrs. The crude product was purified by column chromatography (silica, 85:15 hexanes: EtOAc) to afford **4i** (0.023 g, 0.064 mmol) with an enantiomeric ratio of 5:1 (66% e.e.) in 41% yield as a clear, colorless oil.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +206 (*c* 0.6, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.10 (m, 4H), 7.01 (t, J = 7.3 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 6.80 (d, J = 8.5 Hz, 2H), 6.24 (dd, J = 9.6, 5.1 Hz, 1H), 6.11 – 5.99 (m, 2H), 5.54 (dd, J = 9.3, 2.3 Hz, 1H), 5.19 (d, J = 16.0 Hz, 1H), 5.03 (d, J = 15.9 Hz, 1H), 3.83 (s, 1H), 3.75 (s, 3H), 1.89-1.78 (m, 1H), 0.98 (d, J = 6.9 Hz, 3H), 0.86 (d, J = 6.8 Hz, 4H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 129.2, 128.6, 127.9, 127.7, 127.0, 125.8, 125.5, 123.4, 115.2, 114.0, 55.2, 41.5, 29.4, 18.6, 17.8.; δ_d 172.8, 158.6, 138.6, 129.3, 48.7, 45.8.
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{24}H_{26}O_2N$ 360.1964; found 360.1958.
HPLC: Chiralcel OD-H, n-hexane/isopropanol=97.5:2.5, flow rate=1 mL/min, I=254 nm, t_{R1} =14.62 min. (minor), t_{R2} = 16.72 min. (major).

(6aR,10aR)-6a-Allyl-5-methyl-6a,10a-dihydrophenanthridin-6(5H)-one (4j). Using the general procedure detailed above with diene triflate **3j** (0.065 g, 0.16 mmol) was subjected to the Heck reaction conditions with 15 mol% Pd/20 mol% (R)-BINAP for 21 hrs. The crude product was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford **4j** (0.041 g, 0.16 mmol) with an enantiomeric ratio of 10:1 (82% e.e.) in 100% yield as a yellow oily solid. Note that the compound slowly decomposes to N-methyl-phenanthridinone with loss of propene.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +184 (*c* 0.5, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 1H), 7.19 (d, *J* = 6.6 Hz, 1H), 7.08 (t, *J* = 7.2 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.13 (dd, *J* = 9.4, 5.1 Hz, 1H), 5.99 (dt, *J* = 8.2, 3.7 Hz, 1H), 5.92 (d, *J* = 9.4 Hz, 1H), 5.80 – 5.65 (m, 1H), 5.57 (dd, *J* = 12, 1.0 Hz, 1H), 5.09 (d, *J* = 10.0 Hz, 1H), 4.91 (d, *J* = 17.1 Hz, 1H), 3.71 (s, 1H), 3.36 (s, 3H), 2.39 (dd, *J* = 13.6, 6.1 Hz, 1H), 2.18 (dd, *J* = 13.7, 8.6 Hz, 1H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 133.6, 130.0, 128.63, 128.59, 127.8, 124.9, 123.4, 114.2, 41.0, 29.9. δ_d 172.4, 139.1, 126.0, 118.6, 44.7, 39.5.
GC (method B) t_R= 2.35 min. **EI MS**, m/z (%): 251 (22, M+), 210 (100), 195 (48).
HRMS (ESI-Orbitrap) m/z; $[M+H]^+$ calcd for $C_{17}H_{18}ON$ 252.1388; found 252.1388.

HPLC: Chiralcel OD-H, n-hexane/isopropanol=97.5:2.5, flow rate=1 mL/min, I=254 nm, t_{R1} =9.96 min. (major), t_{R2} = 10.74 min. (minor).

6a-Isobutyl-5-methyl-6a,10a-dihydrophenanthridin-6(5H)-one (4k). Using the general procedure detailed above with diene triflate **3k** (0.111 g, 0.270 mmol) was subjected to the Heck reaction conditions with 20 mol% Pd/24 mol% (R)-BINAP. The crude product was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford **4k** (0.059 g, 0.22 mmol) with an enantiomeric ratio of 7:1 (75% e.e.) in 82% yield as a light-yellow opaque oil.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +285 (*c* 1.33, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (td, *J* = 8.0, 1.6 Hz, 1H), 7.20 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.08 (td, *J* = 7.4, 1.0 Hz, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 6.12 (dd, *J* = 9.3, 5.2 Hz, 1H), 5.99 (tdd, *J* = 9.4, 4.7, 2.0 Hz, 2H), 5.53 (dd, *J* = 9.3, 2.5 Hz, 1H), 3.67 (s, 1H), 3.34 (s, 3H), 1.83 (qd, *J* = 6.7, 4.7 Hz, 1H), 1.42 (qd, *J* = 14.0, 5.9 Hz, 2H), 0.84 (dd, *J* = 14.5, 6.7 Hz, 6H).
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ_u 131.7, 128.6, 128.5, 127.8, 125.1, 124.0, 123.3, 114.2, 41.9, 29.8, 24.7, 24.4, 23.8; δ_d 173.1, 139.1, 126.7, 44.7, 43.8.
GC (method A) t_R= 13.31 min. **EI MS**, m/z (%): 267 (17, M+), 266 (25), 250 (1), 224 (10), 210 (100), 195 (17).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{18}H_{22}ON$ 268.1701; found 268.1692.
HPLC: Chiralcel OD-H, n-hexane/isopropanol=97.5:2.5, flow rate=1 mL/min, I=254 nm, t_{R1} =7.30 min. (major), t_{R2} = 8.00 min. (minor).

(6aR,10aR)-6a-(Cyclopropylmethyl)-5-methyl-6a,10a-dihydrophenanthridin-6(5H)-one (4l). Using the general procedure detailed above with diene triflate **3l** (0.058 g, 0.14 mmol) was subjected to the Heck reaction conditions with 10 mol% Pd/12 mol% (R)-BINAP. The crude product was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford **4l** (0.024 g, 0.091 mmol) with an enantiomeric ratio of 9:1 (80% e.e.) in 65% yield as a white crystalline solid, m.p.=92.5-95.5°C.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +123 (*c* 0.6, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (td, *J* = 7.4, 1.1 Hz, 1H), 7.23 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.07 (td, *J* = 7.4, 1.1 Hz, 1H), 6.96 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.15 (dd, *J* = 9.5, 5.0 Hz, 1H), 6.07 – 5.98 (m, 2H), 5.56 (dt, *J* = 9.4, 1.7 Hz, 1H), 3.93 (t, *J* = 3.1 Hz, 1H), 3.34 (s, 3H), 1.67 (dd, *J* = 13.9, 5.5 Hz, 1H), 1.25 (dd, *J* = 13.9, 7.8 Hz, 1H), 0.75-0.64 (m, 1H), 0.50 – 0.36 (m, 2H), -0.04 – -0.16 (m, 2H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 130.9, 128.8, 128.6, 127.7, 124.9, 124.5, 123.3, 114.2, 41.4, 29.8, 7.1; δ_u 172.9, 139.1, 126.7, 45.7, 40.4, 5.3, 4.2.
GC (method B) t_R= 2.84 min. **EI MS**, m/z (%): 265 (12, M+), 264 (14), 210 (100), 195 (30).
HRMS (ESI-Orbitrap) m/z; $[M+H]^+$ calcd for $C_{18}H_{20}ON$ 266.1545; found 266.1533.
HPLC: Chiralcel OD-H, n-hexane/isopropanol=97.5:2.5, flow rate=1 mL/min, I=254 nm, t_{R1} =9.28 min. (major), t_{R2} = 10.52 min. (minor).

6a-(But-3-en-1-yl)-5-methyl-6a,10a-dihydrophenanthridin-6(5H)-one (4m). Using the general procedure detailed above with diene triflate **3l** (0.060 g, 0.14 mmol) was subjected to the Heck reaction conditions with 10 mol% Pd/14 mol% (R)-BINAP. The crude product was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford **4m** (0.021 g, 0.079 mmol) with an enantiomeric ratio of 8:1 (78% e.e.) in 55% yield as a clear, colorless oil. The cyclized butene product **4m-C** (0.006 g, 0.023 mmol) was isolated separately with an enantiomeric ratio of 6:1 (71% e.e.) in 16% yield.
4m data:
$[\alpha]_D^{20}$ +45 (*c* 0.74, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dt, 1H, *J* = 7.8, 1.6 Hz), 7.22 (dd, 1H, *J* = 7.4, 1.4 Hz), 7.08 (td, 1H, *J* = 7.4, 1.0 Hz), 6.98 (d, 1H, *J* = 8.2 Hz), 6.15 (dd, 1H, *J* = 9.5, 5.2 Hz), 6.01 (dddd, 1H, *J* = 9.3, 5.2, 3.1, 1.0 Hz), 5.95 (dd, 1H, *J* = 9.5, 0.8 Hz), 5.67 (ddt, 1H, *J* = 17.0, 10.3, 6.4 Hz), 5.54 (dd, 1H, *J* = 9.2, 2.6 Hz), 4.96-4.87 (m, 2H), 3.67 (s, 1H), 3.35 (s, 3H), 2.16 – 1.97 (m, 2H), 1.70 – 1.62 (m, 1H), 1.59 – 1.48 (m, 1H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 137.8, 130.2, 128.7, 128.6, 127.9, 125.1, 124.9, 123.4, 114.3, 41.5, 29.9. δ_d 172.7, 139.0, 126.3, 114.9, 44.7, 34.2, 29.0.
GC (method A) t_R= 13.78 min. **EI MS**, m/z (%): 265 (19), 264 (17), 248 (5), 236 (15), 224 (14), 210 (100), 195 (25), 180 (23).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{18}H_{20}ON$ 266.1545; found 266.1532.
HPLC: Chiralcel OD-H, n-hexane/isopropanol=99:1, flow rate=1 mL/min, I=254 nm, t_{R1} =11.29 min. (major), t_{R2} = 11.94 min. (minor).

8-Methyl-4-methylene-3a,4,5,6,8,12b-hexahydrocyclopenta[h]phenanthridin-7(1H)-one (4m-C).
$[\alpha]_D^{20}$ +99 (*c* 0.13, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (td, *J* = 7.8, 4.0 Hz, 1H), 7.16 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.03 (dt, *J* = 7.4,1.0 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.06- 6.02 (m, 1H), 5.70 (qt, *J* = 5.2, 2.0 Hz, 1H), 4. 97 (q, *J* = 2.1 Hz, 2H), 4.88 (d, *J* = 2.2 Hz, 2H), 3.93 (s, 1H), 3.39 (s, 3H), 2.76 (dd, *J* = 11.5, 5.7 Hz, 1H), 2.54-2.39 (m, 2H), 2.18 (dt, *J* = 17.9, 5.2 Hz, 1H), 2.01 (qq, *J*= 11.5, 2.4 Hz, 1H), 1.70-1.58 (m, 2H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 129.2, 128.3, 127.6, 127.3, 124.4, 123.0, 114.8, 44.6, 36.9, 30.05; δ_d 154.0, 139.0, 129.3, 106.9, 50.1, 31.2, 30.1, 30.0.
GC (method A) t_R= 14.67 min. **EI MS**, m/z (%): 265 (100, M+), 250 (58), 236 (29).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{18}H_{20}ON$ 266.1545; found 266.1535.
HPLC: Chiralcel OD-H, n-hexane/isopropanol=97.5:2.5, flow rate=1 mL/min, I=254 nm, t_{R1} =10.14 min. (minor), t_{R2} = 10.42 min. (major).

(6aR,10aR)-6a-(Methoxymethyl)-5-methyl-6a,10a-dihydrophenanthridin-6(5H)-one (4n). Using the general procedure detailed above with diene triflate **3n** (0.084 g, 0.21 mmol) was subjected to the Heck reaction conditions with 10 mol% Pd/14 mol% (R)-BINAP. The crude product was purified by column chromatography (silica, 7:3 hexanes: EtOAc) to afford **4n** (0.047 g, 0.018 mmol) with an enantiomeric ratio of 20:1 (90% e.e.) in 88% yield as a yellow cloudy oil.
$[\alpha]_D^{20}$ +189 (*c* 1.1, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.22 (m, 2H), 7.07 (td, 1H, *J* = 7.5, 1.1 Hz), 6.96 (d, 1H, *J* = 8.1 Hz), 6.14 – 6.08 (m, 1H), 6.05 (dddd, 1H, *J* = 8.8, 5.1, 2.3, 1.1 Hz), 5.80 (dd, *J* = 9.5, 3.3 Hz, 2H), 3.97 (t, 1H, *J* = 3.2 Hz), 3.52 (d, 1H, *J* = 8.8 Hz), 3.42 (d, 1H, *J* = 8.8 Hz), 3.37 (s, 3H), 3.31 (s, 3H) ppm.
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 128.1, 127.7, 127.6, 127.5, 125.7, 124.6, 123.3, 114.1, 59.4, 36.7, 30.1; δ_d 170.7, 139.1, 126.1, 73.3, 47.3.
GC (method A) t_R= 13.18 min. **EI MS**, m/z (%): 255 (3, M+), 254 (9), 224 (11), 210 (100), 195 (35).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{16}H_{18}O_2N$ 256.1338; found 256.1329.
HPLC: Chiralcel OD-H, n-hexane/isopropanol=97.5:2.5, flow rate=1 mL/min, I=254 nm, t_{R1} =17.92 min. (major), t_{R2} = 19.53 min. (minor).

2-((6aR,10aR)-5-(Methoxymethyl)-6-oxo-5,10a-dihydrophenanthridin-6a(6H)-yl)acetonitrile (4o). Using the general procedure detailed above with diene triflate **3o-I** (0.062 g, 0.14 mmol) was subjected to the Heck reaction conditions with 20 mol% Pd/24 mol% (R)-BINAP, but without the addition of LiOAc. The crude product was purified by column chromatography (silica, 7:3 hexanes:

EtOAc) to afford **4o** (0.030 g, 0.011 mmol) with an enantiomeric ratio of 10:1 (82% e.e.) in 74% yield as a cloudy yellow oil.
$[\alpha]_D^{20}$ +107 (*c* 1.24, $CHCl_3$).
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.24 (m, 4H), 7.12 (td, *J* = 7.6, 1.7 Hz, 1H), 6.22 – 6.14 (m, 2H), 6.10 – 6.03 (m, 1H), 5.78 – 5.71 (m, 1H), 5.46 (d, *J* = 10.6 Hz, 1H), 5.30 (d, *J* = 10.6 Hz, 1H), 3.92 (d, *J* = 4.7 Hz, 1H), 3.40 (s, 3H), 2.91 (d, *J* = 16.4 Hz, 1H), 2.69 (d, *J* = 16.4 Hz, 1H).
^{13}C{^{1}H} NMR (101 MHz, DMSO) δ_u 128.6, 127.9, 127.3, 127.2, 126.2, 125.2, 124.4, 115.7, 56.5, 38.7; δ_d 170.6, 137.7, 124.0, 116.9, 74.4, 44.7, 22.9.
GC (method A) t_R= 15.30 min. **EI MS**, m/z (%): 280 (35, M+), 248 (32), 234 (35), 219 (7), 208 (79), 192 (100), 180 (73), 165 (41).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{17}H_{17}O_2N_2$ 281.1290; found 281.1277.
HPLC: Chiralcel OD-H, n-hexane/isopropanol=97.5:2.5, flow rate=1 mL/min, I=254 nm, t_{R1} =36.55 min. (minor), t_{R2} = 43.02 min. (major).

2-((6aR,10aR)-5-Methyl-6-oxo-5,10a-dihydrophenanthridin-6a(6H)-yl)acetonitrile (4p). Using the general procedure detailed above with diene triflate **3p** (0.282 g, 0.70 mmol) was subjected to the Heck reaction conditions with 20 mol% Pd/24 mol% (R)-BINAP, but without the addition of LiOAc. The crude product was purified by column chromatography (silica, 7:3 hexanes: EtOAc) to afford **4p** (0.170 g, 0.679 mmol) with an enantiomeric ratio of 9:1 (80% e.e.) in 97% yield as a yellow opaque oil.
$[\alpha]_D^{20}$ +94 (*c* 2.34, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) d 7.34-7.26 (m, 2H), 7.09 (td, 1H, *J*=7.5, 0.8 Hz), 6.99 (d, 1H, *J*= 8.1 Hz), 6.19-6.12 (m, 2H), 6.07 (dd, 1H, *J*= 9.1, 4.8 Hz), 5.70 (d, 1H, *J*=9.0 Hz), 3.93 (d, 1H, *J*=4.8 Hz), 3.41 (s, 3H), 2.91 (d, 1H, *J* =16.3 Hz), 2.67 (d, 1H, *J*=16.3 Hz).
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) d_u 128.4, 127.8, 127.0, 126.9, 126.5, 125.2, 123.8, 114.4, 38.4, 30.5; d_d 169.3, 139.0, 124.4, 117.1, 44.6, 23.1.
GC (method A) t_R= 14.77 min. **EI MS**, m/z (%): 250 (23, M+), 249 (23), 233 (2), 222 (4), 210 (100), 195 (27).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{16}H_{15}ON_2$ 251.1172; found 251.1184.
HPLC: Chiralcel OD-H, n-hexane/isopropanol=97.5:2.5, flow rate=1 mL/min, I=254 nm, t_{R1} =44.77 min. (minor), t_{R2} = 53.53 min. (major).

Ethyl 2-((6aR,10aR)-5-methyl-6-oxo-5,10a-dihydrophenanthridin-6a(6H)-yl)acetate (4q). Using the general procedure detailed above with diene triflate **3q** (0.129 g, 0.288 mmol) was subjected to the Heck reaction conditions with 10 mol% Pd/12 mol% (R)-BINAP. The crude product was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford **4q** (0.074 g, 0.25 mmol) with an enantiomeric ratio of 7:1 (75% e.e.) in 86% yield as a clear, colorless film.
$[\alpha]_D^{20}$ +85 (*c* 0.5, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, *J* = 8.6, 6.7 Hz, 2H), 7.05 (td, *J* = 7.5, 1.0 Hz, 1H), 6.96 (d, *J* = 7.7 Hz, 1H), 6.12 – 6.02 (m, 2H), 5.89 (dd, *J* = 8.7, 4.3 Hz, 1H), 5.80 (d, *J* = 8.0 Hz, 1H), 4.08 (q, *J* = 7.1 Hz, 3H), 3.38 (s, 3H), 2.70 (q, *J* = 16 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 4H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 128.5, 127.9, 127.8, 127.7, 125.2, 125.0, 123.3, 114.1, 38.5, 30.2, 14.2; δ_d 171.4, 170.9, 139.4, 125.8, 60.6, 44.3, 37.8.
GC (method B) t_R= 3.17 min. **EI MS**, m/z (%): 296 (0.1, M-1+), 280 (0.1), 268 (0.1), 252 (6), 210 (100), 209 (90).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{16}H_{15}ON_2$ 298.1443; found 298.1433.
HPLC: Chiralcel OD-H, n-hexane/isopropanol=60:40, flow rate=1 mL/min, I=254 nm, t_{R1} =6.18 min. (minor), t_{R2} = 21.69 min. (major).

(6aR,10aR)-6a-Cyclohexyl-5-methyl-6a,10a-dihydrophenanthridin-6(5H)-one (4r). Using the general procedure detailed above with diene triflate **3r** (0.064 g, 0.15 mmol) was subjected to the Heck reaction conditions with 20 mol% Pd/24 mol% (R)-BINAP. The crude product was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford **4r** (0.025 g, 0.085 mmol) with an enantiomeric ratio of 6:1 (71% e.e.) in 57% yield as a cloudy oil.
$[\alpha]_D^{20}$ +209 (*c* 0.86, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (td, *J* = 7.8, 1.6 Hz, 3H), 7.19 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.07 (td, *J* = 7.4, 1.0 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.15 (dd, *J* = 9.6, 5.0 Hz, 1H), 5.98 (dd, *J* = 9.0, 5.1 Hz, 2H), 5.48 (dd, *J* = 9.5, 2.3 Hz, 1H), 3.85 (s, 1H), 3.35 (s, 3H), 1.76-1.64 (m, 2H), 1.60-1.53 (m, 1H), 1.49 – 1.24 (m, 4H), 1.07 – 0.94 (m, 3H), 0.93 – 0.82 (m, 1H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 129.2, 128.6, 128.4, 127.7, 124.9, 124.6, 123.3, 114.2, 40.5, 40.2, 29.8; δ_d 172.4, 139.3, 127.0, 48.7, 28.7, 28.3, 26.8, 26.4, 26.2.
GC (method A) t_R= 16.14 min. **EI MS**, m/z (%): 293 (7), 292 (5), 210 (100), 195 (11).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{20}H_{24}ON$ 294.1858; found 294.1851.
HPLC: Chiralcel OD-H, n-hexane/isopropanol=97.5: 2.5, flow rate=1 mL/min, I=254 nm, t_{R1} =8.44 min. (minor), t_{R2} = 9.66 min. (major).

(6aR,10aR)-6a-Benzyl-5-(methoxymethyl)-6a,10a-dihydrophenanthridin-6(5H)-one (4s). Using the general procedure detailed above with diene triflate **3s-I** (0.115 g, 0.239 mmol) was subjected to the Heck reaction conditions with 20 mol% Pd/24 mol% (R)-BINAP. The crude product was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford **4s** (0.065 g, 0.20 mmol) with an enantiomeric ratio of 12:1 (85% e.e.) in 82% yield as a cloudy oil.
$[\alpha]_D^{20}$ +213 (*c* 0.89, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.13 (m, 7H), 7.03 – 7.01 (m, 2H), 6.11 – 6.04 (m, 2H), 5.94 (dddd, 1H, *J* = 9.2, 4.6, 3.0, 1.4 Hz), 5.59 (d, 1H, *J* = 10.6 Hz), 5.55 (dd, 1H, *J* = 9.4, 2.9 Hz), 5.18 (d, 1H, *J* = 10.6 Hz), 3.59 (t, 1H, *J* = 3.0 Hz), 3.39 (s, 3H), 3.01 (d, 1H, *J* = 13.3 Hz), 2.86 (d, 1H, *J* = 13.4 Hz) ppm.
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 130.7, 130.2, 128.7, 128.4, 128.3, 128.1, 126.8, 125.3, 124.7, 124.2, 115.6, 56.4, 40.2; δ_d 174.1, 137.9, 136.3, 125.9, 74.0, 46.8, 40.9.
GC (method A) t_R = 17.71 min. **EI MS**, m/z (%): 331 (0.1, M+), 300 (2), 284 (1), 270 (1), 254 (1), 239 (10), 224 (19), 208 (100), 196 (16), 178 (29), 91 (49).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{22}H_{22}O_2N$ 332.1650; found 332.1634.
HPLC: Chiralcel OD-H, n-hexane/isopropanol=97.5: 2.5, flow rate=1 mL/min, I=254 nm, t_{R1} =8.75 min. (major), t_{R2} = 11.48 min. (minor).

(6aR,10aR)-6a-Benzyl-5-methyl-6a,10a-dihydrophenanthridin-6(5H)-one (4t). Using the general procedure detailed above with diene triflate **3t** (0.074 g, 0.16 mmol) was subjected to the Heck reaction conditions with 20 mol% Pd/24 mol% (R)-BINAP. The crude product was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford **4t** (0.040 g, 0.15 mmol) with an enantiomeric ratio of 11:1 (83% e.e.) in 83% yield as a yellow cloudy oil.
$[\alpha]_D^{20}$ +50 (*c* 0.23, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (td, *J* = 7.8, 1.7 Hz, 1H), 7.28 – 7.14 (m, 4H), 7.10 (td, 1H, *J* = 7.4, 1.1 Hz), 7.00 (ddd, 3H, *J* = 10.7, 8.3, 1.4 Hz), 6.11 – 5.99 (m, 2H), 5.95 (dddd, 1H, *J* = 9.2, 4.5, 2.8, 1.4 Hz), 5.55 (dd, 1H, *J* = 9.3, 3.1 Hz), 3.60 (t, 1H, *J* = 3.0 Hz), 3.38 (s, 3H), 2.95 (d, 1H, *J* = 13.3 Hz), 2.83 (d, 1H, *J* = 13.4 Hz).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 130.6, 130.5, 128.6, 128.3, 128.2, 127.8, 126.7, 125.0, 124.7, 123.5, 114.3, 40.1, 30.0; δ_d 172.6, 139.2, 136.6, 126.2, 46.7, 41.3.
GC (method A) t_R = 17.17 min**. EI MS**, m/z (%): 301 (1, M+), 210 (100), 195 (27).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{21}H_{20}ON$ 302.1545; found 302.1531.
HPLC: Chiralcel OD-H, n-hexane/isopropanol=97.5: 2.5, flow rate=1 mL/min, I=254 nm, t_{R1} =12.55 min. (minor), t_{R2} = 21.02 min. (major).

3-(((6aR,10aR)-5-Methyl-6-oxo-5,10a-dihydrophenanthridin-6a(6H)-yl)methyl)benzonitrile (4u). Using the general procedure detailed above with diene triflate **3u** (0.084 g, 0.18 mmol) was subjected to the Heck reaction conditions with 20 mol% Pd/24 mol% (R)-BINAP. The crude product was purified by column chromatography (silica, 7:3 hexanes: EtOAc) to afford **4u** (0.034 g, 0.10 mmol) with an enantiomeric ratio of 11:1 (83% e.e.) in 59% yield as a white solid, m.p. = 60.2-63.9˚C.
$[\alpha]_D^{20}$ +141 (*c* 1.23, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dt, 1H, *J* = 7.5, 1.5 Hz), 7.36 – 7.26 (m, 4H), 7.18 (dd, 1H, *J* = 7.5, 1.7 Hz), 7.11 (td, 1H, *J* = 7.4, 1.1 Hz), 6.94 (dd, 1H, *J* = 8.2, 1.1 Hz), 6.11 (dd, 1H, *J* = 9.4, 5.1 Hz), 6.03 (dddd, 1H, *J* = 8.9, 5.2, 2.6, 1.0 Hz), 5.92 (d, 1H, *J* = 9.4 Hz), 5.66 (dd, 1H, *J* = 9.4, 3.5 Hz), 3.50 (t, 1H, *J* = 3.0 Hz), 3.36 (s, 3H), 2.97 (q, 2H, *J* = 13.4 Hz).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 134.9, 133.9, 130.5, 129.7, 128.9, 128.2, 128.1, 127.9, 125.5, 125.0, 123.7, 114.3, 39.9, 30.1; δ_d 171.6, 139.0, 138.2, 125.6, 118.8, 112.2, 46.7, 41.0
GC (method A) t_R = 19.76 min**. EI MS**, m/z (%): 326 (4, M+), 325 (3), 210 (100), 195 (25).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{22}H_{19}ON_2$ 327.1497; found 327.1486.
HPLC: Chiralcel OD-H, n-hexane/isopropanol=97.5: 2.5, flow rate=1 mL/min, I=254 nm, t_{R1} =10.68 min. (major), t_{R2} = 11.74 min. (minor).

(6aR,10aR)-5-methyl-6a-(naphthalen-1-ylmethyl)-6a,10a-dihydrophenanthridin-6(5H)-one (4v). Using the general procedure detailed above with diene triflate **3v** (0.066 g, 0.13 mmol) was subjected to the Heck reaction conditions with 20 mol% Pd/24 mol% (R)-BINAP. The crude product was purified by column chromatography (silica, 4:1 hexanes: EtOAc) to afford **4v** (0.030 g, 0.085 mmol) with an enantiomeric ratio of 8:1 (78% e.e.) in 65% yield as a cloudy oil.
$[\alpha]_D^{20}$ +222 (*c* 0.86, $CHCl_3$)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.77 (d, *J* = 6.9 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.42 (s, 2H), 7.32 (t, *J* = 7.1 Hz, 1H), 7.28 – 7.17 (m, 3H), 7.06 (d, *J* = 6.8 Hz, 1H), 6.99 (t, *J* = 7.4 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.13 (d, *J* = 9.8 Hz, 1H), 6.02 (d, *J* = 9.2 Hz, 1H), 5.94 (s, 1H), 5.48 (d, *J* = 9.7 Hz, 1H), 3.75 (s, 1H), 3.46 (d, *J* = 13.5 Hz, 1H), 3.34 (d, *J* = 13.8 Hz, 1H), 3.29 (s, 3H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 129.0, 128.7, 128.7, 128.7, 127.7, 127.7, 125.5, 125.3, 125.0, 124.5, 124.2, 124.1, 123.3, 114.0, 41.7, 30.0; δ_d 172.3, 138.9, 133.8, 132.9, 132.7, 130.2, 126.4, 46.7, 38.1.
GC (method A) t_R = 18.54 min (broad peak due to decomposition)**. EI MS**, m/z (%): 209 (100), 178 (23), 152 (16), 141 (51).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{25}H_{22}ON$ 352.1701; found 352.1687.
HPLC: Chiralcel OD-H, n-hexane/isopropanol=97.5: 2.5, flow rate=1 mL/min, I=254 nm, t_{R1} =19.65 min. (minor), t_{R2} = 24.09 min. (major).

Procedure for MOM (methoxymethyl) group deprotection

(6aR,10aR)-6a-methyl-6a,10a-dihydrophenanthridin-6(5H)-one (5a). Chlorotrimethylsilane (0.06 mL, 0.489 mmol, 4.5 eq.) and CH_3CN (3.0 mL) were combined in a round bottom flask and NaI (0.073 g, 0.489 mmol, 4.5 eq.) was added. The resulting heterogeneous solution was stirred for 15 min at room

temperature. In a second round bottom flask, the MOM-protected Heck product **4a** (0.031 g, 0.129 mmol, 1.0 eq) was dissolved in CH_3CN (2.0 mL) and cooled to 0°C. The TMS-Cl/NaI solution was added to **4a** in CH_3CN solution by syringe. The resulting mixture was stirred at 0°C for 1 h. The reaction progress was monitored by TLC (3:2 hexanes: EtOAc) and GCMS. Upon completion, the reaction mixture was quenched with 1 M NaOH (17 mL/mmol) and stirred overnight.
The aqueous layer was extracted with Et_2O (3 x). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was dissolved in a minimal amount DCM and purified via automated silica gel flash chromatography using hexanes/EtOAc (100/0 to 70/30) gradient. The secondary amide product **5a** was isolated in 81% yield (0.022 g, 0.104 mmol) as a white solid, m.p.= 133.9-136.6.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 – 8.31 (br s, 1H), 7.25 – 7.15 (m, 2H), 7.04 (td, *J* = 7.5, 1.2 Hz, 1H), 6.76 (dd, *J* = 7.9, 1.2 Hz, 1H), 6.11 (dd, *J* = 9.3, 5.1 Hz, 1H), 6.03 (dddd, *J* = 9.1, 5.2, 2.9, 1.0 Hz, 1H), 5.89 – 5.82 (m, 1H), 5.61 (ddt, *J* = 9.3, 3.1, 1.0 Hz, 1H), 3.55 (t, *J* = 3.1 Hz, 1H), 1.32 (s, 3H).
^{13}C{^{1}H} NMR (101 MHz, CDCl3) δ_u 130.6, 130.0, 128.6, 128.5, 127.8, 125.0, 124.70, 123.6, 123.5, 115.1, 44.3, 23.4. δ_d 174.9, 135.9, 124.74, 40.9.
GC (method B) *tR* = 2.08 min. **EI-MS** m/z (%): 210.1 (M+, 60), 196.0 (100), 178.0 (41), 167.0 (30), 152.1 (12).
HRMS (ESI-Orbitrap) m/z; $[M+H]^+$ calcd for $C_{14}H_{14}ON$ 212.1075; found 212.1073.

(6aR,10aR)-6a-Benzyl-6a,10a-dihydrophenanthridin-6(5H)-one (5s). To a solution of MOM protected phenanthridinone **4s** (0.031 g, 0.094 mmol) in CH_3CN at 0˚C was added TMS-I (4.6 eq). The mixture was stirred at 0˚C for 1hr and the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated. The resulting crude product was immediately dissolved in MeOH at room temperature and treated with Et_3N (3.0 eq). The reaction was stirred for 1 h at 55 ˚C. After cooling to room temperature, the reaction was quenched in saturated aq. NH_4Cl and a solution of hexane/EtOAc (1:1 mixture) was added. The organic layer was separated and the aqueous layer was extracted with hexane. The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated. (silica, 4:1 hexanes: EtOAc) to afford **5s** (0.016 g, 0.056 mmol) in 58% yield as a white solid, m.p. = 76.4-81.5˚C. The product retained the enantiomeric ratio (11:1) of the substrate.
$[\alpha]_D^{20}$ +249 (*c* 0.62, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.29 – 7.15 (m, 5H), 7.13 – 7.02 (m, 3H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.10 (dd, *J* = 9.5, 5.0 Hz, 1H), 6.03 – 5.95 (m, 2H), 5.63 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.65 (t, *J* = 2.7 Hz, 1H), 3.00 (s, 2H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 130.6, 129.3, 128.3, 128.2, 128.1, 127.8, 126.8, 125.4, 124.7, 123.8, 115.1, 39.9; δ_d 173.8, 136.5, 136.0, 124.5, 46.9, 40.9.
GC (method A) t_R = 18.33 min. **EI MS**, m/z (%): 289 (15), 208 (2), 196 (100), 178 (44).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{20}H_{18}ON$ 288.1388; found 288.1377.
HPLC: Chiralcel OD-H, n-hexane/isopropanol=97.5: 2.5, flow rate=1 mL/min, I=254 nm, t_{R1} =19.63 min. (minor), t_{R2} = 31.14 min. (major).

Procedures for isomerization of 1,3-diene to 1,4-diene, (R)-5,6a-dimethyl-6a,9-dihydrophenanthridin-6(5H)-one (6e).
tBuOK/t-BuOH alkene isomerization
To a flame dried vial with a stir bar was added the Heck product **4e** (0.031 g, 0.14 mmol, 1.0 eq.) and *t*-BuOK (0.090 g, 0.80 mmol, 6.0 eq.), followed by *t*-BuOH (2.0 mL). The vial was sealed with a pressure relief cap and stirred in a pre-heated (65°C) pie-block reactor overnight. The reaction completion was

checked by TLC (9:1 hexanes: EtOAc) and GCMS (a small aliquot was taken up by a syringe, quenched with 10% HOAc and extracted with Et_2O).

Upon completion, the reaction mixture was cooled to room temperature, quenched with 10% HOAc (3.5 mL), stirred for 5-10 min and then transferred to a separatory funnel. The aqueous layer was extracted with Et_2O (3 x). The combined organic layers were washed with a saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was dissolved in a minimal amount of DCM and purified via automated silica gel flash chromatography using hexanes/EtOAc (100/0 to 90/10) gradient. The 1,4-diene product **6e** was isolated in 79% yield (0.025 g, 0.11 mmol) as a yellow oil.

<u>$RhCl_3 \bullet xH_2O$ catalyzed alkene isomerization</u>
The Heck product **4e** (0.030 g, 0.13 mmol, 1.0 eq.) and $RhCl_3 \bullet xH_2O$ (0.006 g, 0.027, 0.2 eq.) were added to a vial with a stir bar and dissolved in 10:1 EtOH:H_2O (5.0 mL) . The vial was sealed with a pressure relief cap and stirred in a pre-heated (65°C) pie-block reactor overnight. The reaction completion was checked by TLC (9:1 hexanes: EtOAc) and GCMS (a small aliquot was taken up by a syringe and diluted in DCM).

Upon completion, the reaction mixture was cooled to room temperature, diluted in DCM, transferred to a round-bottom flask, and concentrated under reduced pressure. The crude product was purified via automated silica gel flash chromatography using hexanes/EtOAc (100/0 to 90/10) gradient. The 1,4-diene product **6e** was isolated in 83% yield (0.025 g, 0.11 mmol) as a yellow/tan oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.30 – 7.23 (m, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.41 (d, *J* = 8.0 Hz, 1H), 6.07 – 6.01 (m, 2H), 5.89-5.83 (m, 1H), 3.37 (s, 3H), 2.7-2.71 (m, 2H), 1.26 (s, 3H).
^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_u 128.9, 125.5, 124.4, 123.5, 123.1, 117.9, 114.7, 39.9; δ_d 174.0, 138.2, 134.0, 122.4, 29.9, 22.4.
GC (method B) t_R = 2.33 min. **EI MS**, m/z (%): 225.1 (M+, 10), 210.0 (100), 195.1 (39), 180.1 (11), 167.1 (14), 152.1 (13).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{15}H_{16}ON$ 226.1232; found 226.1228.

Procedure for the synthesis of dienone, (R)-5-(methoxymethyl)-6a-methylphenanthridine-6,9(5H,6aH)-dione (7a).
To an argon-flushed flame dried vial with a stir bar, was added the Heck product **4a** (0.0300 g, 0.118 mmol, 1.0 eq.). The vial was imported in a glove box, where CuI (0.0045 g, 0.0236 mmol, 0.2 eq.) and CH_3CN (1.0 mL) were added. The vial was sealed and exported outside the glovebox. The solution was stirred for a few minutes, then tBuOOH (0.24 mL, 10 eq.) was added under argon. The reaction mixture was stirred in the pre-heated (60°C) pie-block reactor for 3 h or once determined to be complete by TLC and GC.

Upon completion, the reaction mixture was cooled to room temperature, washed with 25 % ammonia and water, then extracted with Et_2O (2 x). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was analyzed by TLC, GCMS and NMR. The crude product was purified via automated silica gel flash chromatography using hexanes/EtOAc (100/0 to 70/30) gradient. Fraction purity was assayed by TLC analysis using 3:2 hexanes/EtOAc with UV visualization (Rf = 0.4). The combined product-containing fractions were

concentrated by rotary evaporation and dried under high vacuum. The product **7a** was isolated in 71% yield (0.0227 g, 0.084 mmol) as a yellow solid, m.p.=134.6-136.4°C.
^{1}H NMR (400 MHz, CDCl3) δ 7.70 – 7.60 (m, 2H), 7.50 (ddd, *J* = 8.8, 7.3, 1.5 Hz, 1H), 7.41 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.29 – 7.21 (m, 1H), 6.65 (d, *J* = 1.8 Hz, 1H), 6.44 (dd, *J* = 10.1, 1.8 Hz, 1H), 5.72 (d, *J* = 10.7 Hz, 1H), 5.02 (d, *J* = 10.8 Hz, 1H), 3.43 (s, 3H), 1.52 (s, 3H).
^{13}C{^{1}H} NMR (101 MHz, CDCl3) δ_u 148.4, 132.1, 128.5, 125.6, 124.6, 124.2, 116.3, 56.5, 28.6. δ_d 185.1, 169.6, 154.31, 137.4, 121.8, 74.6, 46.9.
GC (method B) t_R = 3.36 min. **EI MS**, m/z (%): 269.1 (M+, 100), 239.0 (56), 210.0 (39), 196.0 (11), 180.0 (18), 167.0 (22), 152.0 (13).
HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for $C_{16}H_{16}O_3N$ 270.1130; found 270.1126.

Supporting Information
NMR spectra for all new compounds, chiral LC traces for enantioselective Mizoroki-Heck reactions, a table of Heck reaction optimization experiments and X-ray crystallography data for compound **4m-C**. FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for compounds: **1c, 1f-h, 1j, 1k, 1m, 1n; 3a, 3a-I, 3b, 3b-I, 3c, 3c-I, 3d, 3d-I, 3e-3o, 3o-I, 3p-3s, 3s-I, 3t-3v, 4a-4v, 5a, 5s, 6e, 7a**. See FID for Publication for additional information.

Accession Codes
CCDC 2115476 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Acknowledgements
The authors are especially thankful to the National Institutes of Health for financial support (NIGMS, 1-R15-GM123475-01A1). Essential financial support was also received from Bryn Mawr College. GPAY thanks the National Institutes of Health for S10 OD026896A.

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