CHAPTER 2

Enantioselective Synthesis of Pyrroloindolines by a Formal (3 + 2) Cycloaddition[†]

2.1 Introduction

Catalytic, asymmetric methods for the construction of pyrroloindolines were recently reviewed by Dr. Lindsay Repka.[1] At the outset of our efforts in this field, only two such methods existed for the direct preparation of pyrroloindolines from indole precursors: MacMillan's organocatalytic addition-cyclization of tryptamines with α,β-unsaturated aldehydes,[2] and Trost's palladium-catalyzed C3-allylation of 3-substituted indoles.[3]

This chapter describes the development of a novel approach to the enantioselective preparation of pyrroloindolines, utilizing an (*R*)-BINOL•$SnCl_4$-catalyzed formal (3 + 2) cycloaddition of 3-substituted indoles and 2-amidoacrylates. This reaction is tolerant to diverse substitution patterns and incorporates the necessary C2-substitution for advancement to diketopiperazine pyrroloindoline natural products. Mechanistic

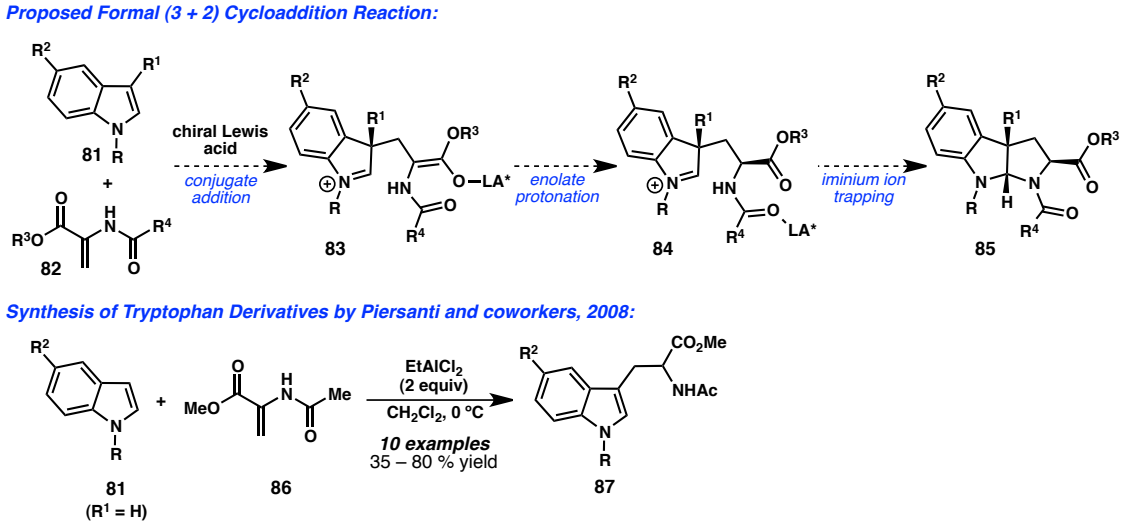
[†] Portions of this chapter have been reproduced from published studies (see references 7 and 19) and the supporting information found therein. The research presented in this chapter was completed in collaboration with Dr. Lindsay M. Repka, formerly a graduate student of the Reisman group, and Haoxuan Wang, a graduate student in the Reisman group.

studies are consistent with the proposal that this reaction proceeds *via* an asymmetric protonation as the enantiodetermining step and has consequently led to the development of related tandem conjugate addition/enantioselective protonation reaction for the synthesis of indoline-containing amino acid derivatives.

2.2 Development of a Formal (3 + 2) Cycloaddition

In our approach to the enantioselective preparation of pyrroloindolines, we aimed to develop a convergent reaction between 3-substituted indoles (**81**) and 2-amidoacrylates (**82**), in what would constitute a formal (3 + 2) cycloaddition. These readily-accessible substrates would facilitate rapid access to a variety of substituted pyrroloindoline products (**85**). We envisioned that this reaction would proceed via Lewis acid-activation of the acrylate leading to nucleophilic attack by the indole in a 1,4-fashion. The transiently generated iminion ion intermediate would then undergo cyclization by the pendant amine to generate the desired product (Figure 1).

Figure 1. Proposed pyrroloindoline synthesis and precedent by Piersanti.



However, we recognized that several challenges might be encountered in putting this proposal to practice. First, 2-amidoacrylates are relatively unreactive conjugate acceptors due to electron donation from the nitrogen lone pair. Second, controlling the absolute stereochemistry of the all-carbon quaternary center formed at C3 of the indole substrate was also anticipated to be a challenge, as it would require a remote chiral ligand to discriminate between prochiral faces of the nucleophilic indole. Finally, Lewis acid binding to the product might prevent turnover.

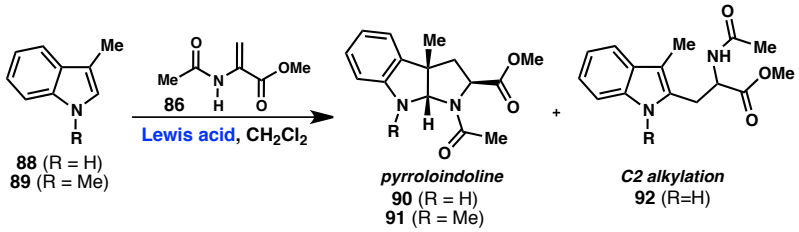
Despite these challenges, we were encouraged by results reported by Piersanti and coworkers; they found that unsubstituted indoles react with 2-amidoacrylates in the presence of two equivalents of $EtAlCl_2$ to give Friedel–Crafts alkylation products in good yield, thus confirming that 2-amidoacrylates can act as competent electrophiles (Figure 1).[4] The C3 substitution of the indole substrates for the proposed pyrroloindoline reaction would preclude formation of the Friedel–Crafts products observed by Piersanti, but reaction at C2 may lead to undesired Friedel–Crafts side products.

2.2.1 Identification of an Optimal Lewis Acid

Our studies began with the model substrates 3-methylindole (**88**) and methyl 2-acetamidoacrylate (**86**). A screen of Lewis acids revealed that use of 2.0 equivalents $EtAlCl_2$ delivered the desired pyrroloindoline (**90**) as the major product in 3:1 dr favoring the *exo* diastereomer (C3 substituent *syn* to ester, as shown), along with the C2 Friedel–Crafts alkylation product (**92**) (Table 1, entry 2). $SnCl_4$ was also found to effectively promote this reaction with 6:1 selectivity for pyrroloindoline formation over alkylation (entry 7). Fortunately, *N*-methylation of the indole improved selectivity for the pyrroloindoline product (entry 8). Attempts to lower the loading of Lewis acid were

unsuccessful: no product was observed when 50 mol % of $SnCl_4$ was employed (entry 9). Under the optimized conditions for the racemic reaction, exposure of 1,3-dimethylindole (**89**) and methyl 2-acetamidoacrylate (**86**) to 1.2 equivalents $SnCl_4$ in dichloroethane gave the desired pyrroloindoline **91** in 64% yield as a 6:1 mixture of *exo* and *endo* diastereomers (entry 10).

Table 1. Initial Lewis acid screen.



Entry	Lewis Acid (equiv)	Substrate	Temperature (°C)	Pyrroloindoline: C-2 alkylation	dr[a]
1	$EtAlCl_2$ (1)	**88**	23	nr	--
2	$EtAlCl_2$ (2)	**88**	8	8:1	3:1
3	$MgClO_4$ (1)	**88**	23	nr	--
4	$Sc(OTf)_2$ (2)	**88**	23	>20:1	5:1
5	$Cu(OTf)_2$ (2)	**88**	23	decomposition	--
6	$Zn(OTf)_2$ (2)	**88**	23	nr	--
7	$SnCl_4$ (1)	**88**	23	6:1	9:1
8	$SnCl_4$ (1)	**89**	23	>20:1[b]	11:1
9	$SnCl_4$ (0.5)	**89**	23	nr	--
10[c]	$SnCl_4$ (1.2)	**89**	23	>20:1 (64)[d]	6:1

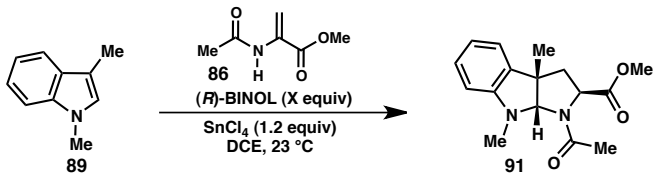
[a] Determined by analysis of the crude ^1H NMR with comparison to reported spectra. [b] Complete conversion to **91** by crude ^1H NMR. [c] Reaction run in DCE. [d] Isolated yield of **91**. nr: no reaction.

2.2.2 Optimization of the Enantioselective Reaction

Having identified a Lewis acid to effect pyrroloindoline formation in a racemic fashion, our next goal was to render this reaction enantioselective. A small screen of chiral ligands revealed that (*R*)-BINOL provided promising enantioselectivity: treatment of 1,3-dimethylindole (**89**) and methyl 2-acetamidoacrylate (**86**) with a 1.1:1 mixture of (*R*)-BINOL and $SnCl_4$ provided pyrroloindoline **91** in 86% yield as a 4:1 mixture of diastereomers, with the *exo* diastereomer formed in 64% ee (Table 2, entry 2).

Performing side-by-side reactions with and without (*R*)-BINOL revealed that the ligand accelerated the rate of reaction.[5] Thus it was hypothesized that high levels of enantioselectivity could be maintained with catalytic quantities of (*R*)-BINOL. Gratifyingly, treatment of 1,3-dimethylindole (**89**) and methyl 2-acetamidoacrylate (**86**) with 1.2 equivalents $SnCl_4$ and 20 mol % (*R*)-BINOL furnished the desired pyrroloindoline **91** in 94% yield as a 5:1 mixture of diastereomers, favoring the *exo* diastereomer in 63% ee (Table 2, entry 4). Remarkably, moderate levels of enantioselectivity are still observed when the reaction is conducted with only 5 mol % (*R*)-BINOL (entry 6).

Table 2. Optimization of (R)-BINOL loading.



Entry	(R)-BINOL (equiv)	Yield (%)[a]	dr[b]	ee (%)[c,d]
1[e]	0.0	64	6:1	--
2[f]	1.1[g]	86	4:1	64/83
3[h]	0.3	96	5:1	62/81
4[h]	0.2	94	5:1	63/83
5[h]	0.1	93	5:1	61/79
6[h]	0.05	82	5:1	51/72

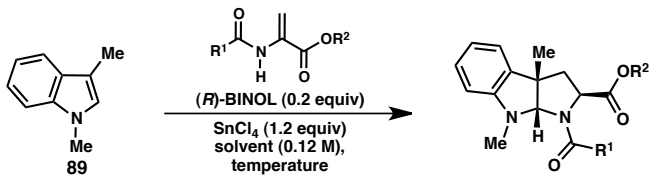
[a] Isolated yield of combined diastereomers. [b] Determined by ^{1}H NMR analysis of crude reaction mixture. [c] Determined by chiral stationary phase SFC. [d] ee of *exo*/*endo* diastereomers. [e] Reaction run for 30 h. [f] Reaction run for 3.5 h. [g] 1.0 equiv of $SnCl_4$ was used. [h] Reaction run for 3 h.

Efforts to improve the enantioselectivity of the formal (3 + 2) cycloaddition started with an investigation of the temperature effects. It was found that ee and dr are reduced at lower temperatures (Table 3, entries 3-4). Alternatively, gentle heating of the

reaction did not significantly alter the selectivity (entry 5). Similar temperature effects in reactions promoted by Lewis acid•BINOL complexes have been reported.[6]

On the other hand, varying substitution on the acrylate was found to significantly improve selectivity in this reaction. Methyl 2-trifluoroacetamidoacrylate (**67**) provided pyrroloindoline product **94** in 86% ee (*exo* diastereomer), while benzyl 2-acetamidoacrylate (**93**) provided pyrroloindoline **95** in 74% ee (Table 3, entries 6-7). These effects were found to be additive: reaction of benzyl 2-trifluoroacetamidoacrylate (**71**) afforded pyrroloindoline **96** in 81% yield as a 3:1 mixture of *exo* and *endo* diastereomers produced in 91% and 90% ee, respectively (entry 8). A solvent screen revealed that chlorinated solvents were optimal and switching from DCE to DCM provided **96** in 86% yield and 94% ee for the *exo* diastereomer (entry 9).

Table 3. Enantioselectivity optimization studies.

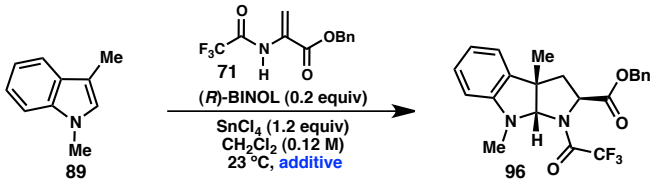


Entry	R^1, R^2	pdt	Temperature (°C) (Time (h))	Solvent	Yield (%)[a]	dr[b]	ee (%)[c,d]
1	Me, Me (**86**)	**91**	23 (4)	DCE	94	5:1	63/83
2[e]	Me, Me (**86**)	**91**	8 (24)	DCE	88[f]	4:1	66/nd
3[e]	Me, Me (**86**)	**91**	–40 (24)	CH_2Cl_2	69[f]	3:1	39/nd
4[e]	Me, Me (**86**)	**91**	–78 (24)	CH_2Cl_2	26[f]	2:1	21/nd
5[e]	Me, Me (**86**)	**91**	40 (0.5)	DCE	97[f]	5:1	66/nd
6	CF_3, Me (**67**)	**94**	23 (4)	DCE	77	6:1	86/nd
7	Me, Bn (**93**)	**95**	23 (4)	DCE	81	2:1	74/82
8	CF_3, Bn (**71**)	**96**	23 (4)	DCE	81	3:1	91/90
9	CF_3, Bn (**71**)	**96**	23 (5.5)	CH_2Cl_2	86	4:1	94/91
10	CF_3, Bn (**71**)	**96**	23 (4)	$CHCl_3$	58	3:1	88/89
11	CF_3, Bn (**71**)	**96**	23 (3.5)	CCl_4	0	--	--

[a] Isolated yield of combined diastereomers. [b] Determined by ^{1}H NMR analysis of crude reaction mixture. [c] Determined by chiral stationary phase SFC or HPLC. [d] ee of *exo*/*endo* diastereomers. [e] 1.0 equiv of $SnCl_4$ and 1.1 equiv (*R*)-BINOL was used. [f] Approximate conversion to **91** based on ratio with acrylate in crude ^{1}H NMR. nd= not determined.

A control reaction performed in the absence of $SnCl_4$ confirmed that the Lewis acid is essential (Table 4, entry 1). Furthermore, the Brønsted acids HCl and Ph_2PO_2H fail to promote the formal (3 + 2) cycloaddition (entries 1-3). Several water and acid scavenging additives were also screened but did not result in significant changes in enantioselectivity (entries 4, 5, and 7).

Table 4. Brønsted acid and additive screen.



Entry	Additive (equiv)	Time (h)	Yield (%)[a]	dr[b]	ee (%)[c,d]
1	--[e]	4	0	--	--
2	HCl (1.2)[e]	7	0	--	--
3	Ph_2PO_2H (1.2)[e]	7	0	--	--
4[f]	molecular sieves	4	70	4:1	93:89
5[f]	MgO (1)	4.5	72	4:1	93:91
6	2,6-lutidine (1)	6	0	--	--
7	2,6-lutidine (0.2)	5	53	6:1	94:89

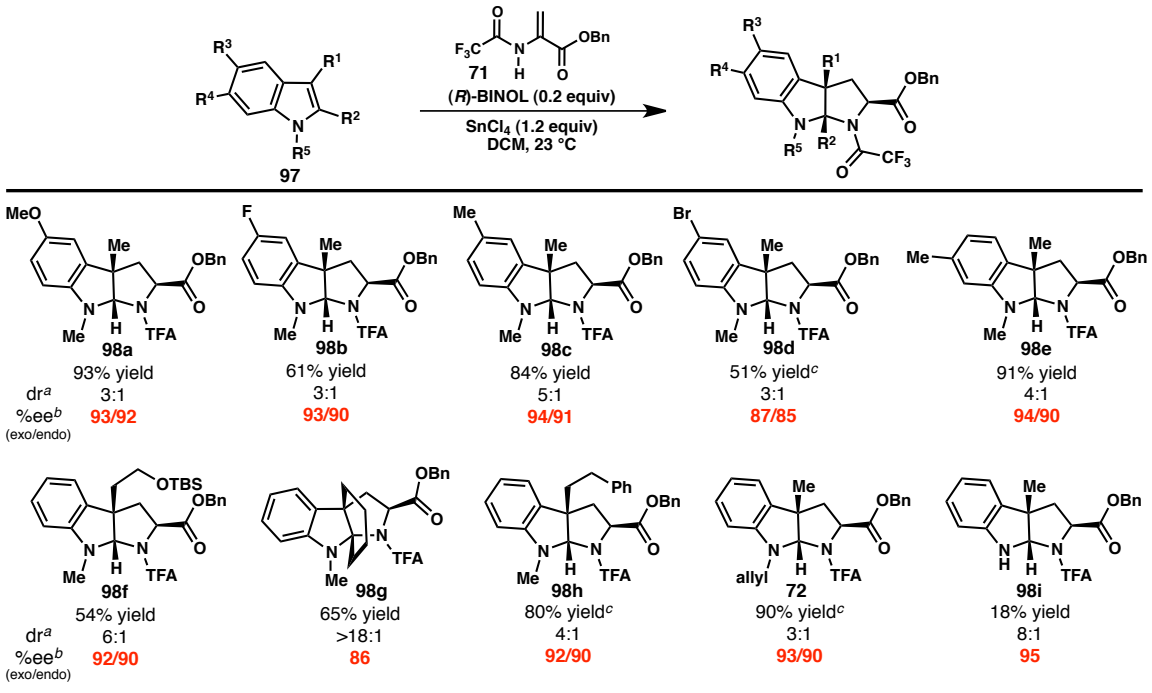
[a] Isolated yield of combined diastereomers. [b] Determined by ^{1}H NMR analysis of crude reaction mixture. [c] Determined by chiral stationary phase SFC. [d] ee of *exo*/*endo* diastereomers. [e] Reaction run without $SnCl_4$. [f] Completed side-by-side with reaction under standard conditions that afforded 74% yield, 4:1 dr, 94:90% ee.

2.2.3 Substrate Scope of the Enantioselective Pyrroloindoline Synthesis

With optimized conditions for the enantioselective formal (3 + 2) cycloaddition, the scope of indole substrates was investigated (Figure 2).[7,8] Indoles substituted at C5 with either electron-donating or electron-withdrawing groups are well-tolerated, although electron-poor indoles react at a slower rate, requiring 1.6 equivalents of $SnCl_4$ in some cases. Indoles with functionalized C3 substituents react in moderate to good yields with high enantioselectivity (**98f** and **98h**). Notably, the reaction of *N*-

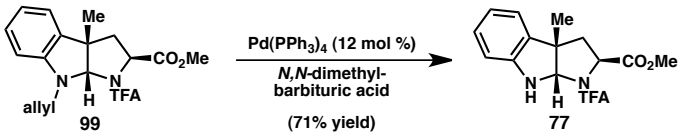
methyltetrahydrocarbazole proceeds with >18:1 diastereoselectivity, delivering the *exo* diastereomer **98g** in 86% ee. This reaction generates the aza-propellane core of the natural products minfiensine,[9] echitamine,[10] and vincorine[11] in a single step. *N*-substitution is important for reactivity: subjection of 3-methylindole to identical conditions provides pyrroloindoline **98i** in only 18% yield, albeit with excellent enantioselectivity. However, *N*-allyl-3-methylindole successfully affords pyrroloindoline **72** in good yield and enantioselectivity. Deallylation of **99** can be effected with $Pd(PPh_3)_4$ and *N*,*N*-dimethylbarbituric acid to give pyrroloindoline **77** with an unprotected indoline nitrogen (Figure 3).[12]

Figure 2. Substrate scope.



[a] Determined by ^{1}H NMR analysis of mixture. [b] Determined by chiral SFC or HPLC analysis. [c] 1.6 equiv $SnCl_4$ was employed.

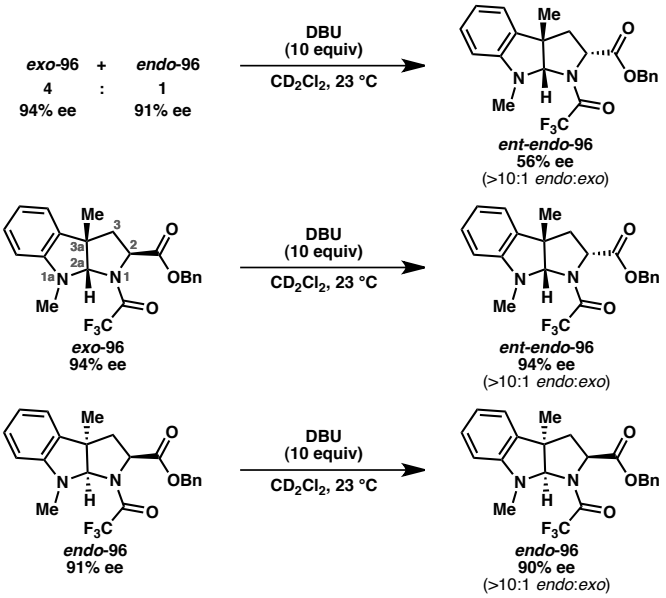
Figure 3. Pyrroloindoline deallylation.



2.2.4 Mechanistic Considerations

The *exo* diasteromer is the predominant product of the formal (3 + 2) cycloaddition reaction. Previously, it was reported that the *exo* diastereomer of related pyrroloindolines is the kinetic product, while the *endo* diastereomer is thermodynamically favored.[13]

Figure 4. Epimerization studies.

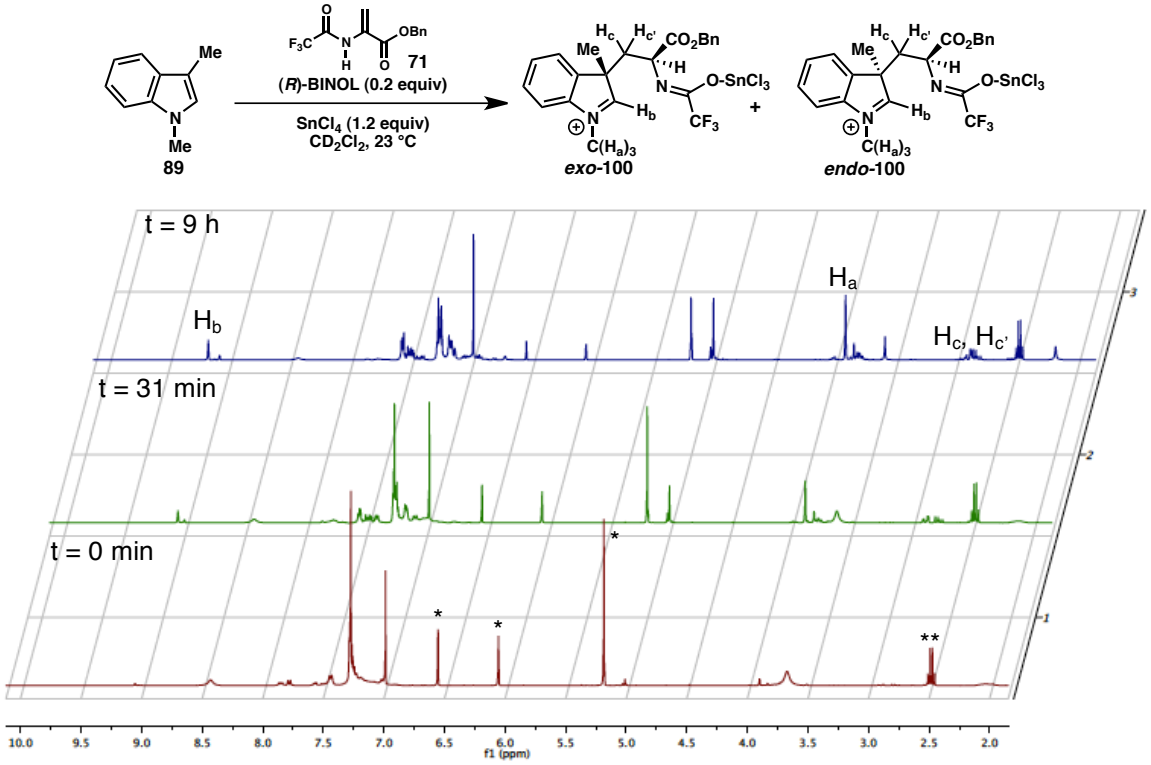


In order to determine whether this applies to the pyrroloindolines produced by the formal (3 + 2) cycloaddition, a 4:1 mixture of *exo*- and *endo*-**96** was exposed to excess DBU. Clean conversion to the *endo* diastereomer was observed, but surprisingly, the

product was isolated in 56% ee favoring the opposite enantiomer (Figure 4). Subsequently, treatment of pure *exo*-**96** with DBU provided *ent-endo*-**96** in 94% ee. Pure *endo*-**96** exposed to the epimerization conditions returned *endo*-**96** without significant erosion of ee. The studies indicate that the initially-formed diastereomers of **96** must possess the same configuration at C2, and the opposite configurations at the C2a and C3a bridgehead carbons.

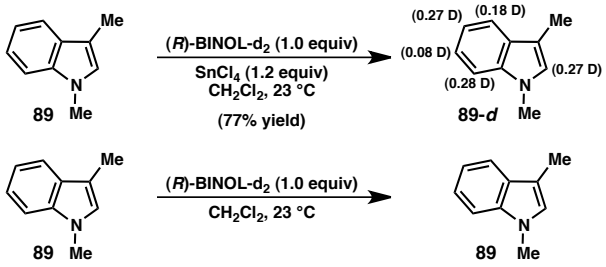
We then sought to obtain further mechanistic insight by monitoring the reaction using ^{1}H NMR spectroscopy. The formal (3 + 2) cycloaddition between 1,3-dimethylindole (**89)** and benzyl trifluoroacetamidoacrylate (**71**) is amenable to in situ NMR monitoring, since it is homogenous over the course of the reaction. Figure 5 shows a sample of ^{1}H NMR spectra taken over the first nine hours of the reaction, and reveals several interesting aspects of this transformation. Notably, upon addition of $SnCl_4$ and (*R*)-BINOL (**7**) to a mixture of **89** and **71**, the indole proton resonances broaden significantly (Figure 5, t = 0). This broadening is also observed in the absence of acrylate **71**; however, $SnCl_4$ alone does not alter the ^{1}H NMR spectrum of **89**. It is possible that this broadening is due to a rapid, dynamic, proton exchange process promoted by (*R*)-BINOL•$SnCl_4$, which is consistent with the finding that (*R*)-BINOL that is deuteurated at the hydroxyl groups undergoes rapid D-H exchange with indole **89** under the reaction conditions (Figure 6). Interestingly, the chemical shifts of the acrylate remain unchanged, indicating that there is no significant accumulation of an acrylate–$SnCl_4$ complex. Over the course of the reaction, resonances corresponding to an indole–acrylate adduct grow in; however, these peaks do not correspond to the pyrroloindoline product.

Figure 5. In situ monitoring of the formal (3 + 2) cycloaddition using ^{1}H NMR.



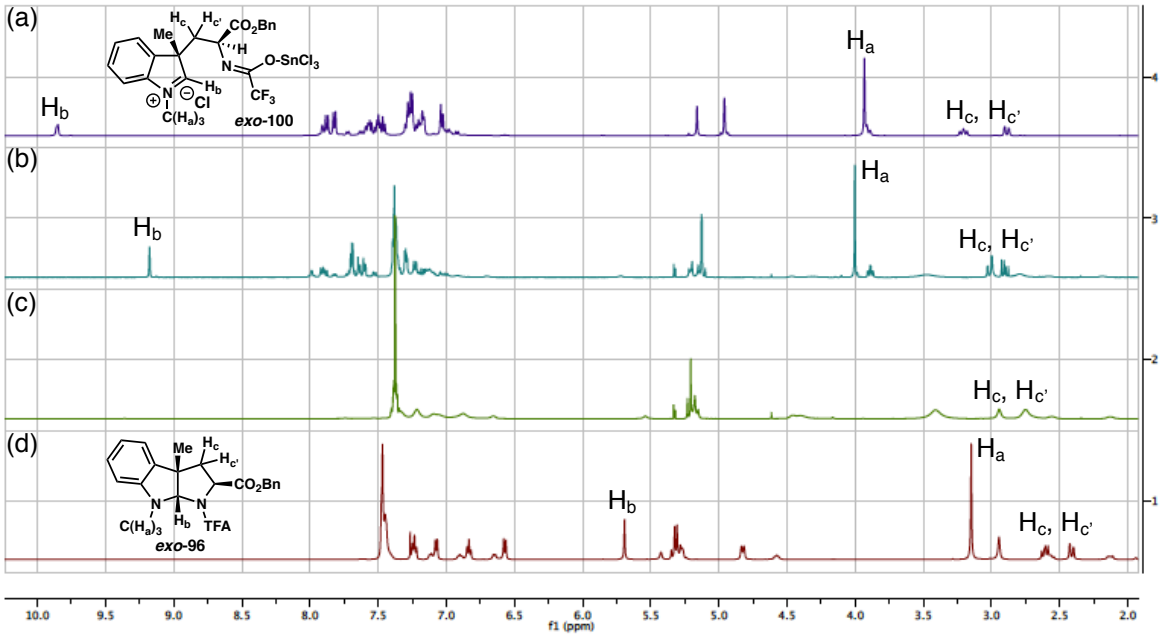
acrylate denoted by *; 1,4-diethylbenzene (internal standard) denoted by **.

*Figure 6. Deuterium-labelling studies with (*R*)-BINOL-d$_2$ and 1,3-dimethylindole.*



We hypothesized that in the presence of a strong Lewis acid, such as $SnCl_4$, coordination of the amide might favor the ring-opened iminium ions ***exo*-100/*endo*-100**. To test this hypothesis, we resubjected diastereomerically-pure ***exo*-100** to $SnCl_4$ (1.2 equiv) and varying equivalents of (*R*)-BINOL (Figure 7).

Figure 7. NMR spectra of (a) pyrroloindoine ***exo-96****, $SnCl_4$ (1.2 equiv), (R)-BINOL (1.2 equiv) (b) pyrroloindoine* ***exo-96****, $SnCl_4$ (1.2 equiv), (R)-BINOL (0.2 equiv) (c) pyrroloindoine* ***exo-96****, $SnCl_4$ (1.2 equiv) (d) pyrroloindoline* ***exo-96****.*



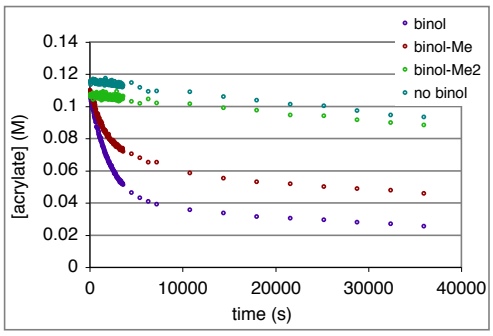
The NMR spectra of the mixtures were dependent on the quantity of (*R*)-BINOL present; in the presence of 20 mol % (*R*)-BINOL, the ^{1}H NMR spectra closely resembled that of the indole–acrylate adduct observed in the in situ ^{1}H NMR experiment. Notably, this species exhibits a resonance between 9 and 10 ppm (depending on concentration of (*R*)-BINOL, Figure 7a and b), which we assign to the indolinium proton (H_b). In addition, the *N*-methyl group (H_a) in this species is shifted downfield relative to the pyrroloindoline (4.0 ppm versus 3.1 and 2.9 ppm for the two rotamers of the *exo* diastereomer), and is consistent with literature data for other iminium ions.[14] This structural assignment is further supported by 2D ^{1}H–^{13}C NMR correlation data. In the presence of $SnCl_4$ alone, the pyrroloindoline peaks broaden, likely due to dynamic interconversion between the ring-opened and -closed forms (Figure 7c). The fact that

addition of 1.0 equivalent (*R*)-BINOL resolves this mixture into one species suggests that (*R*)-BINOL•$SnCl_4$ might preferentially stabilize the open structure. Importantly, following aqueous work up, pyrroloindoline ***exo*-96** is cleanly reisolated with no indication of epimerization or racemization.

In order to help elucidate the mode of activation by (*R*)-BINOL, reactions were carried out with mono- and bis-methylated derivatives (Figure 8). The progress of the reaction can be quantified by integrating the vinyl protons of the acrylate relative to 1,4-diethylbenzene as an internal standard. Use of (*R*)-BINOL-Me results in a moderate decrease in both rate and enantioselectivity (83% ee, exo diastereomer), whereas (*R*)-BINOL-Me_2 shows no rate enhancement over $SnCl_4$ alone. This experiment suggests that BINOL does not activate $SnCl_4$ by dative coordination alone; rather, the free hydroxyl moieties of BINOL are required.

Further kinetic analysis of (*R*)-BINOL-catalyzed reaction has been complicated by several factors, including the presence of the racemic background reaction (particularly at higher $SnCl_4$:(*R*)-BINOL ratios) and product inhibition.

Figure 8. Methylation of BINOL decreases reaction rate.



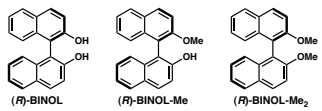
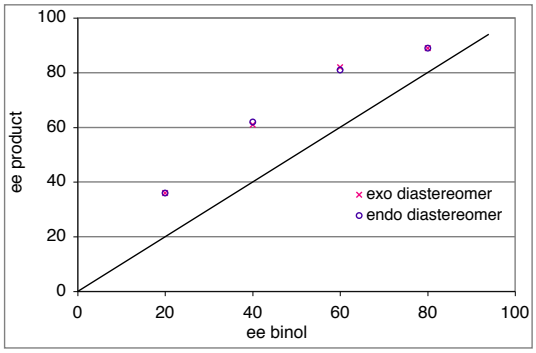
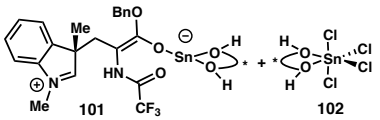


Figure 9. Non-linear effect observed with scalemic BINOL (4:1 d.r. for all reactions).





The pyrroloindoline synthesis was performed with scalemic BINOL to investigate the presence of non-linear effects.[15] Figure 9 shows that a positive non-linear relationship was indeed observed. A possible explanation for the observed non-linear effect is the interaction shown in Figure 27, where BINOL-bound tin enolate **101** is protonated by another BINOL•$SnCl_4$ species. If the heterochiral combination of (*R*)- and (*S*)-BINOL is less reactive than the homochiral combinations (i.e. a reservoir for the minor enantiomer of catalyst), then a positive non-linear effect will be observed. As the observed non-linear effect is not highly pronounced, BINOL-bound tin enolate may only be a minor species, while the majority of tin enolate species in solution are not coordinated by BINOL. This situation is likely because BINOL is present in a catalytic quantity with a large excess of $SnCl_4$.

Although further mechanistic studies are required, our observations lead us to favor a cooperative Lewis acid–Lewis acid-assisted Brønsted acid mechanism, shown in Figure 10. Activation of acrylate **71** by coordination to $SnCl_4$ results in reversible conjugate addition by the indole, generating a racemic mixture of Sn-enolates **101** and

***ent*-101**. Highly face selective protonation of **101/*ent*-101** by (*R*)-BINOL•$SnCl_4$ complex **102** resolves the two enantiomers into diastereomers in a rate- and selectivity-determining step. In this scenario, the ee of the two pyrroloindoline products would reflect the face selectivity of the protonation step, while the dr would reflect the difference in the rate of protonation of the two chiral enolates **101** and ***ent*-101**, due to "matching" and "mismatching" effects with chiral complex **102**.[16] The stoichiometric proton source required to turn over complex **103** could potentially be the N-H of trifluoroacetamide ***exo*-105/*ent-endo*-105**, which upon coordination to $SnCl_4$ would be rendered sufficiently acidic.

Figure 10. Proposed mechanism.

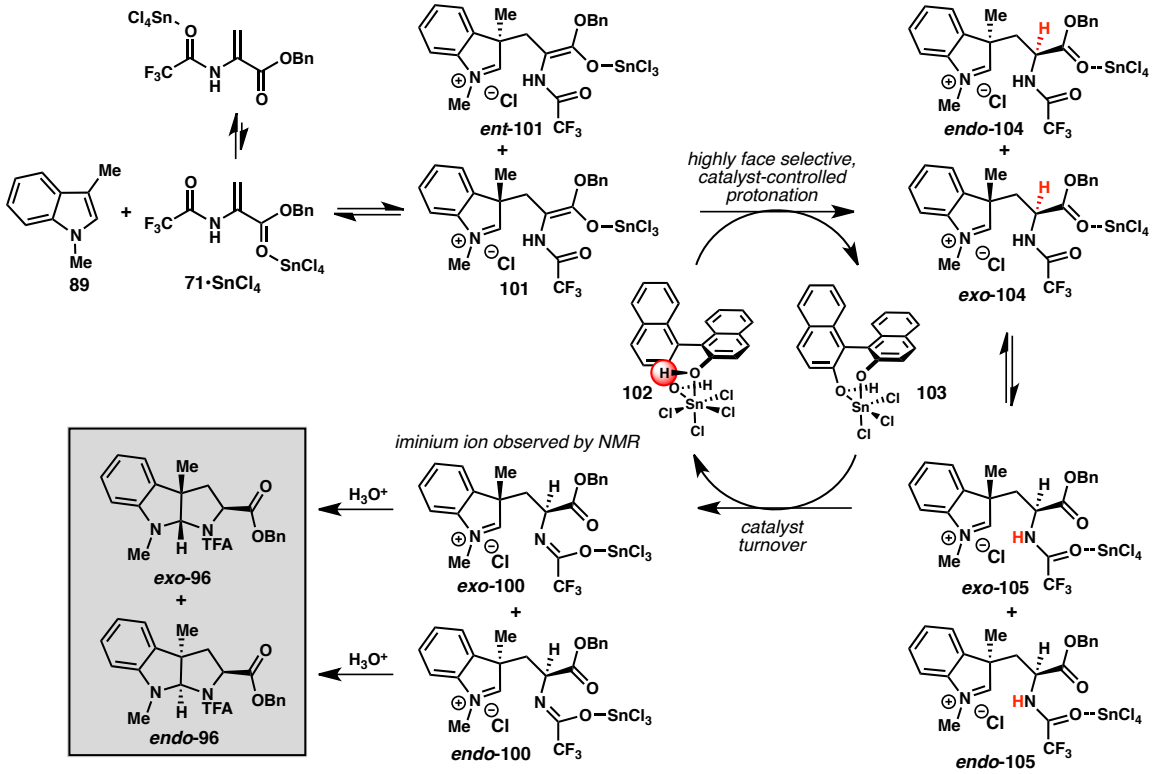
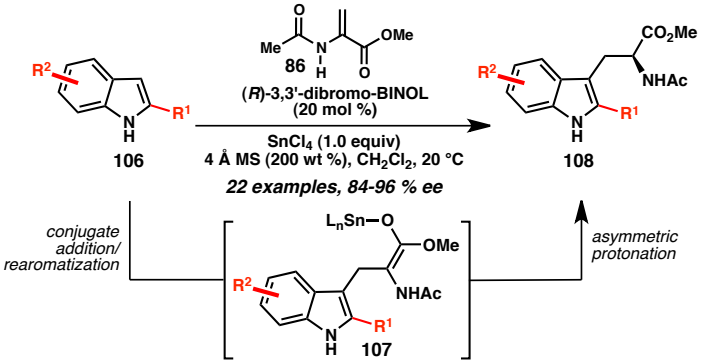


Figure 11. LBA-catalyzed conjugate addition/asymmetric protonation.



The proposed mechanism is consistent with Yamomoto's prior reports that (*R*)-BINOL•$SnCl_4$ (**102**) behaves as a "Lewis acid-assisted Brønsted acid (LBA)," which is capable of catalyzing the enantioselective protonation of silyl enolates.[17] However, the pyrroloindoline formation described above represents the first example of a tandem conjugate addition/asymmetric protonation process catalyzed by **102**. Based on this mechanistic proposal for pyrroloindoline formation, the Reisman group has identified similar conditions for the synthesis of unnatural tryptophan derivatives from 2-substituted indoles (**106**) and methyl 2-acetamidoacrylate (**86**), in which the sole stereogenic center is set during an asymmetric protonation step (Figure 11).[18‡]

2.2.5 Second Generation Reaction Conditions

The fact that diastereomers formed in the pyrroloindoline synthesis are of opposite enantiomeric series presents a practical challenge for synthetic applications. Specifically, in order to preclude racemization via epimerization during subsequent synthetic steps, it is imperative to separate the two diastereomers. Unfortunately,

‡ This work was performed by Maddi Kieffer (a graduate student) and Dr. Lindsay Repka (a former graduate student).

depending on the indole substitution pattern, separation of the diastereomers can be tedious using standard silica gel chromatography. In addition, the modest diastereoselectivity results in lower isolated yields of the pure *exo*-diastereomer. In an effort to identify conditions more amenable to application in total synthesis endeavors, we sought to re-optimize the reaction parameters for the formal (3 + 2) cycloaddition with the objective of improving the *diastereoselectivity* while maintaining synthetically useful enantioselectivity.

The first generation optimization studies determined that the enantio- and diastereoselectivity of pyrroloindoline formation are highly dependent on the substitution of the 2-amidoacrylate: the highest *enantioselectivity* was attained using benzyl 2-trifluoroacetamidoacrylate (**71**), while the highest *diastereoselectivity* was attained using methyl 2-trifluoroacetamidoacrylate (**67**) (Table 3). In the later case, the ee's of two diastereomers were only modestly reduced. Thus, we returned to the use of acrylate **67** in the cycloaddition, and sought to improve the ee and dr by optimizing the catalyst structure.

A screen of other chiral diol scaffolds showed that the (*R*)-BINOL backbone is optimal (Figure 12). A variety of (*R*)-BINOL derivatives were then investigated, revealing that several catalysts containing substitution at the 3- and 3'-positions provided an improvement in both dr and ee (Table 5). Hypothesizing that catalyst selectivity might correlate to the pK_a of the BINOL O-H protons, several 6,6'-derivatives were also prepared in order to isolate the electronic and steric effects; however, no linear correlation was observed. Ultimately, (*R*)-3,3'-Cl_2-BINOL was identified as the catalyst that provided the optimal combination of ee, dr, and overall yield.

Figure 12. Chiral diol screen.

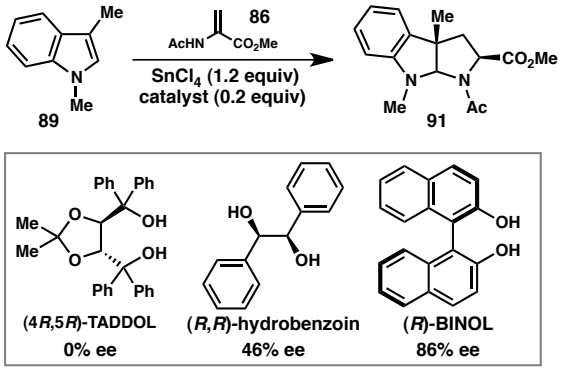
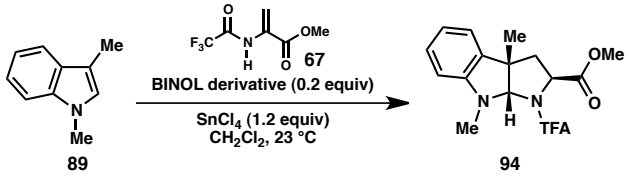


Table 5. (R)-BINOL-derivative screen.

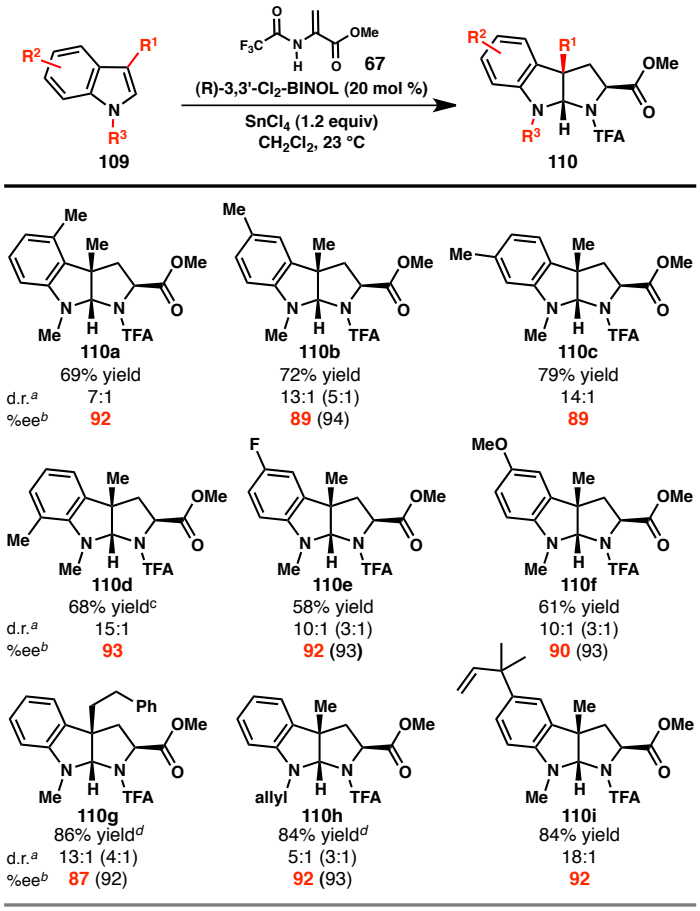


Entry	BINOL derivative	Yield (%)[a]	d.r.[b]	ee (%)[c]
1	H	88	10:1	90
2	6,6'-$(OMe)_2$	63	6:1	82
3	6,6'-Br_2	65	8:1	86
4	3,3'-Me_2	63	8:1	90
5	3,3'-Br_2	63	16:1	90
6	3,3'-Cl_2	73	14:1	91

[a] Isolated yield of *exo*:*endo* mixture. [b] Determined by ^1H NMR analysis of crude reaction mixture. [c] Determined by HPLC using chiral stationary phase.

With these newly optimized conditions in hand, a survey of indole substrates was conducted (Table 6).[19] As previously observed, indoles bearing electron-donating substrates on the aryl backbone provide the highest yields, however, both electron-rich and electron-poor substrates provided high ee's. More sterically-hindered indoles were less reactive and required 1.6 equivalents of $SnCl_4$, but nevertheless yielded the desired pyrroloindoline in good yield with high selectivity.

Table 6. Substrate scope of second generation pyrroloindoline synthesis.



[a] Determined by ^{1}H NMR analysis of crude reaction mixture. Values in parentheses are dr obtained using acrylate **71** and (*R*)-BINOL. [b] Determined by SFC using chiral stationary phase. Values in parentheses are ee obtained using acrylate **71** and (*R*)-BINOL. [c] Isolated yield of *exo*-diastereomer. [d] 1.6 equiv $SnCl_4$ was employed.

2.3 Concluding Remarks

We have developed a novel strategy for the prepararation of enantioenriched pyrroloindolines by an (*R*)-BINOL•$SnCl_4$-catalyzed formal (3 + 2) cycloaddition reaction. The transformation utilizes readily accessible indole and 2-amidoacrylate substrates to directly synthesize a variety of substituted pyrroloindoline products. Catalysis by (*R*)-BINOL allows excellent enantioselectivities to be achieved, even with an excess of Lewis acid.

Mechanistic studies have provided a more thorough understanding of this transformation. It is proposed that this reaction occurs via a highly face-selective catalyst-controlled protonation and that cyclization of the resultant iminium intermediate only occurs upon work-up. Thus, the diastereomeric products possess opposite configurations as the bridgehead quaternary carbon. The implications of these experiments have resulted in the reoptimization of the conditions for this reaction to provide higher levels of selectivity.

The mechanistic proposal has led to the development of other methods for indole alkaloid synthesis, including a tandem conjugate addition/enantioselective protonation reaction to generate tryptophan derivatives,[§] a conjugate addition/in situ reduction to yield indoline amino acid derivatives (Chapter 2), and a conjugate addition/asymmetric protonation/Prins cyclization reaction (Chapter 3).

In addition, this reaction has been utilized to prepare the core pyrroloindoline motifs in the enantioselective total syntheses of the natural products (–)-lansai B[20] and (+)-nocardioazine A.[21**] Further related research within the Reisman laboratory is focused on improving mechanistic understanding of the formal (3 + 2) cycloaddition reaction, application of the asymmetric protonation strategy to new methodologies, and the synthesis of pyrroloindoline natural products.

[§] This work was performed by Maddi Kieffer (a graduate student in the Reisman lab) and Dr. Lindsay Repka (a former graduate student in the Reisman lab).

[**] Research conducted by Haoxuan Wang, a graduate student in the Reisman lab.

2.4 Experimental Section

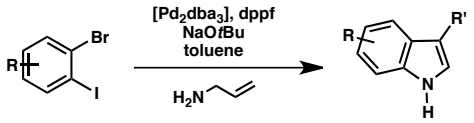
2.4.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran, methylene chloride, toluene, and hexanes were dried by passing through activated alumina columns. Dimethylformamide was dried over activated molecular sieves, and dichloroethane was distilled over calcium hydride. Deuterated methylene chloride (CD_2Cl_2) for the experiments resubjecting the pyrroloindoline products to reaction conditions was dried by passing through a plug of activated alumina. All other commercially obtained reagents were used as received unless specifically indicated. $EtAlCl_2$ (neat) and 1 M $SnCl_4$ in DCM were purchased from Aldrich and (*R*)-BINOL was obtained from Alfa Aesar. (*R*)-6,6'-dimethoxy-BINOL,[18] (*R*)-6,6'-dibromo-BINOL,[22] (*R*)-3,3'-dimethyl-BINOL,[23] (*R*)-3,3'-dibromo-BINOL,[24] and (*R*)-3,3'-dichloro-BINOL[25] were prepared according to literature procedures. Reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, or $KMnO_4$ staining. Flash column chromatography was performed either as described by Still et al. using silica gel (particle size 0.032-0.063) purchased from Silicycle or pre-packaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Diastereomeric ratios were determined by integration of NMR spectra or HPLC or SFC analysis. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz, respectively), a Varian 400 (at 400 MHz and 100 MHz, respectively) or a Varian Inova 500 (at 500 MHz and 125 MHz, respectively), and are reported relative to

internal chloroform (^{1}H, δ = 7.26, ^{13}C, δ = 77.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). Preparative HPLC was performed with either an Agilent 1100 or 1200 Series HPLC utilizing an Agilent Zorbax RX-SIL 5μm column (9.4 x 250 mm). Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing Chiralcel AD or OD-H columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd, with visualization at 254 nm. Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system with Chiralcel AD-H and OJ-H columns (4.6 mm x 25 cm). Melting points were determined using a Büchi B-545 capillary melting point apparatus and the values reported are uncorrected. HRMS were acquired using either an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode, or obtained from the Caltech Mass Spectral Facility.

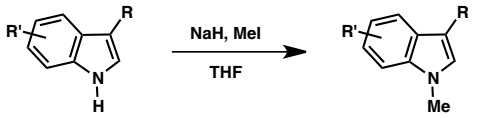
2.4.2 Substrate Synthesis

General Procedure A. Amination-Heck cascade for synthesis of indole derivatives.



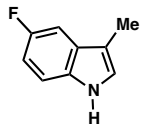
Procedure was adapted from Jørgensen *et al*.[26] To a 50 mL Schlenk tube was added [Pd_2dba_3], dppf, NaO*t*Bu (20.8 mmol, 2.5 equiv), and toluene (10 mL). The mixture was stirred for 5 minutes, then the bromoiodide (8.3 mmol, 1.0 equiv) and allylamine (8.3 mmol, 1.0 equiv) were added. The tube was sealed, heated to 140 °C over 30 minutes, and stirred at 140 °C for 21 h. The reaction was then cooled to room temperature, diluted with 40 mL hexanes, filtered through a plug of celite, and concentrated under reduced pressure. The crude residue was purified by flash chromatography.

General Procedure B. *N*-methylation of indole derivatives.



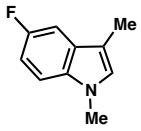
In a flame-dried flask, the indole (1.7 mmol, 1.0 equiv) was dissolved in 11 mL THF. Sodium hydride (60% w/w, 2.5 mmol, 1.5 equiv) was added in one portion, then methyl iodide (3.4 mmol, 2.0 equiv) was added dropwise. The reaction was stirred at room temperature until consumption of starting material was observed by TLC. The reaction was diluted with ethyl acetate and the excess NaH was quenched with water. The organic layer was separated, and the aqueous layer was extracted 3× with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography.

5-Fluoro-3-methyl-1*H*-indole.



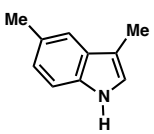
Prepared from 3.75 mmol of 2-bromo-4-fluoro-1-iodobenzene, 0.63 mol % [Pd_2dba_3] and 2.5 mol % dppf using general procedure A. The product was purified by flash chromatography (10% ethyl acetate/hexanes) to yield 5-fluoro-3-methyl-1*H*-indole (**128b**, 0.22 g, 38% yield). Spectral data matches that reported in the literature.[26]

5-Fluoro-1,3-dimethyl-1*H*-indole (97b).



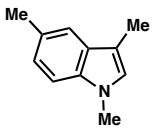
Prepared from 1.07 mmol of 5-fluoro-3-methyl-1*H*-indole using general procedure B. The product was purified by flash chromatography (3% ethyl acetate/hexanes) to yield **97b** (0.97 g, 55% yield) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.13 (m, 2H), 7.00 – 6.92 (m, 1H), 6.86 (s, 1H), 3.72 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 132.4, 128.8, 127.2, 111.6, 109.8, 109.5, 100.8, 32.6, 9.6. IR (NaCl/thin film): 2918, 1581, 1493, 1457, 1423, 1225, 1062, 786 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $[M+H]^+$ 164.0870, found 164.0873.

3,5-dimethyl-1*H*-indole.



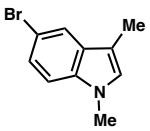
Prepared from 2.88 mmol of 2-bromo-1-iodo-4-methylbenzene,[27] 2.5 mol % [Pd_2dba_3] and 10 mol % dppf using general procedure A. The product was purified by flash chromatography (5→13% ethyl acetate/hexanes) to yield 3,5-dimethyl-1*H*-indole (0.11 g, 14% yield). Spectral data matches that reported in the literature.[26]

1,3,5-trimethyl-1*H*-indole (97c).



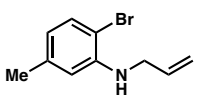
Prepared from 0.70 mmol of 3,5-dimethyl-1*H*-indole using general procedure B. The product was purified by flash chromatography (2% ethyl acetate/hexanes) to yield **97c** (0.048 g, 43% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 1H), 7.18 (d, *J* = 8.3 Hz, 1H), 7.05 (dd, *J* = 8.3, 1.4 Hz, 1H), 6.78 (s, 1H), 3.71 (s, 3H), 2.49 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 128.8, 127.6, 126.6, 123.0, 118.6, 109.5, 108.7, 32.5, 21.5, 9.5. IR (NaCl/thin film): 2918, 1494, 1460, 1388, 1298, 1250, 1149, 1058, 885, 866, 784 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $[M+H]^+$ 160.1121, found 160.1116.

5-Bromo-1,3-dimethyl-1*H*-indole (97d).



Prepared from 0.95 mmol of 5-bromo-3-methyl-1*H*-indole[28] using general procedure B. The product was purified by flash chromatography (5% ethyl acetate/hexanes) to yield **97d** (0.20 g, 90% yield) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 1.5 Hz, 1H), 7.30 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.14 (d, *J* = 8.6 Hz, 1H), 6.82 (s, 1H), 3.70 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6, 130.3, 127.7, 124.1, 121.5, 111.9, 110.5, 109.7, 32.6, 9.4. IR (NaCl/thin film): 2918, 1563, 1479, 1422, 1279, 812, 785 cm^{-1}; HRMS (APCI) calc'd for $[M+H]^+$ 224.0069, found 224.0070.

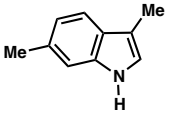
***N*-allyl-2-bromo-5-methylaniline.**



Procedure was adapted from Sørensen and Pombo-Villar.[29] To a solution of 2-bromo-5-methylaniline (10.8 mmol, 1.0 equiv) in 29 mL THF at –78°C was added MeLi (2.9 M solution in dimethoxymethane, 11.8 mmol, 1.1 equiv), and stirred for 30 minutes. Allyl bromide was added dropwise, followed by

stirring at –78 °C for 10 minutes, then at room temperature for 5 h. Then saturated $NaHCO_{3\,(aq)}$ solution was added, and the aqueous layer was extracted with ethyl acetate 3×. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield *N*-allyl-2-bromo-5-methylaniline (1.63 g, 67% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.0 Hz, 1H), 6.46 (d, *J* = 1.5 Hz, 1H), 6.41 (ddd, *J* = 8.0, 2.0, 0.6 Hz, 1H), 5.97 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.31 (ddd, *J* = 17.2, 3.3, 1.7 Hz, 1H), 5.21 (dq, *J* = 10.3, 1.5 Hz, 1H), 4.41 (s, 1H), 3.83 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 138.4, 134.7, 132.0, 118.8, 116.3, 112.4, 106.5, 46.2, 21.5. IR (NaCl/thin film): 3411, 2920, 1596, 1506, 1416, 1016, 921, 787 cm^{-1}. HRMS (MM: ESI–APCI) calc'd for $[M+H]^+$ 226.0226, found 226.0216.

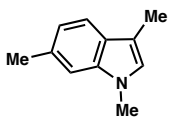
3,6-dimethyl-1*H*-indole.



Procedure was adapted from Sørensen and Pombo-Villar.[29] A solution of *N*-allyl-2-bromo-5-methylaniline (1.6 mmol, 1.0 equiv), $Pd(OAc)_2$ (0.16 mmol, 0.1 equiv), dppp (0.16 mmol, 0.1 equiv), Bu_4NCl (1.6 mmol, 1.0 equiv), and NaOAc (6.2 mmol, 4.0 equiv) in 24 mL DMF was heated to 120 °C in a flask equipped with a reflux condenser for 16 h. The reaction was cooled to room temperature, saturated $NaHCO_{3\,(aq)}$ solution and 100 mL water were added, then the aqueous layer was extracted with ethyl acetate 3×. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (5→10% ethyl acetate/hexanes) to yield 3,6-dimethyl-1*H*-indole (0.19 g, 85% yield) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (br s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.13-7.11 (m, 1H), 6.94 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 6.87 (dd, *J* = 2.1 Hz,

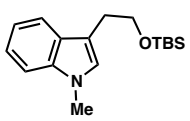
1.1 Hz, 1H), 2.45 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 131.6, 126.2, 120.9, 120.8, 118.5, 111.6, 110.9, 21.7, 9.7. IR (NaCl/thin film): 3409, 2922, 1452, 1329, 1086, 908, 803, 733 cm^{-1}. HRMS (MM: ESI–APCI) calc'd for $[M+H]^+$ 146.0964, found 146.0970.

1,3,6-trimethyl-1*H*-indole (97e).



Prepared from 0.70 mmol of 3,6-dimethyl-1*H*-indole using general procedure B. The product was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield **97e** (62 mg, 56% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.0 Hz, 1H), 7.07 (s, 1H), 6.94 (dd, *J* = 8.0, 0.7 Hz, 1H), 6.75 (d, *J* = 0.9 Hz, 1H), 3.70 (s, 3H), 2.50 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 131.1, 126.5, 125.8, 120.2, 118.6, 109.9, 109.0, 32.4, 21.9, 9.6. IR (NaCl/thin film): 3027, 2917, 2860, 1625, 1478, 1388, 1369, 1328, 1248, 799 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $[M+H]^+$ 160.1121, found 160.1114.

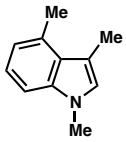
1-methyl-3-*t*-butyldimethylsiloxyethyl-1*H*-indole (97f).



Prepared from 2.66 mmol of 3-*t*-butyldimethylsiloxyethyl-1*H*-indole[30] using general procedure B. The product was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield **97f** (0.67 g, 87% yield) as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.31 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.26 – 7.23 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.13 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 6.91 (s, 1H), 3.90 (t, J = 7.2 Hz, 2H), 3.76 (s, 3H), 3.02 (ddd, *J* = 7.9, 7.1, 0.8 Hz, 2H), 0.95 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 128.1, 126.9, 121.4, 119.0, 118.6, 111.5, 109.1, 64.1, 32.5, 29.0, 26.0, 18.4, -5.3; IR (NaCl/thin film):

3056, 2954, 2929, 2857, 1472, 1251, 1095, 836, 737 cm^{-1}; HRMS (ESI) calc'd for $[M+H]^+$ 290.1940, found 290.1933.

1,3,4-trimethyl-1*H*-indole



Procedure for Vilsmeier-Haack reaction followed by $LiAlH_4$ reduction was adapted from Petit et al.[31] In a flame-dried flask under nitrogen, $POCl_3$ (0.42 mL, 4.6 mmol) was added at 0 °C to 4-methyl-1*H*-indole (0.5 g, 3.8 mmol) in DMF (7.6 mL). The reaction was stirred at room temperature overnight. 2N $NaOH_{(aq)}$ was added, the solution was stirred for 2 h, and then poured into EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude aldehyde was carried forward without further purification.

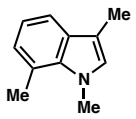
In a flame-dried flask under nitrogen, a solution of the Vilsmeier-Haack product (0.39 g, 2.5 mmol) in THF (5 mL) was added dropwise to a suspension of $LiAlH_4$ (0.19 g, 5 mmol) in THF (1.6 mL). The reaction was heated to reflux for 4 h, then cooled to room temperature and stirred overnight. The reaction was diluted with Et_2O and cooled to 0 °C. Water (0.19 mL) was added slowly, then 15% $NaOH_{(aq)}$ (0.19 mL), and then water (0.6 mL) were added. The mixture was warmed to room temperature and stirred for 15 minutes. Some $MgSO_4$ was added, the mixture was stirred for 15 minutes, filtered, and concentrated. The crude indole was carried forward without further purification.

In a flame-dried flask, the indole (0.3 g, 2.1 mmol) was dissolved in THF (13 mL). Sodium hydride (60% w/w, 124 mg, 3.1 mmol) was added in one portion, then methyl iodide (0.26 mL, 4.1 mmol) was added dropwise. The reaction was stirred at room temperature until consumption of starting material was observed by TLC. The reaction was diluted with ethyl acetate and the excess NaH was quenched with water. The organic

layer was separated, and the aqueous layer was extracted 3× with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (44% yield over three steps).

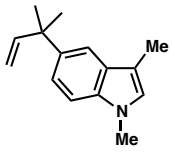
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12-7.05 (m, 2H), 6.81 (ddd, *J* = 6.6, 1.4, 0.8 Hz, 1H), 6.76 (d, *J* = 0.9 Hz, 1H), 3.69 (s, 3H), 2.72 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 131.4, 126.9, 126.7, 121.5, 120.0, 110.9, 107.0, 32.5, 20.0, 12.8; IR (NaCl/thin film): 2918, 1608, 1573, 1551, 1497, 1453, 1417, 1313, 1250, 1205, 1157, 1057, 767, 739 cm^{-1}.

1,3,7-trimethyl-1*H*-indole



Prepared according to the procedure for 1,3,4-trimethyl-1*H*-indole. Spectral data matches that reported in the literature.[32]

1,3-dimethyl-5-reverse prenyl-1*H*-indole



In glovebox, $Pd_2(dba)_3$ (51 mg, 6 mmol) and SPhos (91 mg, 22 mmol) was stirred at room temperature in THF (3 mL) for 1 h until a dark yellow homogeneous solution was formed. Then the solution was transferred into a schlenk tube. Iododimethyl indole (300 mg, 1.11 mmol), trifluorosilane[33] (256 mg in 2.1 mL THF, 1.66 mmol), TBAF (1 M solution in THF, 1.66 mL), and THF (7 mL) were added to the schlenk tube. The reaction mixture was heated to 60°C for 36 h. More TBAF (1M solution in THF, 0.55 mL) was added at 12-h intervals. The reaction was quenched with 5% EtOAc in hexanes and filtered through a silica plug. The organic solution was concentrated to give orange oil. It was then purified by flash chromatography (5% to 9% EtOAc in hexanes) to give reverse prenylated indole

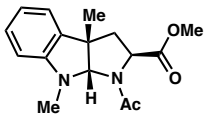
XX as a light yellow oil (177 mg, 0.84 mmol, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$) 7.51 (t, J = 0.9 Hz, 1H), 7.24 (dd, J = 8.7, 1.83 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H), 6.80 (d, J = 1.0 Hz, 1H), 6.13 (dd, J = 17.5, 10.6 Hz, 1H), 5.09 (dd, J = 17.6, 1.5 Hz, 1H), 5.04 (dd, J = 10.5, 1.5 Hz, 1H), 3.71 (s, 3H), 2.32 (d, J = 1.0 Hz, 3H), 1.49 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) 149.1, 138.8, 135.4, 128.3, 126.7, 120.6, 115.5, 110.1, 109.9, 108.5, 41.1, 32.5, 28.8, 9.5; IR (NaCl/thin film): 3080, 2964, 2920, 1634, 1489, 1455, 1425, 1387, 1376, 1365, 1292, 1256, 1201, 1152, 1053, 1004, 909, 874, 788; HRMS (MM) calc'd for $C_{15}H_{19}N$ $[M+H]^+$ 214.1590, found 214.1592.

2.4.3 General Procedure C. Formal (3 + 2) Cycloaddition of Indoles and Acrylates

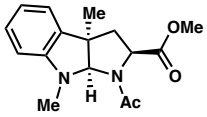
To a flame-dried flask was added indole (0.20 mmol, 1.00 equiv), acrylate (0.20 mmol, 1.00 equiv), and (*R*)-BINOL (0.04 mmol, 0.20 equiv). The flask was charged with DCM (1.5 mL), followed by addition of $SnCl_4$ (0.24 mmol, 1.20 equiv unless specifically indicated, 1 M in DCM), then stirred at room temperature. The reaction was quenched by diluting with 1 mL MeCN and 1 mL 1 M HCl, followed by addition of 5 mL H_2O. The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic layers were washed with either saturated $NaHCO_{3(aq)}$ or 1 M $NaOH_{(aq)}$ (10 mL). The aqueous layer was back extracted with EtOAc (10 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified by flash chromatography.

2.4.4 Pyrroloindoline Products under General Procedure C

Pyrroloindoline 91.



(a) *exo* diastereomer



(b) *endo* diastereomer

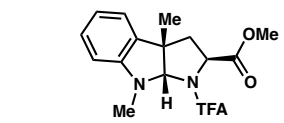
Screen varying (*R*)–BINOL loading. All reactions were run at room temperature for 3 h in DCE with 1,3-dimethyl-1*H*-indole[34] (**89**, 0.2 mmol, 1 equiv), methyl 2-acetamidoacrylate[35] (**86**, 0.2 mmol, 1 equiv) and $SnCl_4$ (1.2 equiv, 1 M in DCM). Purified by flash chromatography (0→50% ethyl acetate/hexanes). The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. The diastereomers were separated by flash chromatography (30→50% ethyl acetate/hexanes). The enantiomeric excess was determined for both diastereomers by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in hexanes, λ = 254 nm).

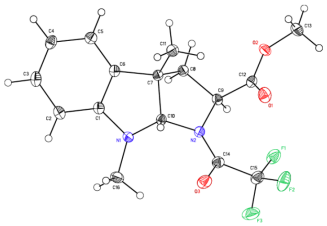
Exo diastereomer: pale yellow oil. t_R(major) = 9.5 min t_R(minor) = 6.2 min. ^{1}H NMR (400 MHz, $CDCl_3$; compound exists as a 1:1 mixture of rotamers) δ 7.10 – 7.01 (m, 1H), 6.95 (d, *J* = 7.3 Hz, 0.5H), 6.91 (d, *J* = 7.3 Hz, 0.5H), 6.68 (t, *J* = 7.4 Hz, 0.5H), 6.62 (t, *J* = 7.4 Hz, 0.5H), 6.43 (d, *J* = 7.8 Hz, 0.5H), 6.38 (d, J=7.8 Hz, 0.5H), 5.47 (s, 0.5H), 5.04 (s, 0.5H), 4.43 (dd, *J* = 10.0, 1.9 Hz, 0.5H), 4.30 (dd, *J* = 9.7, 4.7 Hz, 0.5H), 3.73 (s, 1.5H), 3.66 (s, 1.5H), 2.98 (s, 1.5H), 2.80 (s, 1.5H), 2.44 (dd, *J* = 13.4, 10.0 Hz, 0.5H), 2.32 (dd, *J* = 13.3, 9.8 Hz, 0.5H), 2.22 (s, 0.5H), 2.18 (dd, *J* = 13.5, 2.0 Hz, 0.5H), 1.97 – 1.90 (m, 2H), 1.46 (s, 1.5H), 1.32 (s, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$; compound exists as a 1:1 mixture of rotamers) δ 172.8, 171.7, 171.5, 169.4, 149.4, 148.5, 134.2, 128.04, 128.02, 121.0, 120.8, 118.6, 117.6, 107.7, 107.1, 91.8, 90.8, 60.5, 59.6, 52.2, 51.8, 51.6, 49.2, 43.4, 41.0, 35.9, 33.8, 22.5, 22.3, 21.9; IR (NaCl/thin film): 2954, 2877,

1746, 1660, 1608, 1489, 1393, 1299, 1200, 1178, 744 cm^{-1}; $[\alpha]_D^{25}$ –69.7° (c = 0.85, DCM); HRMS (FAB+) calc'd for $[M+H]^+$ 289.1552, found 289.1559.

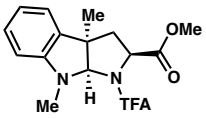
Endo diastereomer: bright yellow oil. t_R(major) = 4.0 min t_R(minor) = 4.7 min. ^1H NMR (400 MHz, $CDCl_3$; compound exists as a 3:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.11 (t, *J* = 7.6 Hz, 1H§), 7.06 (t, *J* = 7.8 Hz, 1H*), 7.01 (d, *J* = 7.1 Hz, 1H§), 6.96 (d, *J* = 7.2 Hz, 1H*), 6.68 (t, *J* = 7.4 Hz, 1H§), 6.61 (t, *J* = 7.3 Hz, 1H*), 6.40 (d, *J* = 7.8 Hz, 1H§), 6.32 (d, *J* = 7.8 Hz, 1H*), 5.55 (s, 1H*), 5.09 (s, 1H§), 4.98 (dd, J= 8.8, 5.8 Hz, 1H§), 4.46 (d, *J* = 8.3 Hz, 1H*), 3.46 (s, 3H§), 3.25 (s, 3H*), 2.99 (s, 3H*), 2.91 (s, 3H§), 2.68 (d, *J* = 13.6 Hz, 1H*), 2.44 – 2.16 (m, 1H*, 5H§), 2.05 (s, 3H*), 1.42 (s, 3H§), 1.41 (s, 3H*); ^{13}C NMR (100 MHz, $CDCl_3$; compound exists as a 3.0**:**1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 171.4§, 171.1*, 170.7*, 169.6§, 150.6*, 149.0§, 133.1§, 132.4*, 128.7*, 128.6§, 122.3*, 121.8§, 118.0§, 117.1*, 106.4§, 105.6*, 91.1§, 86.4*, 61.1*, 59.1§, 52.3§, 52.2*, 52.1§, 50.8*, 42.6*, 41.7§, 32.2*, 31.6§, 24.7*, 22.8§, 22.4*, 21.9§; IR (NaCl/thin film): 2953, 2869, 1740, 1656, 1610, 1493, 1407, 1302, 1236, 1204, 744 cm^{-1}; $[\alpha]_D^{25}$ +146.5° (c = 0.79, DCM) ; HRMS (FAB+) calc'd for $[M+H]^+$ 289.1552 , found 289.1549.

Pyrroloindoline 94.





(a) *exo* diastereomer



(b) *endo* diastereomer

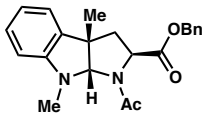
Prepared from 1,3-dimethyl-1*H*-indole **89** and methyl 2-trifluoroacetamidoacrylate[36] **67** using general procedure C (with DCE as the solvent). The reaction was allowed to run for 4 h. The crude residue was purified by flash chromatography (20→35% ethyl acetate/hexanes) to yield 53.0 mg (77% yield) of **94** in a 6:1 ratio of diastereomers (determined by ^{1}H NMR analysis of the purified product). The diastereomers were separated by preparatory HPLC (0→8% ethyl acetate/hexanes).

Exo diastereomer: pale yellow oil that crystallized upon standing in the fridge to give crystals suitable for single crystal X-ray diffraction. The enantiomeric excess was determined to be 86% by chiral SFC analysis (AD-H, 2.5 mL/min, 7% IPA in CO_2, λ = 254 nm): t_R(major) = 2.8 min t_R(minor) = 2.4 min. ^{1}H NMR (400 MHz, $CDCl_3$; compound exists as a 2.4:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.18 (t, J = 7.6 Hz, 1H*, 1H§), 7.03 (d, J = 7.2 Hz, 1H*, 1H§), 6.82 (br s, J = 7.4 Hz, 1H§), 6.77 (t, J = 7.3 Hz, 1H*), 6.56 (br s, 1H§), 6.51 (d, J = 7.8 Hz, 1H*), 5.62 (s, 1H*), 5.34 (br s, 1H§), 4.72 (d, J = 9.2 Hz, 1H*), 4.44 (br s, 1H§), 3.82 (br s, 3H*), 3.77 (br s, 3H§), 3.08 (br s, 3H*), 2.87 (br s, 3H§), 2.60 (dd, J = 13.0, 9.9 Hz, 1H*), 2.55 – 2.44 (br m, 1H§), 2.37 (d, J = 12.7 Hz, 1H*), 2.13-2.00 (br m, 1H§), 1.51 (s, 3H§), 1.40 (s, 3H*); ^{13}C NMR (100 MHz, $CDCl_3$; compound exists as a 2.4:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.6*, 170.5§, 159.2* (q, $J_{C\text{-}F}$ = 37.2 Hz), 149.4*, 149.2§, 134.2*§, 128.8*§, 121.5*§, 119.9§,

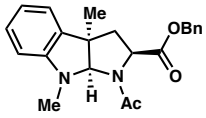
118.7*, 116.1* (q, $J_{C\text{-}F}$ = 288.4 Hz), 109.4[§], 108.0*, 93.3*, 91.7[§], 61.3[§], 60.3*, 53.0*, 52.6[§], 49.2*[§], 44.0*, 40.6[§], 36.8*, 34.4[§], 23.5*, 22.8[§]; IR (NaCl/thin film): 2959, 1751, 1696, 1610, 1490, 1435, 1204, 1155, 988, 744 cm^{-1}; melting point: 105.5 – 107.5 °C; $[\alpha]_D^{25}$ = –118.1° (*c* = 0.78, DCM). HRMS (ESI) calc'd for $[M+H]^+$ 343.1270, found 343.1267.

Endo diastereomer: pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$; compound exists as a 9.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 7.13 (t, *J* = 7.7 Hz, 1H[§]), 7.10 (t, *J* = 7.7 Hz, 1H*), 7.04 (d, *J* = 7.5 Hz, 1H[§]), 6.98 (d, *J* = 7.3 Hz, 1H*), 6.73 (t, *J* = 7.4 Hz, 1H[§]), 6.66 (t, *J* = 7.4 Hz, 1H*), 6.43 (d, *J* = 7.8 Hz, 1H[§]), 6.37 (d, *J* = 7.8 Hz, 1H*), 5.59 (s, 1H*), 5.33 (s, 1H[§]), 5.07 (dd, *J* = 9.4, 5.2 Hz, 1H[§]), 4.74 (d, *J* = 8.2 Hz, 1H*), 3.57 (s, 3H[§]), 3.16 (s, 3H*), 3.05 (s, 3H*), 2.80 (s, 3H[§]), 2.80 (d, *J* = 12.7 Hz, 1H*), 2.42 (dd, *J* = 13.3, 5.3 Hz, 1H[§]), 2.37 (dd, *J* = 12.9, 8.3 Hz, 1H*), 2.26 (dd, *J* = 13.2, 9.7 Hz, 1H[§]), 1.45 (s, 3H*), 1.43 (s, 3H[§]); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 9.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 169.9*, 156.8* (q, $J_{C\text{-}F}$ = 36.9 Hz), 150.4*, 148.5[§], 133.0[§], 131.8*, 129.1*, 128.7[§], 122.5*, 121.6[§], 118.6[§], 117.8*, 116.1* (q, $J_{C\text{-}F}$ = 288.7 Hz), 106.9[§], 105.7*, 90.8[§], 88.5*, 60.3[§], 60.1*, 52.5*, 52.2[§], 50.4*[§], 42.9*, 41.1[§], 32.1*[§], 25.1*, 22.2[§]; IR (NaCl/thin film): 2954, 2923, 1741, 1694, 1608, 1494, 1435, 1206, 1147, 998, 860, 844, 742 cm^{-1}; $[\alpha]_D^{25}$ = +201.5° (*c* = 0.11, DCM). HRMS (ESI) calc'd for $[M+H]^+$ 343.1270, found 343.1278.

Pyrroloindoline 95.



(a) *exo* diastereomer



(b) *endo* diastereomer

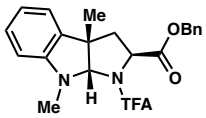
Prepared from 1,3-dimethyl-1*H*-indole **89** and benzyl 2-acetamidoacrylate[37] **93** using general procedure C (with DCE as the solvent). The reaction was allowed to run for 4 h. The product **95** was formed in a 2:1 ratio of diastereomers (determined by ^{1}H NMR analysis of the crude reaction mixture), and purified by flash chromatography (20→35% ethyl acetate/hexanes) to yield 41.3 mg (57% yield) of the *exo* diastereomer and 17.3 mg (24% yield) of the *endo* diastereomer.

Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 74% by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in CO_2, λ = 254 nm): t_R(major) = 24.6 min t_R(minor) = 19.1 min. ^{1}H NMR (300 MHz, $CDCl_3$; compound exists as a 1.1:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.43 – 7.29 (m, 5H*, 5H§), 7.19 – 7.09 (m, 1H*, 1H§), 7.01 (d, *J* = 7.3 Hz, 1H§), 6.96 (d, *J* = 7.3 Hz, 1H*), 6.76 (t, *J* = 8.4 Hz, 1H§), 6.70 (t, *J* = 7.4 Hz, 1H*), 6.50 (d, *J* = 8.2 Hz, 1H§), 6.46 (d, *J* = 8.0 Hz, 1H*), 5.54 (s, 1H*), 5.28 (d, *J* = 12.0 Hz, 1H*), 5.21 (d, *J* = 9.7 Hz, 1H§), 5.20 (s, 1H*, 1H§), 5.09 (s, 1H§), 4.51 (dd, *J* = 10.1, 2.1 Hz, 1H*), 4.45 (dd, *J* = 9.8, 4.8 Hz, 1H§), 3.06 (s, 3H*), 2.89 (s, 3H§), 2.53 (dd, *J* = 13.4, 10.0 Hz, 1H*), 2.42 (dd, *J* = 13.3, 9.7 Hz, 1H§), 2.31 (s, 3H§), 2.22 (dd, *J* = 13.5, 2.0 Hz, 1H*), 2.01 (dd, *J* = 13.3, 4.8 Hz, 1H§), 1.95 (s, 3H*), 1.49 (s, 3H§), 1.32 (s, 3H*); ^{13}C NMR (100 MHz, $CDCl_3$; compound exists as a 1.1:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.6*, 172.0§, 171.6*, 170.0§, 149.9*, 148.9§, 135.7§, 134.9*, 134.7*, 134.6§, 128.8§, 128.7*, 128.7*, 128.5§, 128.5*, 128.2*, 128.2§, 121.5§, 121.2*, 119.1§, 118.1*, 108.1§, 107.7*, 92.4§, 91.4*, 67.6*, 66.9§, 61.1*, 60.2§, 52.3§,

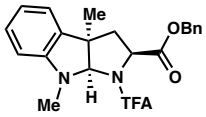
49.7*, 43.8*, 41.4§, 36.5*, 34.3§, 23.0§, 22.7*, 22.7*, 22.4§; IR (NaCl/thin film): 3032, 2962, 2877, 1745, 1661, 1609, 1489, 1390, 1175, 1117, 744 cm^{-1}; $[\alpha]_D^{25}$ = –66.9° (*c* = 0.98, DCM). HRMS (ESI) calc'd for $[M+H]^+$ 365.1865, found 365.1875.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 82% by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in CO_2, λ = 254 nm): t_R(major) = 11.1 min t_R(minor) = 12.6 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 3.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.36 – 7.28 (m, 3H*, 3H§), 7.23 – 7.20 (m, 2H§), 7.19 – 7.15 (m, 2H*), 7.12 (td, *J* = 7.7, 1.3 Hz, 1H§), 7.08 (td, *J* = 7.7, 1.3 Hz, 1H*), 7.01 (dd, *J* = 7.3, 0.9 Hz, 1H§), 6.98 (dd, *J* = 7.3, 0.9 Hz, 1H*), 6.69 (td, *J* = 7.4, 0.9 Hz, 1H§), 6.64 (td, *J* = 7.4, 0.9 Hz, 1H*), 6.36 (d, *J* = 7.8 Hz, 1H§), 6.28 (d, *J* = 7.8 Hz, 1H*), 5.56 (s, 1H*), 5.09 (s, 1H§), 5.05 (dd, *J* = 9.0, 6.0 Hz, 1H§), 4.92 (d, *J* = 12.4 Hz, 1H§), 4.88 (d, *J* = 12.4 Hz, 1H§), 4.69 (d, *J* = 12.2 Hz, 1H*), 4.55 (d, *J* = 12.2 Hz, 1H*), 4.51 (dd, *J* = 8.5, 1.9 Hz, 1H*), 2.93 (s, 3H*), 2.81 (s, 3H§), 2.73 (dd, *J* = 12.8, 1.8 Hz, 1H*), 2.37 (dd, *J* = 13.0, 6.0 Hz, 1H§), 2.33 (dd, *J* = 12.8, 8.5 Hz, 1H*), 2.31 (s, 3H§), 2.26 (dd, *J* = 13.0, 9.0 Hz, 1H§), 2.05 (s, 3H*), 1.42 (s, 3H§), 1.41 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 3.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 170.8*, 170.5*, 169.6§, 150.4*, 148.9§, 135.5§, 134.9*, 133.1§, 132.5*, 128.8*, 128.6§, 128.5*, 128.4§, 128.4*, 128.2*, 128.1§, 128.0§, 122.4*, 121.8§, 118.0§, 117.2*, 106.5§, 105.7*, 91.3§, 86.5*, 67.3*, 66.7§, 61.3*, 59.3§, 52.3§, 50.8*, 42.6*, 41.8§, 32.3*, 31.6§, 24.8*, 22.7§, 22.5*, 21.9§; IR (NaCl/thin film): 2956, 1741, 1656, 1608, 1493, 1404, 1301, 1219, 1194, 1152, 1105, 992, 743 cm^{-1}; $[\alpha]_D^{25}$ = +114.4° (*c* = 0.57, DCM). HRMS (ESI) calc'd for $[M+H]^+$ 365.1865, found 365.1862.

Pyrroloindoline 96.



(a) ***exo*** **diastereomer**



(b) ***endo*** **diastereomer**

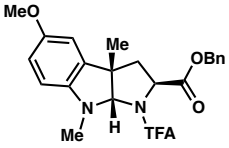
Prepared from 1,3-dimethyl-1*H*-indole (**89**, 0.15 mmol) and benzyl 2-trifluoroacetamidoacrylate[38] (**71**, 0.15 mmol) using general procedure C. The reaction was allowed to run for 5.5 h. The crude residue was purified by flash chromatography (5→8% ethyl acetate/hexanes) to yield 54 mg (86% yield) of **96** in a 4:1 ratio of diastereomers (determined by NMR analysis of the crude reaction mixture). The diastereomers were separated by flash chromatography (5→8% ethyl acetate/hexanes). The enantiomeric excesses of both diastereomers were determined by chiral SFC analysis (OJ-H, 2.5 mL/min, 3% IPA in CO_2, λ = 254 nm).

Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 94%. t_R(major) = 12.5 min t_R(minor) = 10.7 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 2.6:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.53-7.36 (m, 5H*, 5H§), 7.23 (br t, *J* = 7.6 Hz, 1H*, 1H§), 7.11 (br d, *J* = 6.7 Hz, 1H§), 7.07 (br d, *J* = 7.2 Hz, 1H*), 6.93 – 6.86 (m, 1H§), 6.83 (br t, *J* = 7.3 Hz, 1H*), 6.64 (br d, *J* = 7.3 Hz, 1H§), 6.57 (br d, *J* = 7.8 Hz, 1H*), 5.69 (s, 1H*), 5.42 (s, 1H§), 5.36 – 5.21 (m, 2H*, 2H§), 4.82 (br d, *J* = 9.2 Hz, 1H*), 4.57 (m, 1H§), 3.14 (br s, 3H*), 2.94 (br s, 3H§), 2.60 (br dd, *J* = 13.3, 9.7 Hz, 1H*), 2.60 – 2.52 (m, 1H§), 2.41 (br d, *J* = 14.7 Hz, 1H*), 2.12 (br dd, *J* = 12.7, 6.0 Hz, 1H§), 1.54 (s, 3H§), 1.34 (s, 3H*); ^{13}C NMR (100 MHz, $CDCl_3$; compound exists as a 2.6:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 171.9*, 169.6§, 158.9 (q, $J_{C\text{-}F}$ = 37.0 Hz)*, 157.3 (q, $J_{C\text{-}F}$ = 38.1 Hz)§, 149.2*, 149.0§, 135.1§, 134.5*, 134.2*, 134.0§, 128.6*, 128.6*, 128.5*, 128.4§, 128.2§, 128.1§, 121.3*, 119.8§, 188.5*, 116.0 (q, $J_{C\text{-}F}$ =

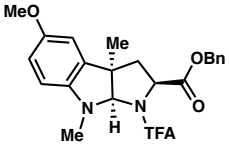
288.6 Hz)*, 109.3§, 107.8*, 93.1*, 91.6§, 67.8*, 67.1§, 61.2§, 60.2 (q, $J_{C\text{-}F}$ = 2.44 Hz)*, 52.9§, 49.0*, 43.6*, 40.2§, 36.5*, 34.2§, 23.1*, 22.5§; IR (NaCl/thin film): 3034, 2966, 1747, 1695, 1610, 1490, 1456, 1432, 1188, 1156, 745 cm^{-1}; $[\alpha]_D^{25}$ –90.1° (c = 1.11, DCM); HRMS (FAB+) calc'd for $[M+H]^+$ 419.1583, found 419.1562.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 91%. t_R(major) = 5.8 min t_R(minor) = 5.0 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 10.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.43 – 7.30 (m, 3H*, 3H§) 7.22 (dd, *J* = 6.8, 2.8 Hz, 1H§), 7.20-7.09 (m, 2H*, 1H§), 7.04 (d, *J* = 7.3 Hz, 1H§), 7.00 (d, *J* = 7.3 Hz, 1H*), 6.78 – 6.72 (m, 1H§), 6.68 (t, *J* = 7.4 Hz, 1H*), 6.36 (d, *J* = 7.8 Hz, 1H§), 6.27 (d, *J* = 7.8 Hz, 1H*), 5.60 (s, 1H*), 5.32 (s, 1H§), 5.14 (dd, *J* = 9.5, 4.9 Hz, 1H§), 5.04 (d, *J* = 12.4 Hz, 1H§), 4.94 (d, *J* = 12.4 Hz, 1H§), 4.79 (d, *J* = 8.1 Hz, 1H*), 4.63 (d, *J* = 12.1 Hz, 1H*), 4.36 (d, *J* = 12.1 Hz, 1H*), 2.95 (s, 3H*), 2.85 (d, *J* = 12.9 Hz, 1H*), 2.65 (s, 3H§), 2.46 (dd, *J* = 13.3, 5.3 Hz, 1H§), 2.39 (dd, *J* = 13.0, 8.4 Hz, 1H*), 2.28 (dd, *J* = 13.3, 9.7 Hz, 1H§), 1.46 (s, 3H*), 1.43 (s, 3H§); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 10.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 169.3§, 169.2*, 156.9 (q, $J_{C\text{-}F}$ = 36.7 Hz)§, 150.3*, 148.5§, 135.2§, 134.6*, 133.1§, , 131.8*, 129.1*, 128.7§, 128.5§, 128.44*, 128.40*, 128.3*, 128.2§, 122.5*, 121.6§, 118.6§, 117.7*, 116.1 (q, J=288.8)*, 107.0§, 105.9*, 90.9§, 88.6*, 67.6*, 67.2§, 60.5§, 60.3 (q, $J_{C\text{-}F}$= 3.1 Hz)* , 52.2§, 50.4*, 42.9*, 41.1§, 32.0*, 29.7§, 25.2*, 22.3§; IR (NaCl/thin film): 3034, 2960, 1752, 1741, 1697, 1609, 1494, 1442, 1211, 1149, 742 cm^{-1}; $[\alpha]_D^{25}$ +187.7° (c = 0.78, DCM) ; HRMS (FAB+) calc'd for $[M+H]^+$ 418.1504, found 418.1517.

Pyrroloindoline 98a.



(a) *exo* diastereomer



(b) *endo* diastereomer

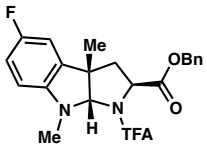
Prepared from 5-methoxy-1,3-dimethyl-1*H*-indole[39] and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 4 h. The crude residue was purified by flash chromatography (5→10% ethyl acetate/hexanes) to yield 83.1 mg (93% yield) of **98a** in a 3:1 ratio of diastereomers (determined by HPLC analysis of the purified product). The diastereomers were separated by preparatory HPLC (0→10% ethyl acetate/hexanes). The enantiomeric excesses of both diastereomers were determined by chiral HPLC analysis (OD-H, 1 mL/min, 10% IPA in hexanes, λ = 254 nm).

Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 93%. t_R(major) = 11.3 min t_R(minor) = 9.9 min. ^{1}H NMR (400 MHz, $CDCl_3$; compound exists as a 1.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.46 – 7.29 (m, 5H*, 5H§), 6.72 (d, J = 8.4 Hz, 1H*, 1H§), 6.63 (d, J = 13.4 Hz, 1H*, 1H§), 6.55 (d, J = 8.4 Hz, 1H§), 6.44 (d, J = 8.5 Hz, 1H*), 5.53 (br s, 1H*), 5.24 (br s, 2H*, 1H§), 5.19 (br s, 2H§), 4.76 (br d, J = 9.3 Hz, 1H*), 4.44 (t, J = 7.8 Hz, 1H§), 3.75 (br s, 3H*, 3H§), 3.04 (br s, 3H*), 2.86 (br s, 3H§), 2.61 – 2.48 (m, 1H*, 1H§), 2.31 (d, J = 13.4 Hz, 1H*), 2.09 – 1.99 (m, 1H§), 1.45 (br s, 3H§), 1.26 (br s, 3H*); ^{13}C NMR (100 MHz, $CDCl_3$; compound exists as a 1.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.0*, 169.9§, 159.0* (q, $J_{C\text{-}H}$ = 36.8 Hz), 154.7§, 153.6*, 143.7*§, 135.8§, 135.8*, 135.2§, 134.6*, 128.8§, 128.8*, 128.7*, 128.6§, 128.4§, 128.3*, 116.1* (q, $J_{C\text{-}F}$ = 288.6 Hz), 113.4§, 113.1*, 111.5*, 109.0*, 108.8§, 94.2*, 92.4§, 68.1*, 67.3§, 61.2§, 60.4*, 55.9*, 53.6§, 49.3§, 43.8*, 39.9§, 38.1*,

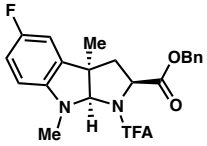
36.9[§], 23.5[§], 23.4*; IR (NaCl/thin film): 2963, 2833, 1748, 1694, 1497, 1432, 1156, 1030, 991, 754 cm^{-1}; $[\alpha]_D^{25}$ = –78.1° (*c* 1.07, DCM); HRMS (ESI) calc'd for $[M+H]^+$ 449.1683, found 449.1676.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 92%. t_R(major) = 6.6 min t_R(minor) = 7.4 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 6.1:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.37 – 7.29 (m, 3H*, 3H[§]), 7.24 – 7.21 (m, 2H[§]), 7.19 – 7.12 (m, 2H*), 6.68 (dd, *J* = 8.4, 2.5 Hz, 1H*, 1H[§]), 6.67 (d, *J* = 2.5 Hz, 1H[§]), 6.63 (d, *J* = 2.5 Hz, 1H*), 6.31 – 6.26 (m, 1H[§]), 6.19 (d, *J* = 8.4 Hz, 1H*), 5.57 (s, 1H*), 5.22 (br d, *J* = 1.8 Hz, 1H§), 5.13 (dd, *J* = 9.7, 5.3 Hz, 1H[§]), 5.07 (d, *J* = 12.3 Hz, 1H[§]), 4.97 (d, *J* = 12.3 Hz, 1H[§]), 4.78 (d, *J* = 8.4 Hz, 1H*), 4.66 (d, *J* = 12.1 Hz, 1H*), 4.46 (d, *J* = 12.1 Hz, 1H*), 3.75 (s, 3H[§]), 3.72 (s, 3H*), 2.92 (s, 3H*), 2.81 (d, *J* = 13.0 Hz, 1H*), 2.59 (d, *J* = 1.3 Hz, 3H[§]), 2.45 (dd, *J* = 13.3, 5.3 Hz, 1H[§]), 2.36 (dd, *J* = 13.0, 8.4 Hz, 1H*), 2.26 (dd, *J* = 13.3, 9.7 Hz, 1H[§]), 1.44 (s, 3H*), 1.40 (s, 3H[§]); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 6.1:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 169.4[§], 169.1*, 156.9* (q, $J_{C\text{-}F}$ = 36.7 Hz), 153.4[§], 152.8*, 144.7*, 142.7[§], 135.3[§], 134.7*, 134.5[§], 133.2*, 128.5*, 128.4*, 128.3*, 128.3[§], 128.1[§], 116.2* (q, $J_{C\text{-}F}$ = 288.8 Hz), 113.5*, 112.8[§], 110.0*, 109.4[§], 107.7[§], 106.4*, 91.6[§], 89.4*, 67.7*, 67.2[§], 60.5[§], 60.2*, 56.0*, 56.9[§], 52.2[§], 50.6*, 42.8*, 40.8[§], 32.6*, 32.0[§], 25.1*, 22.2[§]; IR (NaCl/thin film): 2957, 1750, 1697, 1500, 1446, 1282, 1210, 1157, 1031, 994, 850 cm^{-1}; $[\alpha]_D^{25}$ = +162.4° (*c* 1.41, DCM); HRMS (ESI) calc'd for $[M+H]^+$ 449.1683, found 449.1682.

Pyrroloindoline 98b.



(a) ***exo*** **diastereomer**



(b) ***endo*** **diastereomer**

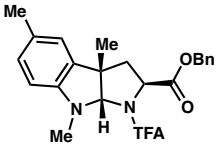
Prepared from 5-fluoro-1,3-dimethyl-1*H*-indole **97b** and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 5.5 h. The crude residue was purified by flash chromatography (5→12% ethyl acetate/hexanes) to yield 53.0 mg (61% yield) of **98b** in a 3:1 ratio of diastereomers (determined by ^{1}H NMR analysis of the purified product). The diastereomers were separated by preparatory HPLC (0→8% ethyl acetate/hexanes). The enantiomeric excesses of both diastereomers were determined by chiral HPLC analysis (OD-H, 1 mL/min, 3% IPA in hexanes, λ = 254 nm).

Exo diastereomer: pale yellow oil. The ee was determined to be 93%. t_R(major) = 14.7 min t_R(minor) = 18.0 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 2.3:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.38 (br s, 5H*, 5H§), 6.85 (br t, J = 7.8 Hz, 1H*, 1H§), 6.75 (br s, 1H§), 6.71 (br d, J = 7.8 Hz, 1H*), 6.50 (br s, 1H§), 6.39 (dd, J = 8.4, 3.8 Hz, 1H*), 5.58 (br s, 1H*), 5.34 – 5.16 (m, 2H*, 3H§), 4.75 (br d, J = 9.3 Hz, 1H*), 4.47 (br t, J = 6.8 Hz, 1H§), 3.04 (br s, 3H*), 2.85 (br s, 3H§), 2.55 (dd, J = 13.2, 9.9 Hz, 1H*), 2.55 – 2.45 (m, 1H§), 2.31 (br d, J = 13.4 Hz, 1H*), 2.10 – 1.97 (m, 1H§), 1.45 (br s, 3H§), 1.24 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 2.3:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 171.9*, 169.7§, 159.1* (q, $J_{C\text{-}F}$ = 37.1 Hz), 157.0* (d, $J_{C\text{-}F}$ = 236.5 Hz), 145.6*, 145.4§, 135.7* (d, $J_{C\text{-}F}$ = 7.3 Hz), 135.1§, 134.6*, 128.9*, 128.8*, 128.7*, 128.6§, 128.5§, 128.4§, 116.2* (q, $J_{C\text{-}F}$ = 267.0 Hz), 114.9§, 114.7* (d, $J_{C\text{-}F}$ = 23.0 Hz), 110.5§, 109.3* (d, $J_{C\text{-}F}$ = 24.3 Hz), 108.6* (d, $J_{C\text{-}F}$ = 7.8 Hz), 93.9*,

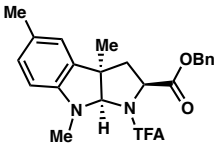
92.2[§], 68.2*, 67.5[§], 61.3[§], 60.3*, 53.2[§], 49.2*, 43.7*, 40.1[§], 37.6*, 35.6[§], 23.3*, 22.9[§]; IR (NaCl/thin film): 2966, 1748, 1698, 1495, 1434, 1350, 1270, 1157, 994, 843 cm^{-1}; $[\alpha]_D^{25}$ = –81.7° (*c* 1.14, DCM); HRMS (ESI) calc'd for $[M+H]^+$ 437.1483, found 437.1476.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 90%. t_R(major) = 9.1 min t_R(minor) = 10.5 min. ^1H NMR (500 MHz, $CDCl_3$; compound exists as a 9.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 7.37 – 7.30 (m, 3H*, 3H[§]), 7.24 – 7.20 (m, 2H[§]), 7.18 – 7.12 (m, 2H*), 6.83 – 6.74 (m, 1H*, 2H[§]), 6.71 (dd, *J* = 8.0, 2.6 Hz, 1H*), 6.23 (dd, *J* = 8.5, 4.0 Hz, 1H[§]), 6.14 (dd, *J* = 8.5, 4.0 Hz, 1H*), 5.60 (s, 1H*), 5.29 (d, *J* = 1.7 Hz, 1H[§]), 5.14 (dd, *J* = 9.6, 5.0 Hz, 1H[§]), 5.06 (d, *J* = 12.2 Hz, 1H[§]), 4.97 (d, *J* = 12.2 Hz, 1H[§]), 4.79 (d, *J* = 8.5 Hz, 1H*), 4.70 (d, *J* = 12.0 Hz, 1H*), 4.50 (d, *J* = 12.1 Hz, 1H*), 2.93 (s, 3H*), 2.78 (d, *J* = 13.1 Hz, 1H*), 2.60 (d, *J* = 1.3 Hz, 3H[§]), 2.45 (dd, *J* = 13.3, 5.0 Hz, 1H[§]), 2.37 (dd, *J* = 13.1, 8.5 Hz, 1H*), 2.26 (dd, *J* = 13.4, 9.7 Hz, 1H[§]), 1.44 (s, 3H*), 1.41 (s, 3H[§]); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 9.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 169.2[§], 169.0*, 156.9* (q, $J_{C\text{-}F}$ = 36.7 Hz), 156.3* (q, $J_{C\text{-}F}$ = 235.3 Hz), 146.5*, 144.7[§], 135.2[§], 134.5*, 133.3* (d, $J_{C\text{-}F}$ = 7.2 Hz), 128.5*, 128.4*, 128.2[§], 116.1* (q, $J_{C\text{-}F}$ = 288.6 Hz), 115.0* (d, $J_{C\text{-}F}$ = 23.0 Hz), 114.5[§] (d, $J_{C\text{-}F}$ = 23.1 Hz), 110.2* (d, $J_{C\text{-}F}$ = 24.4 Hz), 109.6* (d, $J_{C\text{-}F}$ = 24.6 Hz), 107.3[§] (d, $J_{C\text{-}F}$ = 7.7 Hz), 106.0* (d, $J_{C\text{-}F}$ = 7.9 Hz), 91.3[§], 89.1*, 67.8*, 67.3[§], 60.4[§], 60.2*, 52.2[§], 50.4*, 42.8[§], 40.9[§], 32.4*, 31.5[§], 25.1*, 22.3[§]; IR (NaCl/thin film): 2961, 1749, 1698, 1498, 1439, 1270, 1207, 1157, 995, 852, 752 cm^{-1}; $[\alpha]_D^{25}$ = +156.8° (*c* 1.16, DCM); HRMS (ESI) calc'd for $[M+H]^+$ 437.1483, found 437.1490.

Pyrroloindoline 98c.



(a) *exo* diastereomer



(b) *endo* diastereomer

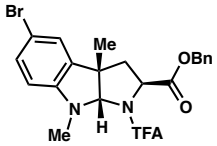
Prepared from 5-methyl-1,3-dimethyl-1*H*-indole (**97c**) and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 4 h. The crude residue was purified by flash chromatography (5→15% ethyl acetate/hexanes) to yield 72.9 mg (84% yield) of **98c** in a 5:1 ratio of diastereomers (determined by ^{1}H NMR analysis of the purified product). The diastereomers were separated by preparatory HPLC (0→10% ethyl acetate/hexanes).

Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 94% by chiral SFC analysis (OJ-H, 2.5 mL/min, 2% IPA in CO_2, λ = 254 nm): t_R(major) = 20.5 min t_R(minor) = 16.6 min. ^{1}H NMR (400 MHz, $CDCl_3$; compound exists as a 2.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.39 (br s, 5H*, 5H§), 6.97 (br d, J = 7.7 Hz, 1H*, 1H§), 6.85 (br s, 1H§), 6.81 (br s, 1H*), 6.50 (br d, J = 7.6 Hz, 1H§), 6.42 (br d, J = 7.9 Hz, 1H*), 5.56 (br s, 1H*), 5.32 – 5.15 (br m, 2H*, 3H§), 4.76 (br d, J = 9.3 Hz, 1H*), 4.47 (br t, J = 7.5 Hz, 1H§), 3.05 (br s, 3H*), 2.87 (br s, 3H§), 2.61 – 2.46 (m, 1H*, 1H§), 2.30 (d, J = 21.3 Hz, 1H*), 2.27 (s, 3H*, 3H§), 2.09 – 1.98 (br m, 1H§), 1.45 (br s, 3H§), 1.26 (s, 3H§); ^{13}C NMR (100 MHz, $CDCl_3$; compound exists as a 2.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.0*, 169.9§, 159.1* (q, $J_{C\text{-}F}$ = 36.8 Hz), 157.7§ (q, $J_{C\text{-}F}$ = 37.9 Hz), 147.3*§, 135.2§, 134.6*, 134.5*, 134.4§, 129.7§, 129.2§, 129.0*, 128.8*, 128.8*, 128.7*, 128.6*, 128.4*, 128.2§, 122.3*§, 116.1* (q, $J_{C\text{-}F}$ = 288.7 Hz), 110.0§, 108.2*, 93.8*, 92.1§, 68.0*, 67.3§, 61.4§, 60.4*, 53.3§, 49.2*, 43.9*, 40.2§, 37.4*, 35.6§, 23.4*, 23.2§, 20.7*§; IR (NaCl/thin film): 2965, 1748, 1697, 1499, 1456, 1433, 1348,

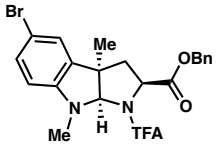
1194, 1153, 992, 754 cm^{-1}; $[\alpha]_D^{25}$ = –87.1° (*c* 0.90, DCM); HRMS (APCI) calc'd for $[M+H]^+$ 433.1734, found 433.1713.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 91% by chiral HPLC analysis (OD-H, 1 mL/min, 3% IPA in hexanes, λ = 254 nm): t_R(major) = 6.5 min t_R(minor) = 7.3 min. ^{1}H NMR (300 MHz, $CDCl_3$; compound exists as a 6.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.40 – 7.29 (m, 3H*, 3H§), 7.23 – 7.18 (m, 2H§), 7.18 – 7.10 (m, 2H*), 6.96 – 6.84 (m, 1H*, 2H§), 6.81 (br s, 1H*), 6.27 (d, *J* = 7.9 Hz, 1H§), 6.18 (d, *J* = 7.9 Hz, 1H*), 5.57 (s, 1H*), 5.25 (br d, *J* = 1.9 Hz, 1H§), 5.12 (dd, *J* = 9.6, 5.4 Hz, 1H§), 5.05 (d, *J* = 12.4 Hz, 1H§), 4.94 (d, *J* = 12.2 Hz, 1H§), 4.78 (d, *J* = 8.4 Hz, 1H*), 4.63 (d, *J* = 12.2 Hz, 1H*), 4.41 (d, *J* = 12.2 Hz, 1H*), 2.92 (s, 3H*), 2.82 (d, *J* = 13.0 Hz, 1H*), 2.61 (d, *J* = 1.4 Hz, 3H§), 2.44 (dd, *J* = 13.3, 5.3 Hz, 1H§), 2.37 (dd, *J* = 13.0, 8.4 Hz, 1H*), 2.26 (s, 3H§), 2.23 (s, 3H*), 1.44 (s, 3H*), 1.41 (s, 3H§); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 6.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 169.4§, 169.2*, 156.9* (q, $J_{C\text{-}F}$ = 36.6 Hz), 148.2*, 135.3§, 134.7*, 133.3§, 132.0*, 129.3*, 128.9§, 128.5§, 128.5*, 128.4*, 128.3§, 128.2*, 128.1§, 126.9*§, 123.2*, 122.5§, 116.2* (q, $J_{C\text{-}F}$ = 288.8 Hz), 107.0§, 105.9*, 91.3§, 89.0*, 67.6*, 67.2§, 60.5§, 60.2*, 52.2§, 50.4*, 42.9*, 41.1§, 32.2*, 31.4§, 25.2*§, 22.2§, 20.7*; IR (NaCl/thin film): 2958, 1752, 1698, 1619, 1505, 1443, 1210, 1158, 995, 851, 752 cm^{-1}; $[\alpha]_D^{25}$ = +176.4° (*c* 0.97, DCM); HRMS (ESI) calc'd for $[M+H]^+$ 433.1734, found 433.1737.

Pyrroloindoline 98d.



(a) *exo* diastereomer



(b) *endo* diastereomer

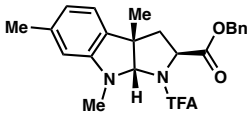
Prepared from 5-bromo-1,3-dimethyl-1*H*-indole (**97d)** and benzyl 2-trifluoroacetamidoacrylate using general procedure C, in DCE with 1.6 equivalents $SnCl_4$. The reaction was allowed to run for 57 h. The crude residue was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield 50 mg (51% yield) of **98d** in a 3:1 ratio of diastereomers (determined by ^{1}H NMR analysis of the pure product). The diastereomers were separated by prepatory HPLC (0→10% ethyl acetate/hexanes).

Exo diastereomer: The enantiomeric excess was determined to be 87% by chiral HPLC analysis (OD-H, 2.5 mL/min, 5% IPA in hexanes, λ = 254 nm): t_R(major) = 14.7 min t_R(minor) = 12.5 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 3.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.38 (br s, 5H*, 5H§), 7.24 (br d, *J* = 8.3 Hz, 1H*, 1H§), 7.11 (br s, 1H§), 7.05 (br s, 1H*), 6.41 (br d, *J* = 7.1 Hz, 1H§), 6.35 (br d, *J* = 8.3 Hz, 1H*), 5.60 (br s, 1H*), 5.34 (br s, 1H§), 5.28 – 5.15 (m, 2H*, 2H§), 4.74 (br d, *J* = 9.0 Hz, 1H*), 4.50 (br t, *J* = 7.0 Hz, 1H§), 3.03 (br s, 3H*), 2.83 (br s, 3H§), 2.53 (br dd, *J* = 12.9, 10.2 Hz, 1H*), 2.47 (br t, *J* = 11.1 Hz, 1H§), 2.30 (br d, *J* = 13.4 Hz, 1H*), 2.02 (br dd, *J* = 12.2, 6.5 Hz, 1H§), 1.45 (br s, 1H§), 1.23 (br s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 3.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 171.9*, 169.6§, 159.18 (q, $J_{C\text{-}F}$ = 37.1 Hz)*, 157.42 (d, $J_{C\text{-}F}$ = 39.7 Hz)§, 148.4*, 148.0§, 136.4*, 136.2§, 135.0§, 134.5*, 131.5§, 131.4*, 128.9*, 128.8*, 128.7*, 128.4§, 124.7*, 116.0 (q, $J_{C\text{-}F}$ = 288.5 Hz)*, 111.5§, 110.5*, 110.2§, 109.4*, 93.1*, 91.5§, 68.2*, 67.5§, 61.4§, 60.2*, 52.9§, 49.1*, 43.7*, 40.4§, 36.7*, 33.9§, 23.2*, 22.3§; IR (NaCl/thin film):

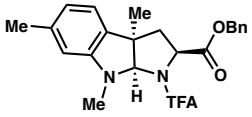
3034, 2965, 2931, 1747, 1698, 1602, 1489, 1205, 1154, 806, 751 cm^{-1}; $[\alpha]_D^{25}$ –86.4° (c = 0.60, DCM); HRMS (FAB+) calc'd for $[M+H]^+$ 498.0589, found 498.0576.

Endo diastereomer: The enantiomeric excess was determined to be 85% by chiral HPLC analysis (OD-H, 2.5 mL/min, 5% IPA in hexanes, λ = 254 nm): t_R(major) = 7.3 min t_R(minor) = 8.1 min. ^{1}H NMR (400 MHz, $CDCl_3$; compound exists as a 12.5:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.39 – 7.30 (m, 3H*, 3H§), 7.23 – 7.13 (m, 3H*, 3H§), 7.11 (s, 1H§), 7.08 (s, 1H*), 6.19 (d, *J* = 8.5 Hz, 1H§), 6.13 (d, *J* = 8.3 Hz, 1H*), 5.59 (s, 1H*), 5.33 (s, 1H§), 5.14 (dd, *J* = 10.0, 4.9 Hz, 1H§), 5.06 (d, J=11.9 Hz, 1H§), 4.93 (dd, *J* = 11.9 Hz, 1H§), 4.79 (d, *J* = 8.4 Hz, 1H*), 4.64 (d, *J* = 12.0 Hz, 1H*), 4.56 (d, J=12.0, 1H*), 2.94 (s, 3H*), 2.78 (d, *J* = 13.2 Hz, 1H*), 2.61 (s, 3H§), 2.45 (dd, *J* = 13.7, 3.9 Hz, 1H§), 2.37 (dd, *J* = 13.1, 8.4 Hz, 1H*), 2.26 (dd, *J* = 14.3, 9.9 Hz, 1H§), 1.44 (s, 3H*), 1.41 (s, 3H§); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 12.5:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 169.0*, 156.9 (q, J_{C-F} = 37.0 Hz)*, 149.4*, 134.4*, 134.2*, 131.8*, 131.4§, 125.5*, 124.9§, 116.1(q, J_{C-F} = 288.6 Hz)*, 108.9*, 108.3§, 107.5§, 107.3*, 90.6§, 88.5*, 67.9*, 67.4§, 60.4§, 60.2*, 50.4*, 42.8*, 41.1§, 32.1*, 25.3*, 22.5§; IR (NaCl/thin film): 3034, 2962, 2930, 1749, 1698, 1602, 1493, 1442, 1261, 1211, 1151, 804, 750 cm^{-1}; $[\alpha]_D^{25}$ + 156.3° (c = 0.24, DCM) ; HRMS (FAB+) calc'd for $[M+H]^+$ 498.0589, found 498.0606.

Pyrroloindoline 98e.



(a) ***exo*** **diastereomer**



(b) ***endo*** **diastereomer**

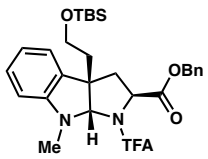
Prepared from 6-methyl-1,3-dimethyl-1*H*-indole (**97e**) and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 6 h. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield 78.3 mg (91% yield) of **98e** in a 4:1 ratio of diastereomers (determined by ^{1}H NMR analysis of the purified product). The diastereomers were separated by preparatory HPLC (0→10% ethyl acetate/hexanes). The enantiomeric excesses of both diastereomers were determined by chiral HPLC analysis (OD-H, 1 mL/min, 3% IPA in hexanes, λ = 254 nm).

Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 94%. t_R(major) = 14.5 min t_R(minor) = 12.9 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 2.2:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.40 (br s, 5H*, 5H§), 6.93 (br d, J = 7.1 Hz, 1H§), 6.89 (br d, J = 7.4 Hz, 1H*), 6.65 (br d, J = 6.8 Hz, 1H§), 6.58 (br d, J = 7.3 Hz, 1H*), 6.42 (br s, 1H§), 6.35 (br s, 1H*), 5.60 (br s, 1H*), 5.32 (br s, 1H§), 5.29 – 5.14 (m, 2H*, 2H§), 4.76 (br d, J = 9.2 Hz, 1H*), 4.50 (br t, J = 7.2 Hz, 1H§), 3.07 (br s, 3H*), 2.88 (br s, 3H§), 2.61 – 2.42 (m, 1H*, 1H§), 2.32 (br s, J = 5.8 Hz, 4H*, 3H§), 2.10 – 1.98 (m, 1H§), 1.46 (s, 3H§), 1.27 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 2.2:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.1*, 169.9§, 159.2* (q, $J_{C\text{-}F}$ = 37.0 Hz), 157.7§ (q, $J_{C\text{-}F}$ = 38.4 Hz), 149.6*, 149.5§, 139.0§, 138.8*, 135.2§, 134.7*, 131.7*, 131.4§, 128.9*, 128.8*, 128.7*, 128.6*, 128.5§, 128.4§, 121.3§, 121.2*, 120.7§, 119.3*, 116.1* (q, $J_{C\text{-}F}$ = 288.4 Hz), 116.0§ (q, $J_{C\text{-}F}$ = 286.5 Hz), 110.5§, 108.9*, 93.6*,

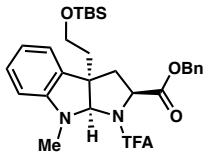
92.0[§], 68.1*, 67.4[§], 61.5[§], 60.5*, 52.9[§], 49.0*, 43.9*, 40.4[§], 36.8*, 34.7[§], 23.5*, 23.0[§], 21.7*[§]; IR (NaCl/thin film): 2964, 1748, 1697, 1616, 1499, 1456, 1423, 1160, 1004, 752 cm^{-1}; $[\alpha]_D^{25}$ = –85.6º (*c* 0.93, DCM); HRMS (EI+) calc'd for $M^{+\bullet}$ 432.1661, found 432.1663.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 90%. t_R(major) = 7.8 min t_R(minor) = 8.3 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 9.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 7.38 – 7.29 (m, 3H*, 3H[§]), 7.21 (dd, *J* = 6.6, 2.9 Hz, 2H[§]), 7.16 – 7.10 (m, 2H*), 6.92 (d, *J* = 7.4 Hz, 1H[§]), 6.86 (d, *J* = 7.4 Hz, 1H*), 6.55 (d, *J* = 7.4 Hz, 1H[§]), 6.49 (dd, *J* = 7.4, 0.6 Hz, 1H*), 6.17 (s, 1H[§]), 6.06 (s, 1H*), 5.57 (s, 1H*), 5.28 (d, *J* = 1.9 Hz, 1H[§]), 5.12 (dd, *J* = 9.6, 5.2 Hz, 1H[§]), 5.03 (d, *J* = 12.3 Hz, 1H[§]), 4.95 (d, *J* = 12.3 Hz, 1H[§]), 4.78 (d, *J* = 8.4 Hz, 1H*), 4.67 (d, *J* = 12.1 Hz, 1H*), 4.33 (d, *J* = 12.2 Hz, 1H*), 2.91 (s, 3H*), 2.82 (d, *J* = 12.9 Hz, 1H*), 2.62 (d, *J* = 1.4 Hz, 3H[§]), 2.43 (dd, *J* = 13.3, 5.2 Hz, 1H[§]), 2.36 (dd, *J* = 12.9, 8.3 Hz, 1H*), 2.30 (s, 3H[§]), 2.28 (s, 3H*), 2.24 (dd, *J* = 13.3, 9.6 Hz, 1H[§]), 1.43 (s, 3H*), 1.40 (s, 3H[§]); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 9.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 169.4[§], 169.3*, 156.9* (q, $J_{C\text{-}F}$ = 36.8 Hz), 150.4*, 148.7[§], 139.0*, 138.7[§], 135.2[§], 134.7*, 130.3[§], 129.0*, 128.5[§], 128.4*, 128.4*, 128.3[§], 128.2*, 122.3*, 121.3[§], 119.1[§], 118.4*, 116.2* (q, $J_{C\text{-}F}$ = 288.7 Hz), 108.0[§], 106.8*, 91.1[§], 88.9*, 67.6*, 67.2[§], 60.5[§], 60.3*, 52.0[§], 50.2*, 42.9*, 41.1[§], 32.0*, 31.0[§], 25.3*[§], 22.4[§], 21.8*; IR (NaCl/thin film): 2923, 1740, 1698, 1612, 1501, 1440, 1214, 1150, 1011, 849, 746 cm^{-1}; $[\alpha]_D^{25}$ = +165.5º (*c* 0.53, DCM); HRMS (ESI) calc'd for $[M+H]^+$ 433.1739, found 433.1756.

Pyrroloindoline 98f.



(a) *exo* diastereomer



(b) *endo* diastereomer

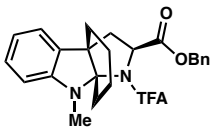
Prepared from 1-methyl-3-*t*-butyldimethylsiloxyethyl-1*H*-indole (**97f**) and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 20 h. The crude residue was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield 61 mg (54% yield) of **98f** in a 6:1 ratio of diastereomers (determined by ^{1}H NMR analysis of the purified product). The diastereomers were separated by preparatory HPLC (0→5% ethyl acetate/hexanes).

Exo diastereomer: The enantiomeric excess was determined to be 92% by chiral HPLC analysis (OD-H, 1 mL/min, 0.6% EtOH in hexanes, λ = 254 nm): t_R(major) = 10.7 min t_R(minor) = 12.1 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.38 (br s, 5H*, 5H§), 7.17 (t, *J* = 7.6 Hz, 1H*, 1H§), 7.00 (br d, *J* = 6.7 Hz, 1H*, 1H§), 6.87-6.78 (br m, 1H§), 6.76 (br t, *J* = 6.7 Hz, 1H*), 6.59 (br d, *J* = 6.0 Hz, 1H§), 6.51 (br d, *J* = 7.4 Hz, 1H*), 5.89 (br s, 1H*), 5.79 (br s, 1H§), 5.30 – 5.10 (m, 2H*, 2H§), 4.61 (br s, 1H*), 4.32 (br s, 1H§), 3.60 (br d, *J* = 22.3 Hz, 2H§), 3.49 (br s, 2H*), 3.10 (s, 3H*), 2.94 (br s, 3H§), 2.74 – 2.64 (m, 1H*), 2.63 – 2.52 (m, 1H§), 2.39 (br d, *J* = 10.1 Hz, 1H*), 2.18 (br t, *J* = 9.9 Hz, 1H§), 1.97 (br s, 2H§), 1.82 (br td, *J* = 13.6, 7.9 Hz, 2H*), 0.86 (br s, 9H*, 9H§), 0.02 – -0.06 (m, 6H*, 6H§); ^{13}C NMR (100 MHz, $CDCl_3$; compound exists as a 1.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.0*, 169.9§, 159.0 (q, $J_{C\text{-}F}$ = 37.9 Hz)*, 157.7 (q, $J_{C\text{-}F}$ = 38.1 Hz)§, 150.5§, 150.0*, 135.2§, 134.7*, 131.7§, 131.5*, 128.8*§, 128.6*§, 128.4*§, 122.4*§, 119.9§, 118.4*, 116.0 (q, $J_{C\text{-}F}$ = 288.0 Hz)*, 110.0§, 108*, 90.8*, 89.5§, 67.9*, 67.3§,

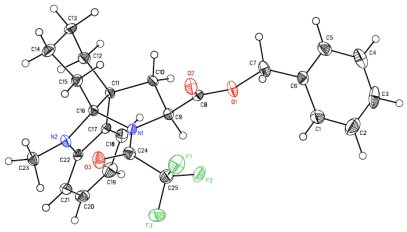
60.5[§], 59.6*, 56.4[§], 52.3*, 43.5*, 39.9[§], 39.1[§], 39.0*, 36.4*, 35.7[§], 25.8*, 18.1[§], -5.6*[§]; IR (NaCl/thin film): 3035, 2955, 2930, 2857, 2884, 1750, 1694, 1492, 1432, 1257, 1201, 1158, 1106, 837 cm^{-1}; $[\alpha]_D^{25} = -95.3°$ (c =1.38, DCM); HRMS (FAB+) calc'd for $[M+H]^+$ 562.2475, found 562.2468.

Endo diastereomer: The enantiomeric excess was determined to be 90% by chiral HPLC analysis (AD-H, 1 mL/min, 0.5% EtOH in hexanes, λ = 254 nm): t_R(major) = 6.5 min t_R(minor) = 5.8 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 16.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 7.38 – 7.29 (m, 3H*, 3H[§]), 7.20 – 7.07 (m, 3H*, 3H[§]), 6.96 (d, *J* = 7.2 Hz, 1H*, 1H[§]), 6.69 (t, *J* = 7.5 Hz, 1H[§]), 6.65 (t, *J* = 7.4 Hz, 1H*), 6.27 (d, *J* = 8.2 Hz, 1H[§]), 6.25 (d, *J* = 7.9 Hz, 1H*), 5.90 (s, 1H[§]), 5.83 (s, 1H*), 5.12 (dd, *J* = 9.3, 3.0 Hz, 1H[§]), 4.86 (d, 12.2 Hz, 1H[§]), 4.79 (d, *J*= 12.2 Hz, 1H[§]), 4.77 (d, *J* = 8.2 Hz, 1H*), 4.60 (d, *J* = 12.1 Hz, 1H*), 4.33 (d, *J* = 12.2 Hz, 1H*), 3.65 – 3.49 (m, 2H*, 2H[§]), 2.92 (s, 3H*), 2.88 (d, *J* = 13.1 Hz, 1H*), 2.67 (s, 3H[§]), 2.58 (dd, *J* = 13.1, 3.3 Hz, 1H[§]), 2.49 (dd, *J* = 13.1, 8.4 Hz, 1H*), 2.28 (dd, *J* = 13.7, 10.1 Hz, 1H[§]), 2.07 – 1.84 (m, 2H*, 2H[§]), 0.87 (s, 9H*), 0.80 (s, 9H[§]), 0.00 (d, *J* = 4.0 Hz, 6H*), -0.09 (d, *J* = 13.9 Hz, 6H[§]); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 16.7:1 mixture of rotamers, only the major rotamer is reported) δ 169.3, 156.8 (q, $J_{C\text{-}F}$ = 37.9 Hz), 151.2, 134.7, 129.6, 129.2, 128.43, 128.37, 128.2, 123.5, 117.5, 116. 2 (q, $J_{C\text{-}F}$ = 289.0 Hz), 107.5, 105.9, 87.1, 67.5, 59.9, 59.4, 53.0, 42.2, 40.4, 31.9, 25.9, 18.2, -5.6 (*J* = 6.1 Hz); IR (NaCl/thin film): 3034, 2954, 2930, 2857, 1742, 1699, 1609, 1494, 1441, 1255, 1207, 1146, 1104, 837, 745 cm^{-1}; $[\alpha]_D^{25}$ +148.5° (c = 0.33, DCM); HRMS (FAB+) calc'd for $[M+H]^+$ 562.2475, found 562.2458.

Pyrroloindoline 98g.



exo diastereomer

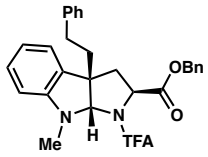


Prepared from 9-methyl-2,3,4,9-tetrahydro-1*H*-carbazole [40] and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 11 h. The crude residue was purified by flash chromatography (5→20% ethyl acetate/hexanes) to yield 60 mg (65% yield) of **98g** in a >18:1 ratio of diastereomers (determined by ^{1}H NMR analysis of the pure product). The diastereomers were separated by prep HPLC (0→10% ethyl acetate/hexanes).

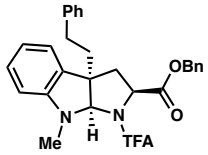
Exo diastereomer: pale yellow oil. The oil was crystallized from ethyl acetate/hexanes to give crystals suitable for single crystal X-ray diffraction. The enantiomeric excess was determined to be 86% by chiral SFC analysis (OJ-H, 2.5 mL/min, 6% IPA in hexanes, λ = 254 nm): t_R(major) = 4.5 min t_R(minor) = 6.9 min. ^{1}H NMR (300 MHz, $CDCl_3$; compound exists as a >20:1 mixture of rotamers) δ 7.44 – 7.29 (m, 5H), 7.16 (t, *J* = 7.2 Hz, 1H), 7.02 (d, *J* = 7.0 Hz, 1H), 6.72 (t, *J* = 7.4 Hz, 1H), 6.51 (d, *J* = 7.8 Hz, 1H), 5.20 (dd, *J* = 29.3, 12.1 Hz, 2H), 4.43 (t, *J* = 8.2 Hz, 1H), 3.20 (d, *J* = 15.5 Hz, 1H), 3.10 (s, 3H), 2.75 (dd, *J* = 13.0, 8.6 Hz, 1H), 2.28 (dd, *J* = 13.0, 9.3 Hz, 1H), 2.02 – 1.75 (m, 2H), 1.75 – 1.55 (m, *J* = 12.9 Hz, 1H), 1.53 – 1.38 (m, 1H), 1.36 – 1.07 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a >20:1 mixture of rotamers) δ 172.4, 157.7 (q, $J_{C\text{-}F}$ = 36.3 Hz), 148.0, 134.9, 133.7, 128.7, 128.6, 128.4, 120.8, 118.0, 115.8 (q, $J_{C\text{-}F}$ = 289.8 Hz), 112.3, 107.1, 95.6, 67.6, 58.4 (q, $J_{C\text{-}F}$ = 3.5 Hz), 52.3, 35.2, 33.9, 30.7, 26.8, 21.5, 20.4 ; IR (NaCl/thin film): 3034, 2928, 2857, 1749,

1693, 1609, 1490, 1214, 1186, 1160, 741 cm^{-1}; melting point: 106 – 108 °C; $[\alpha]_D^{25} = -92.6°$ (c = 1.40, DCM); HRMS (ESI+) calc'd for $[M+H]^+$ 459.1890, found 459.1892.

Pyrrolidinoindoline 98h.



(a) *exo* diastereomer



(b) *endo* diastereomer

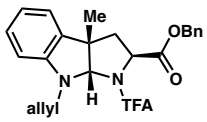
Prepared from 3-phenethyl-1-methyl-1*H*-indole [41] and benzyl 2-trifluoroacetamidoacrylate using general procedure C, with 1.6 equivalents $SnCl_4$. The reaction was allowed to run for 9.5 h. The crude residue was purified by flash chromatography (5→20% ethyl acetate/hexanes) to yield 81 mg (80% yield) of **98h** in a 4:1 ratio of diastereomers (determined by ^1H NMR analysis of the crude reaction mixture). The diastereomers were separated by preparatory HPLC (0→6% ethyl acetate/hexanes). The enantiomeric excess of both diastereomers was determined by chiral SFC analysis (OJ-H, 2.5 mL/min, 6% IPA in hexanes, λ = 254 nm).

Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 92%. t_R(major) = 33.3 min t_R(minor) = 28.0 min. ^1H NMR (500 MHz, $CDCl_3$; compound exists as a 2.6:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H*, 5H§), 7.28 – 7.16 (m, 4H*, 4H§), 7.12 – 7.06 (br s, 3H§), 7.02 (m, 3H*), 6.90-6.81 (br s, 1H§), 6.81 (t, *J* = 6.9 Hz, 1H*), 6.63 – 6.57 (m, *J* = 9.8 Hz, 1H§), 6.55 (br d, *J* = 7.5 Hz, 1H*), 5.70 (br s, 1H*), 5.45 (br s, 1H§), 5.25-5.15 (m, 2H*, 2H§), 4.69 (br d, *J* = 7.4 Hz, 1H*), 4.39 (br s, 1H§), 3.12 (br s, 3H*), 2.90 (br s, 3H§), 2.78 – 1.73 (m, 6H*, 6H§); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 2.6:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.0*, 169.8§, 159.0 (q, J_{C-F} = 36.7 Hz)*, 157.60 (q, J_{C-}

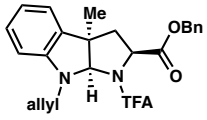
$_F$ = 32.9 Hz)[§], 150.3*[§], 141.0*[§], 135.1[§], 134.5*, 132.0*, 131.6[§], 129.1[§], 128.9[§], 128.8[§], 128.7*, 128.4*, 128.2*, 126.0*[§], 122.3[§], 121.9*, 120.1[§], 118.9*, 116.0 (q, $J_{C\text{-}F}$ = 288.4 Hz)*, 109.7[§], 108.3*, 90.4*, 89.2[§], 68.1*, 67.4[§], 60.7[§], 59.5*, 57.5[§], 53.7*, 43.5*, 40.0[§], 39.0*, 38.6[§], 36.9*, 35.1[§], 31.9*[§] ; IR (NaCl/thin film): 3030, 2921, 2852, 1747, 1694, 1607, 1492, 1455, 1433, 1190, 1152, 750 cm^{-1}; $[\alpha]_D^{25}$ –113.8° (c =1.17, DCM); HRMS (ESI) calc'd for $[M+H]^+$ 509.2047, found 509.2052.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 90%. t_R(major) = 11.6 min t_R(minor) = 17.5 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 14.5:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 7.37 – 7.30 (m, 3H*, 3H[§]), 7.23 (d, *J* = 7.6 Hz, 2H*, 2H[§]), 7.19 – 7.12 (m, 4H*, 4H[§]), 7.07 (d, *J* = 7.3 Hz, 2H*, 2H[§]), 7.03 (d, *J* = 7.2 Hz, 1H*, 1H[§]), 6.76 (t, *J* = 7.3 Hz, 1H[§]), 6.71 (t, *J* = 7.3 Hz, 1H*), 6.33 (d, *J* = 7.8 Hz, 1H[§]), 6.28 (d, *J* = 7.8 Hz, 1H*), 5.70 (s, 1H*), 5.49 (s, 1H[§]), 5.13 (dd, *J* = 9.4, 3.5 Hz, 1H[§]), 4.91 (d, *J* = 12.2 Hz, 1H[§]), 4.83 (d, *J* = 12.2 Hz, 1H[§]), 4.80 (d, *J* = 8.2 Hz, 1H*), 4.63 (d, *J* = 12.1 Hz, 1H*), 4.37 (d, *J* = 12.1 Hz, 1H*), 2.94 (s, 3H*), 2.86 (d, *J* = 12.9 Hz, 1H*), 2.65 (s, 3H[§]), 2.59 (td, *J* = 12.9, 5.3 Hz, 1H*), 2.53 – 2.46 (m, 1H[§]), 2.45 – 2.32 (m, 2H*), 2.27 (dd, *J* = 13.2, 9.6 Hz, 1H[§]), 2.23 – 2.18 (m, 1H[§]), 2.15 – 1.89 (m, 2H*, 2H[§]); ^{13}C NMR (125 MHz, $CDCl_{3;}$; compound exists as a 14.5:1 mixture of rotamers, only the major rotamer is reported) δ 169.2, 156.8 (q, $J_{C\text{-}F}$ = 36.9 Hz), 151.3, 141.2, 134.7, 129.6, 129.4, 128.5, 128.43, 128.41, 128.3, 128.2, 126.0, 123.1, 117.8, 116.2 (q, *J* = 288.9 Hz), 105.9, 86.9, 67.7, 60.0 (q, $J_{C\text{-}F}$ = 3.2 Hz). 54.3, 47.5, 42.2, 41.0, 31.9, 31.1; IR (NaCl/thin film): 2919, 2850, 1738, 1694, 1607, 1493, 1455, 1441, 1204, 1142, 744 cm^{-1}; $[\alpha]_D^{25}$ +119.6° (c = 0.87, DCM); HRMS (ESI) calc'd for $[M+H]^+$ 509.2047, found 509.2048.

Pyrroloindoline 72.



(a) ***exo*** diastereomer



(b) ***endo*** diastereomer

Prepared from 1-allyl-3-methyl-1*H*-indole [42] and benzyl 2-trifluoroacetamidoacrylate using general procedure C, with 1.6 equivalents $SnCl_4$. The reaction was allowed to run for 15 h. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield 79.7 mg (90% yield) of **72** in a 3:1 ratio of diastereomers (determined by SFC analysis of the purified products, before the diastereomers were separated). The diastereomers were separated by flash chromatography (0→10% ethyl acetate/hexanes).

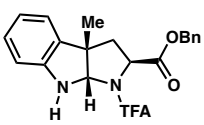
Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 93% by chiral SFC analysis (OJ-H, 2.5 mL/min, 6% IPA in CO_2, λ = 254 nm): t_R(major) = 5.7 min t_R(minor) = 4.3 min. ^{1}H NMR (400 MHz, $CDCl_3$; compound exists as a 5.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.40 (br s, 5H*, 5H§), 7.14 (t, *J* = 7.7 Hz, 1H*, 1H§), 7.09 – 6.95 (br m, 1H§), 7.00 (br d, *J* = 7.2 Hz, 1H*), 6.90 – 6.71 (br m, 1H§), 6.76 (br t, *J* = 7.3 Hz, 1H*), 6.68 – 6.44 (br m, 1H§), 6.54 (br d, *J* = 7.9 Hz, 1H*), 5.82 (br ddd, *J* = 21.5, 10.5, 5.7 Hz, 1H*, 1H§), 5.73 (br s, 1H*), 5.52 (br s, 1H§), 5.34 – 5.09 (m, 4H*, 4H§), 4.75 (br d, *J* = 9.2 Hz, 1H*), 4.40 (br s, 1H§), 4.26 (br d, *J* = 13.1 Hz, 1H*), 4.04 (br dd, *J* = 16.3, 5.9 Hz, 1H*, 1H§), 3.83 (br s, 1H§), 2.60 (br dd, *J* = 13.3, 9.8 Hz, 1H*, 1H§), 2.36 (br d, *J* = 13.4 Hz, 1H*), 2.20 – 2.03 (m, 1H§), 1.46 (s, *J* = 10.6 Hz, 3H§), 1.27 (s, *J* = 8.7 Hz, 3H*); ^{13}C NMR (100 MHz, $CDCl_3$; compound exists as a 5.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.0*, 169.8§, 158.9* (q, $J_{C\text{-}F}$ = 37.0 Hz), 148.4*§, 134.8*, 134.6*, 133.8*, 133.4§, 128.8*, 128.7*, 128.7*, 121.5*, 120.3§, 118.7*, 117.7§,

116.7*, 116.0* (q, $J_{C\text{-}F}$ = 288.5 Hz), 110.8[§], 108.4*, 91.3*, 89.7[§], 68.0*, 67.4[§], 61.1[§], 60.0*, 53.6[§], 51.8*, 50.5[§], 49.4*, 44.1*, 40.7[§], 23.5*[§]; IR (NaCl/thin film): 3035, 2968, 1748, 1694, 1609, 1488, 1424, 1339, 1257, 1148, 1026, 921, 744 cm^{-1}; $[\alpha]_D^{25}$ = –94.3º (*c* 1.14, DCM); HRMS (ESI) calc'd for $[M+H]^+$ 445.1734, found 445.1750.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 89% by chiral SFC analysis (OJ-H, 2.5 mL/min, 2% IPA in CO_2, λ = 254 nm): t_R(major) = 5.9 min t_R(minor) = 5.1 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 15.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 7.36 – 7.30 (m, 3H*, 3H[§]), 7.19 (dd, *J* = 6.5, 3.0 Hz, 2H[§]), 7.16 – 7.11 (m, 2H*), 7.08 (td, *J* = 7.7, 1.3 Hz, 1H*, 1H[§]), 7.04 (d, *J* = 7.4 Hz, 1H[§]), 6.99 (dd, *J* = 7.4, 0.9 Hz, 1H*), 6.73 (t, *J* = 7.0 Hz, 1H[§]), 6.68 (td, *J* = 7.4, 0.9 Hz, 1H*), 6.35 (d, *J* = 7.4 Hz, 1H§), 6.34 (d, *J* = 7.8 Hz, 1H*), 5.77 (dddd, *J* = 17.1, 10.4, 5.5, 5.1 Hz, 1H*), 5.73 – 5.67 (m, 1H[§]), 5.58 (s, 1H*), 5.55 – 5.53 (m, 1H[§]), 5.22 (dq, *J* = 17.1, 1.6 Hz, 1H*), 5.16 (dd, *J* = 9.6, 4.3 Hz, 1H[§]), 5.14 – 5.10 (m, 2H[§]), 5.05 (dq, *J* = 10.2, 1.5 Hz, 1H*), 4.97 (d, *J* = 12.3 Hz, 1H[§]), 4.91 (d, *J* = 12.3 Hz, 1H[§]), 4.80 (d, *J* = 8.5 Hz, 1H*), 4.68 (d, *J* = 12.1 Hz, 1H*), 4.36 (d, *J* = 12.1 Hz, 1H*), 4.15 (ddt, *J* = 16.7, 5.9, 1.5 Hz, 1H*), 4.01 (ddt, *J* = 16.7, 5.0, 1.6 Hz, 1H*), 3.68 – 3.64 (m, 1H[§]), 2.88 (d, *J* = 13.0 Hz, 1H*), 2.53 (dd, *J* = 13.3, 4.3 Hz, 1H[§]), 2.40 (dd, *J* = 13.0, 8.5 Hz, 1H*), 2.26 (dd, *J* = 13.3, 9.6 Hz, 1H[§]), 1.44 (s, 1H[§]), 1.43 (s, 1H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 15.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by [§]) δ 169.3*, 156.9* (q, $J_{C\text{-}F}$ = 36.9 Hz), 149.3*, 147.7[§], 134.7*, 134.1*, 133.2[§], 132.4[§], 132.0*, 128.9*, 128.6[§], 128.5[§], 128.5*, 128.4*, 128.3*, 128.2[§], 122.6*, 121.7[§], 118.7[§], 118.0*, 117.1[§], 116.3*, 116.2* (q, $J_{C\text{-}F}$ = 288.7 Hz), 108.0[§], 106.9*, 88.1*, 67.6*, 67.3[§], 60.4[§],

60.2*, 52.7§, 50.6*, 48.8*, 42.5*, 41.5§, 25.8*, 23.1§; IR (NaCl/thin film): 2962, 1739, 1697, 1608, 1491, 1447, 1269, 1211, 1145, 851, 742 cm^{-1}; $[\alpha]_D^{25}$ = +166.6º (*c* 1.52, DCM); HRMS (ESI) calc'd for $[M+H]^+$ 445.1734, found 445.1740.

Pyrroloindoline 98i.



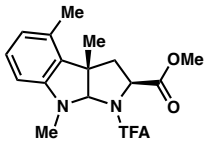
***exo* diastereomer**

Prepared from 3-methyl-1*H*-indole (0.15 mmol) and benzyl 2-trifluoroacetamidoacrylate (0.15 mmol) using general procedure C. The reaction was allowed to run for 5.5 h. The crude residue was purified by flash chromatography (0→20% ethyl acetate/hexanes) to yield 10.7 mg (18% yield) of **98i** in an 8:1 ratio of diastereomers (determined by NMR analysis of the pure product). The diastereomers were separated by prepatory HPLC (5→12% ethyl acetate/hexanes).

Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 95% by chiral SFC analysis (OJ-H, 2.5 mL/min, 7% IPA in hexanes, λ = 254 nm): t_R(major) = 9.6 min t_R(minor) = 7.4 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1:1 mixture of rotamers) δ 7.43 – 7.31 (m, 5H), 7.12 (t, *J* = 8.1 Hz, 0.5H), 7.10 (t, *J* = 8.1 Hz, 0.5H), 7.05 (d, *J* = 4.1 Hz, 0.5H), 7.04 (d, *J* = 3.9 Hz, 0.5H), 6.82 (t, *J* = 7.5 Hz, 0.5H), 6.77 (t, *J* = 7.5 Hz, 0.5H), 6.64 (d, *J* = 7.8 Hz, 0.5H), 6.60 (d, *J* = 7.8 Hz, 0.5H), 5.63 (s, 0.5 H), 5.57 (s, 0.5H), 5.30 (s, 0.5H), 5.23 (s, 1H), 5.22 (d, *J* = 12.2 Hz, 0.5H), 5.17 (d, *J* = 12.2 Hz, 0.5H), 4.76 (s, 0.5H), 4.68 – 4.62 (m, 0.5H), 4.50 (t, *J* = 7.7 Hz, 0.5H), 2.72 (dd, *J* = 13.5, 9.2 Hz, 0.5H), 2.58 (dd, *J* = 13.1, 8.5 Hz, 0.5H), 2.33 (dd, *J* = 13.4, 3.9 Hz, 0.5H), 2.17 (dd, *J* = 13.1, 6.9 Hz, 0.5H), 1.44 (s, 1.5H), 1.31 (s, 1.5H) ; ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 1:1 mixture of rotamers) δ 171.5, 170.2, 156.8 (q, J_{C-F} = 38.7 Hz), 146.8, 146.3, 135.2, 134.7, 133.2, 133.1, 128.9, 128.8, 128.7,

128.6, 128.5, 128.4, 122.3, 122.1,120.2, 119.3, 116.1 (q, $J_{C\text{-}F}$ = 287.2), 115.7 (q, $J_{C\text{-}F}$ = 287.2), 109.9, 109.3, 86.5, 84.5, 68.10, 67.5, 61.3, 59.6, 54.5, 50.3, 43.7, 40.3, 24.2, 23.9 ; IR (NaCl/thin film): 3390, 3034, 2961, 2920, 1748, 1687, 1610, 1486, 1469, 1456, 1189, 1158, 745 cm^{-1}; $[\alpha]_D^{25}$ –111.8° (c = 0.22, DCM); HRMS (EI+) calc'd for $M^{+\bullet}$ 404.1348, found 404.1344.

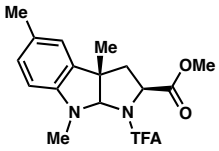
Pyrroloindoline 110a.



The d.r. was determined to be 7:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield 46.4 mg (66% yield) of **110a**. The enantiomeric excess was determined to be 95% by chiral SFC analysis (AD-H, 2.5 mL/min, 7% IPA in CO_2, λ = 254 nm): t_R(major) = 3.1 min t_R(minor) = 2.3 min. The major diastereomer was separated by flash chromatography (0→10% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 3.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.08 (t, J = 7.8 Hz, 1H*, 1H§), 6.65-6.57 (m, 1H§), 6.55 (d, J = 7.6 Hz, 1H*), 6.45-6.40 (m, 1H§), 6.38 (d, J = 7.8 Hz, 1H*), 5.49 (s, 1H*), 5.29 (s, 1H§), 4.74 (d, J = 9.3 Hz, 1H*), 4.45 (m, 1H§), 3.83 (s, 3H*), 3.78 (s, 3H§), 3.12 (s, 3H*), 2.85 (s, 3H§), 2.68 (dd, J = 13.3, 9.7 Hz, 1H*), 2.64-2.59 (m, 1H§), 2.53 (dd, J = 13.3, 1.6 Hz, 1H*), 2.33 (s, 3H§), 2.31 (s, 3H*), 2.20-2.10 (m, 1H§), 1.60 (s, 3H§), 1.47 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 3.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.7*, 170.5§, 159.0§ (q, $J_{C\text{-}F}$ = 37.2 Hz), 150.6*, 149.7§, 133.1§, 132.7*, 131.6*, 130.9§, 128.8*§, 122.6§, 121.5*, 116.1* (q, $J_{C\text{-}F}$ = 288.3 Hz), 107.3§, 106.2*,

94.0*, 92.0§, 61.3§, 60.0*, 53.1*, 52.6§, 50.0*, 42.7*, 39.4§, 37.4*, 34.6§, 24.1*, 23.3§, 18.5*§; IR (NaCl/thin film): 3047, 2957, 2930, 2880, 2825, 1752, 1701, 1596, 1477, 1434, 1385, 1356, 1338, 1293, 1263, 1254, 1216, 1204, 1155, 1097, 1064, 1020, 989, 854, 772, 744, 727 cm^{-1}; $[\alpha]_D^{25}$ = –158.8 (*c* = 1.01, $CHCl_3$). HRMS (APCI) calc'd for $C_{17}H_{19}F_3N_2O_3$ $[M+H]^+$ 357.1421, found 357.1426.

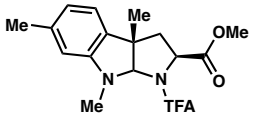
Pyrroloindoline 110b.



The d.r. was determined to be 13:1 by ^1H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield 48.2 mg (68% yield) of **110b**. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 254 nm): t_R(major) = 4.4 min t_R(minor) = 2.7 min. The major diastereomer was separated by flash chromatography (0→10% ethyl acetate/hexanes). ^1H NMR (500 MHz, $CDCl_3$; compound exists as a 1.9:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 6.98 (d, *J* = 7.4 Hz, 1H*, 1H§), 6.87 (s, 1H§), 6.84 (s, 1H*), 6.50 (d, *J* = 7.8 Hz, 1H§), 6.43 (d, *J* = 8.0 Hz, 1H*), 5.57 (s, 1H*), 5.27 (s, 1H§), 4.73 (d, *J* = 9.3 Hz, 1H*), 4.41 (t, *J* = 7.6 Hz, 1H§), 3.82 (s, 3H*), 3.76 (s, 3H§), 3.05 (s, 3H*), 2.86 (s, 3H§), 2.59 (dd, *J* = 13.3, 9.7 Hz, 1H*), 2.55-2.48 (m, 1H§), 2.35 (dd, *J* = 13.5, 2.2 Hz, 1H*), 2.28 (br s, 3H§), 2.20-2.10 (m, 1H§), 1.49 (s, 3H§), 1.38 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 1.9:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.6*, 170.7§, 159.1§ (q, $J_{C\text{-}F}$ = 37.0 Hz), 147.3*, 147.2§, 134.4*§, 129.7§, 129.2§, 129.1*, 128.2*, 122.3*§, 116.1* (q, $J_{C\text{-}F}$ = 288.2 Hz), 109.9§, 108.2*, 93.8*, 92.1§, 61.2§, 60.3*, 53.2§, 53.0*, 52.5§, 49.2*, 44.0*, 40.3§, 37.4*, 35.5§, 23.5*, 23.2§, 20.8*§; IR

(NaCl/thin film): 2958, 2924, 2873, 2822, 1750, 1699, 1618, 1500, 1435, 1384, 1356, 1339, 1288, 1257, 1201, 1152, 1117, 1094, 1057, 1035, 986, 874, 844, 807, 761, 728 cm^{-1}; $[\alpha]_D^{25}$ = –128.4 (*c* = 1.08, $CHCl_3$). HRMS (APCI) calc'd for $C_{17}H_{19}F_3N_2O_3$ $[M+H]^+$ 357.1421, found 357.1407.

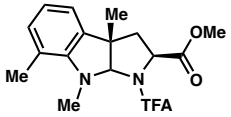
Pyrroloindoline 110c.



The d.r. was determined to be 14:1 by ^1H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield 58.8 mg (83% yield) of **110c**. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 254 nm): t_R(major) = 3.4 min t_R(minor) = 2.8 min. The major diastereomer was separated by flash chromatography (0→10% ethyl acetate/hexanes). ^1H NMR (500 MHz, $CDCl_3$; compound exists as a 2.4:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 6.99-6.93 (m, $1H^{\S}$), 6.91 (d, *J* = 7.4 Hz, 1H*), 6.65 (d, *J* = 6.7 Hz, $1H^{\S}$), 6.58 (d, *J* = 7.3 Hz, 1H*), 6.41 (s, $1H^{\S}$), 6.34 (s, 1H*), 5.60 (s, 1H*), 5.31 (s, $1H^{\S}$), 4.72 (d, *J* = 9.0 Hz, 1H*), 4.48-4.39 (m, $1H^{\S}$), 3.82 (s, 3H*), 3.77 (s, $3H^{\S}$), 3.06 (s, 3H*), 2.86 (s, $3H^{\S}$), 2.58 (dd, *J* = 13.2, 9.2 Hz, 1H*), 2.52-2.45 (m, $1H^{\S}$), 2.39-2.33 (m, 1H*), 2.32 (br s, 3H*, $3H^{\S}$), 2.10-2.00 (m, $1H^{\S}$), 1.49 (s, $3H^{\S}$), 1.38 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 2.4:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.6*, $170.6^{\S}$, $159.1^{\S}$ (q, $J_{C\text{-}F}$ = 37.9 Hz), 149.6*, $149.4^{\S}$, $139.0^{\S}$, 138.9*, 131.5*, $131.4^{\S}$, $121.2^{*\S}$, $120.6^{\S}$, 119.3*, 116.1* (q, $J_{C\text{-}F}$ = 288.4 Hz), $110.4^{\S}$, 108.9*, 93.5*, $91.9^{\S}$, $61.3^{\S}$, 60.3*, 53.0*, $52.9^{\S}$, $52.5^{\S}$, 49.0*, 44.0*, $40.5^{\S}$, 36.7*, $34.6^{\S}$, 23.6*, $23.0^{\S}$, 21.7*; IR (NaCl/thin film): 2958, 2929, 2875, 2813, 1750, 1697, 1617, 1594, 1499, 1435, 1382,

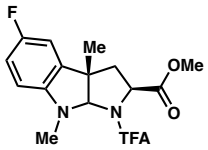
1356, 1341, 1294, 1257, 1203, 1190, 1148, 1111, 1094, 1059, 1034, 1006, 985, 877, 852, 803, 763, 729 cm^{-1}; $[\alpha]_D^{25}$ = –115.4 (*c* = 1.54, $CHCl_3$). HRMS (MM) calc'd for $C_{17}H_{19}F_3N_2O_3$ $[M+H]^+$ 357.1421, found 357.1434.

Pyrroloindoline 110d.



The d.r. was determined to be 15:1 by ^1H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→25% ethyl acetate/hexanes) to yield 48.1 mg (68% yield) of **110d** (major diastereomer only). The enantiomeric excess was determined to be 93% by chiral SFC analysis (AD-H, 2.5 mL/min, 7% IPA in CO_2, λ = 254 nm): t_R(major) = 3.6 min t_R(minor) = 2.5 min. ^1H NMR (500 MHz, $CDCl_3$; compound exists as a 6.1:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.05-7.00 (m, 1H*), 7.00-6.93 (m, 2H*, 1H§), 6.91 (d, *J* = 7.2 Hz, 1H§), 6.82 (t, *J* = 7.4 Hz, 1H§), 5.27 (s, 1H§), 5.14 (d, *J* = 1.6 Hz, 1H*), 4.59 (dd, *J* = 9.1, 2.3 Hz, 1H§), 4.06 (dd, *J* = 11.2, 6.6 Hz, 1H*), 3.80 (s, 3H§), 3.72 (s, 3H*), 3.26 (s, 3H§), 2.99 (s, 3H*), 2.67 (dd, *J* = 12.6, 6.6 Hz, 1H*), 2.57 (dd, *J* = 13.4, 9.2 Hz, 1H§), 2.30 (s, 3H§), 2.22 (s, 3H*), 2.13-2.03 (m, 1H*, 1H§), 1.47 (s, 3H*), 1.42 (s, 3H§); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 6.1:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.6§, 171.1*, 158.7*, 149.9*, 148.8§, 136.6*§, 131.4§, 131.0*, 126.6*, 124.01*, 122.6§, 121.2§, 119.6*, 119.4§, 116.0* (q, $J_{C\text{-}F}$ = 285.8 Hz), 95.6§, 92.5*, 60.3*, 59.2§, 55.1*, 52.9§, 52.4*, 49.7§, 44.0§, 41.9§, 41.0*, 38.6*, 26.3*, 26.0§, 18.9§, 17.5*; IR (NaCl/thin film): 2963, 1753, 1684, 1437, 1359, 1269, 1162, 1120, 1103, 1086, 1067, 977 cm^{-1}; $[\alpha]_D^{25}$ = –27.0 (*c* = 0.91, CH_2Cl_2). HRMS (MM) calc'd for $C_{17}H_{19}F_3N_2O_3$ $[M+H]^+$ 357.1421, found 357.1434.

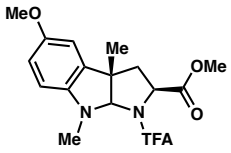
Pyrroloindoline 110e.



The d.r. was determined to be 10:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→25% ethyl acetate/hexanes) to yield 41.4 mg (58% yield) of **110e**. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 254 nm): t_R(major) = 3.7 min t_R(minor) = 2.3 min. The major diastereomer was separated by flash chromatography (0→10% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 2.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 6.92-6.82 (m, 1H*, 1H§), 6.81-6.76 (m, 1H§), 6.74 (dd, J = 8.0, 2.7 Hz, 1H*), 6.50 (dd, J = 8.6, 4.1 Hz, 1H§), 6.40 (dd, J = 8.6, 4.1 Hz, 1H*), 5.60 (s, 1H*), 5.31 (s, 1H§), 4.74 (d, J = 9.3 Hz, 1H*), 4.43 (t, J = 7.8 Hz, 1H§), 3.82 (s, 3H*), 3.77 (s, 3H§), 3.04 (s, 3H*), 2.85 (s, 3H§), 2.58 (dd, J = 13.5, 9.6 Hz, 1H*), 2.53-2.45 (m, 1H§), 2.40-2.32 (m, 1H*), 2.06 (dd, J = 13.3, 6.6 Hz, 1H§), 1.49 (s, 3H§), 1.38 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 2.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.4*, 170.5§, 159.0§ (q, $J_{C\text{-}F}$ = 35.8 Hz), 157.9*, 156.7§, 156.0*, 145.6*, 145.4§, 135.8§ (d, $J_{C\text{-}F}$ = 8.7 Hz), 135.6* (d, $J_{C\text{-}F}$ = 7.5 Hz), 116.0* (q, $J_{C\text{-}F}$ = 289.2 Hz), 115.1§, 114.8* (d, $J_{C\text{-}F}$ = 23.2 Hz), 110.5§ (d, $J_{C\text{-}F}$ = 7.3 Hz), 110.2§ (d, $J_{C\text{-}F}$ = 24.3 Hz), 109.4§ (d, $J_{C\text{-}F}$ = 24.1 Hz), 109.3* (d, $J_{C\text{-}F}$ = 24.4 Hz), 108.6* (d, $J_{C\text{-}F}$ = 8.1 Hz), 105.9§ (d, $J_{C\text{-}F}$ = 8.0 Hz), 93.8*, 92.1§, 61.1§, 60.2*, 53.2§, 53.1*, 52.6§, 49.2§, 43.8*, 40.1§, 37.6*, 35.5§, 23.4*, 22.9§; IR (NaCl/thin film): 2959, 2880, 2825, 1750, 1699, 1611, 1495, 1436, 1386, 1356, 1339, 1270, 1229, 1202, 1178, 1152, 1118, 1091, 1052, 1034, 986, 872, 845,

808, 756, 728 cm^{-1}; $[\alpha]_D^{25}$ = –108.5 (*c* = 1.08, $CHCl_3$). HRMS (APCI) calc'd for $C_{16}H_{16}F_4N_2O_3$ $[M+H]^+$ 361.1170, found 361.1187.

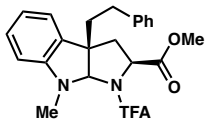
Pyrroloindoline 110f.



The d.r. was determined to be 10:1 by ^1H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield 44.8 mg (61% yield) of **110f**. The enantiomeric excess was determined to be 90% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 254 nm): t_R(major) = 3.8 min t_R(minor) = 2.5 min. The major diastereomer was separated by flash chromatography (0→10% ethyl acetate/hexanes). ^1H NMR (500 MHz, $CDCl_3$; compound exists as a 1.8:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 6.75-6.70 (m, 1H*, 1H§), 6.67-6.65 (m, 1H§), 6.64 (d, *J* = 2.4 Hz, 1H*), 6.55 (d, *J* = 8.5 Hz, 1H§), 6.45 (d, *J* = 8.5 Hz, 1H*), 5.55 (s, 1H*), 5.24 (s, 1H§), 4.74 (d, *J* = 9.4 Hz, 1H*), 4.38 (t, *J* = 8.0 Hz, 1H§), 3.81 (s, 3H*), 3.77 (s, 3H§), 3.76 (s, 3H*, 3H§), 3.04 (s, 3H*), 2.86 (s, 3H§), 2.59 (dd, *J* = 13.5, 9.6 Hz, 1H*), 2.52 (dd, *J* = 13.0, 8.7 Hz, 1H§), 2.35 (dd, *J* = 13.5, 2.5 Hz, 1H*), 2.09-2.00 (m, 1H§), 1.48 (s, 3H§), 1.38 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 1.8:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.5*, 170.7§, 159.0§ (q, $J_{C\text{-}F}$ = 37.1, 36.6 Hz), 154.6§, 153.6*, 143.7*, 143.6§, 135.9§, 135.7*, 116.1* (q, $J_{C\text{-}F}$ = 288.3 Hz), 113.3§, 113.0*, 111.4§, 109.02*, 108.98*, 108.8§, 94.1*, 92.3§, 61.0§, 60.3*, 56.0*, 55.9§, 53.6§, 53.1*, 52.6§, 49.3*, 43.9*, 39.9§, 38.1*, 36.8§, 23.5*§; IR (NaCl/thin film): 2958, 2833, 1750, 1691, 1598, 1497, 1434, 1384, 1356, 1341, 1281, 1259, 1231, 1203, 1154, 1093, 1062,

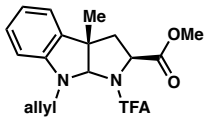
1031, 986, 870, 844, 808, 756, 728 cm^{-1}; $[\alpha]_D^{25}$ = –103.2 (*c* = 0.82, $CHCl_3$). HRMS (APCI) calc'd for $C_{17}H_{19}F_3N_2O_4$ $[M+H]^+$ 373.1370, found 373.1383.

Pyrroloindoline 110g.



The diastereomeric ratio was determined to be 13:1 by ^1H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→20% ethyl acetate/hexanes) to yield 74.1 mg (86% yield) of **110g**. The enantiomeric excess was determined to be 87% by chiral SFC analysis (AD-H, 2.5 mL/min, 8% IPA in CO_2, λ = 254 nm): t_R(major) = 5.3 min t_R(minor) = 8.1 min. The major diastereomer was separated by flash chromatography (5% ethyl acetate/hexanes). ^1H NMR (500 MHz, $CDCl_3$; compound exists as a 2.6:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.32-7.15 (m, 4H*, 4H§), 7.08 (br t, *J* = 7.7 Hz, 3H*, 3H§), 6.95-6.75 (m, 1H*, 1H§), 6.65-6.50 (m, 1H*, 1H§), 5.72 (br s, 1H*), 5.46 (br s, 1H§), 4.65 (br d, *J* = 6.3 Hz, 1H*), 4.33 (br s, 1H§), 3.78 (br s, 3H*, 3H§), 3.13 (br s, 3H*), 2.90 (br s, 3H§), 2.76-1.87 (m, 6H*, 6H§); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 2.6:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.6*, 170.6§, 159.0* (q, $J_{C\text{-}F}$ = 37.5 Hz), 150.3*§, 141.1*§, 131.9*, 131.7§, 129.0*§, 128.5*§, 128.2*§, 126.1*§, 122.0*, 121.2* (q, $J_{C\text{-}F}$ = 278.2 Hz), 119.0*, 117.2§, 114.9§, 109.8§, 108.3*, 90.5*, 89.2§; IR (NaCl/thin film): 3026, 2952, 1751, 1701, 1607, 1491, 1437, 1355, 1204, 1151, 985, 749 cm^{-1}; $[\alpha]_D^{25}$ = –128.3 (*c* = 1.22, CH_2Cl_2). HRMS (MM) calc'd for $C_{23}H_{23}F_3N_2O_3$ $[M+H]^+$ 433.1734, found 433.1750.

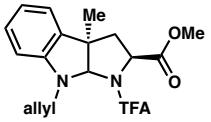
Pyrroloindoline *exo*-110h.



The diastereomeric ratio was determined to be 5:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→15% ethyl acetate/hexanes) to yield 61.1 mg of white needles (84% yield). The enantiomeric excess was determined to be 90% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ = 254 nm): t_R(major) = 7.8 min t_R(minor) = 3.5 min. The major and minor diastereomers were separated by reverse phase preparatory HPLC (50→95% acetonitrile/water, 0.05% trifluoroacetic acid). ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 4.9:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.14 (td, *J* = 7.7, 1.3 Hz, 1H*, 1H§), 7.03 (br d, *J* = 7.3 Hz, 1H*, 1H§), 6.90-6.80 (br s, 1H§), 6.76 (t, *J* = 7.4 Hz, 1H*), 6.67-6.58 (br s, 1H§), 6.54 (d, *J* = 7.9 Hz, 1H*), 5.81 (dtd, *J* = 16.5, 11.6, 11.1, 6.2 Hz, 1H*, 1H§), 5.74 (s, 1H*), 5.51 (br s, 1H§), 5.27 (br d, *J* = 17.1 Hz, 1H*, 1H§), 5.14 (br d, *J* = 10.2 Hz, 1H*, 1H§), 4.72 (d, *J* = 9.1 Hz, 1H*), 4.34 (br s, 1H§), 4.25 (dd, *J* = 16.5, 3.6 Hz, 1H*), 4.04 (dd, *J* = 16.5, 6.2 Hz, 1H*), 4.00-3.94 (m, 1H§), 3.82 (s, 3H*), 3.76 (s, 3H§), 2.62 (dd, *J* = 13.3, 9.7 Hz, 1H*), 2.58-2.49 (m, 1H§), 2.40 (dd, *J* = 13.5, 2.6 Hz, 1H*), 2.11 (br s, 1H§), 1.48 (s, 3H§), 1.39 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 4.9:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.6*, 170.6§, 158.9§ (q, $J_{C\text{-}F}$ = 36.9 Hz), 148.4*, 134.7*, 133.8*, 133.3§, 128.7*, 121.7§, 121.5*, 120.3§, 118.8*, 117.8§, 116.8*, 116.0* (q, $J_{C\text{-}F}$ = 288.4 Hz), 110.8§, 108.5*, 91.3*, 89.6§, 60.9§, 59.9*, 53.0*, 52.5§, 51.8*, 50.4§, 49.4*, 44.3*, 40.8§, 23.7*, 23.4§; IR (NaCl/thin film): 3053, 2958, 2877, 1751, 1700, 1691, 1685, 1642, 1608, 1487, 1437, 1384, 1356, 1340, 1309, 1257, 1205, 1151, 1106, 1093, 1027, 991, 925, 841, 817, 792,

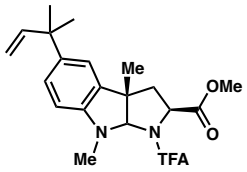
744 cm^{-1}; $[\alpha]_D^{25}$ = –146.2 (*c* = 1.60, $CHCl_3$). HRMS (APCI) calc'd for $C_{18}H_{19}F_3N_2O_3$ $[M+H]^+$ 369.1421, found 369.1416.

Pyrroloindoline *endo*-110h.



^1H NMR (500 MHz, $CDCl_3$; compound exists as a 15.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.11-7.07 (m, 1H§), 7.06 (td, *J* = 7.6, 1.3 Hz, 1H*), 7.06-7.03 (m, 1H§), 6.98 (dd, *J* = 7.3, 0.7 Hz, 1H*), 6.73 (td, *J* = 7.4, 1.0 Hz, 1H§), 6.66 (td, *J* = 7.4, 1.0 Hz, 1H*), 6.46-6.44 (m, 1H§), 6.44 (d, *J* = 7.9 Hz, 1H*), 5.87 (dddd, *J* = 17.1, 10.3, 5.9, 5.1 Hz, 1H*), 5.82-5.75 (m, 1H§), 5.57 (s, 1H*), 5.53 (d, *J* = 1.4 Hz, 1H§), 5.30 (dq, *J* = 17.2, 1.7 Hz, 1H*), 5.22-5.19 (m, 1H§), 5.16 (dq, *J* = 10.2, 1.5 Hz, 1H*), 5.10 (dd, *J* = 9.5, 4.5 Hz, 1H§), 4.75 (dt, *J* = 8.4, 1.3 Hz, 1H*), 4.24-4.13 (m, 2H*), 3.85 (ddd, *J* = 49.3, 17.2, 5.1 Hz, 2H§), 3.53 (s, 3H§), 3.17 (s, 3H*), 2.85 (d, *J* = 13.0 Hz, 1H*), 2.50 (dd, *J* = 13.2, 4.5 Hz, 1H§), 2.39 (dd, *J* = 13.0, 8.4 Hz, 1H*), 2.25 (dd, *J* = 13.3, 9.6 Hz, 1H§), 1.44 (s, 3H§), 1.42 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 15.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 170.0*, 156.8§ (q, $J_{C\text{-}F}$ = 36.8 Hz), 149.3*, 147.8§, 134.2*, 133.2§, 132.6§, 132.0*, 128.9*, 128.6§, 122.5*, 121.7§, 118.7§, 118.0*, 117.1§, 116.3*, 116.1* (q, $J_{C\text{-}F}$ = 288.6 Hz), 108.0§, 106.8*, 88.7§, 88.1*, 60.3§, 60.1* (q, $J_{C\text{-}F}$ = 3.1 Hz), 52.6§, 52.5§, 52.4*, 50.6*, 49.0*, 46.6§, 42.5*, 41.4§, 25.7*, 22.9§; IR (NaCl/thin film): 3055, 2954, 2869, 1760, 1742, 1699, 1607, 1490, 1447, 1436, 1338, 1317, 1274, 1254, 1208, 1183, 1144, 1105, 1093, 1032, 999, 942, 922, 887, 842, 859, 742 cm^{-1}; $[\alpha]_D^{25}$ = +188.1 (*c* = 0.275, $CHCl_3$). HRMS (APCI) calc'd for $C_{18}H_{19}F_3N_2O_3$ $[M+H]^+$ 369.1421, found 369.1429.

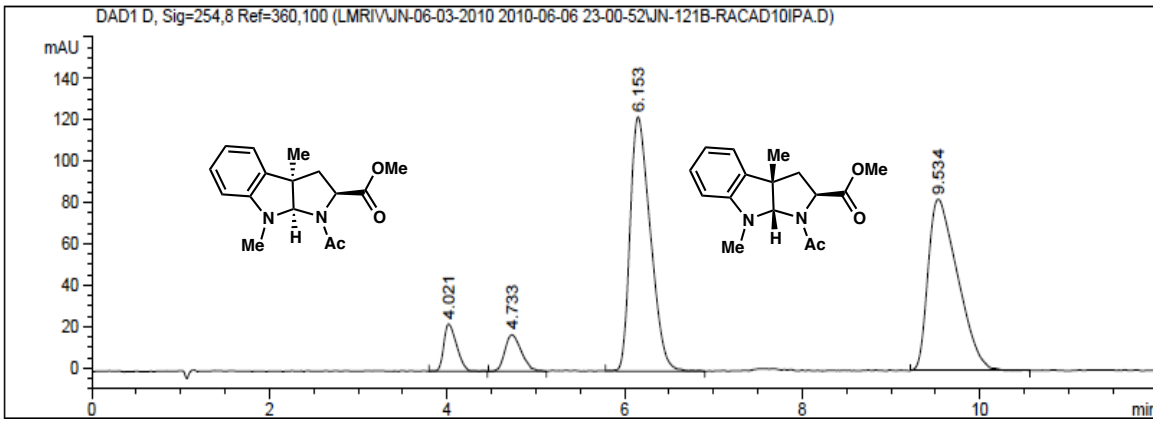
Pyrroloindoline 110i.



The diastereomeric ratio was determined to be 18:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield 68.6 mg (84% yield) of **110i.** The enantiomeric excess was determined to be 92% by chiral SFC analysis (OD, 2.5 mL/min, 3% IPA in CO_2, λ = 254 nm): t_R(major) = 6.5 min t_R(minor) = 5.6 min. The major diastereomer was separated by flash chromatography (0→10% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 2.1:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.16 (d, *J* = 8.1 Hz, 1H*, 1H§), 7.02 (s, 1H§), 6.99 (s, 1H*), 6.52 (d, *J* = 7.7 Hz, 1H§), 6.45 (d, *J* = 8.2 Hz, 1H*), 6.00 (dd, *J* = 17.3, 10.5 Hz, 1H*, 1H§), 5.60 (s, 1H*), 5.31 (s, 1H§), 5.07 – 4.96 (m, 2H*, 2H§), 4.73 (d, *J* = 9.3 Hz, 1H*), 4.47 – 4.41 (m, 1H§), 3.82 (s, 1H*), 3.77 (s, 1H§), 3.06 (s, 1H*), 2.86 (s, 1H§), 2.60 (dd, *J* = 13.1, 9.9 Hz, 1H*), 2.52 (t, *J* = 10.7 Hz, 1H§), 2.38 (d, *J* = 12.5 Hz, 1H*), 2.14 – 1.98 (m, 1H§), 1.57 – 1.31 (m, 9H*, 9H§); ^{13}C NMR (126 MHz, $CDCl_3$) ; IR (NaCl/thin film): 3081, 2965, 2874, 2822, 1753, 1698, 1618, 1496, 1434, 1359, 1283, 1257, 1204, 1156, 1117, 1054, 995, 912, 844, 813; $[\alpha]_D^{25}$ = -115 (*c* = 0.450, $CHCl_3$). HRMS (ESI) calc'd for $C_{21}H_{25}F_3N_2O_3$ $[M+H]^+$ 411.1890, found 411.1901.

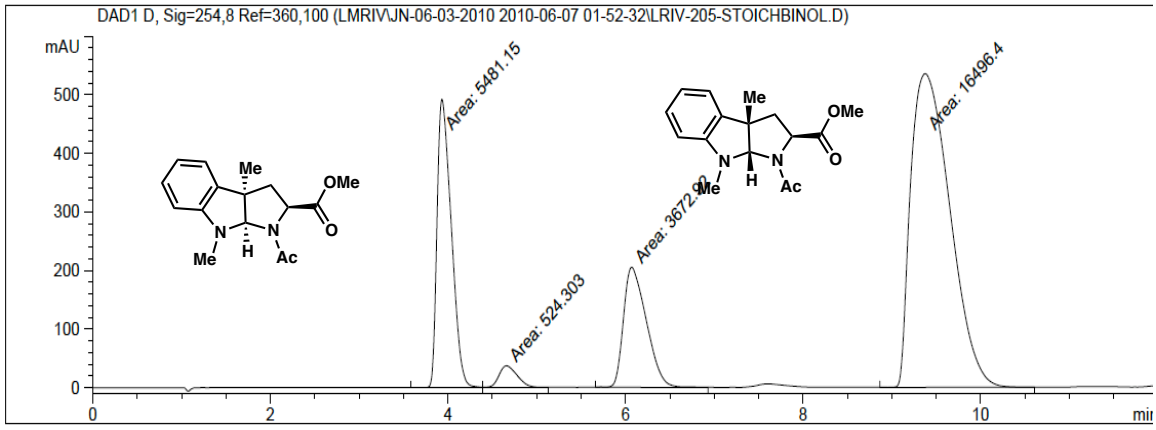
2.4.5 SFC and HPLC Traces for Racemic and Enantioenriched Products

91: racemic



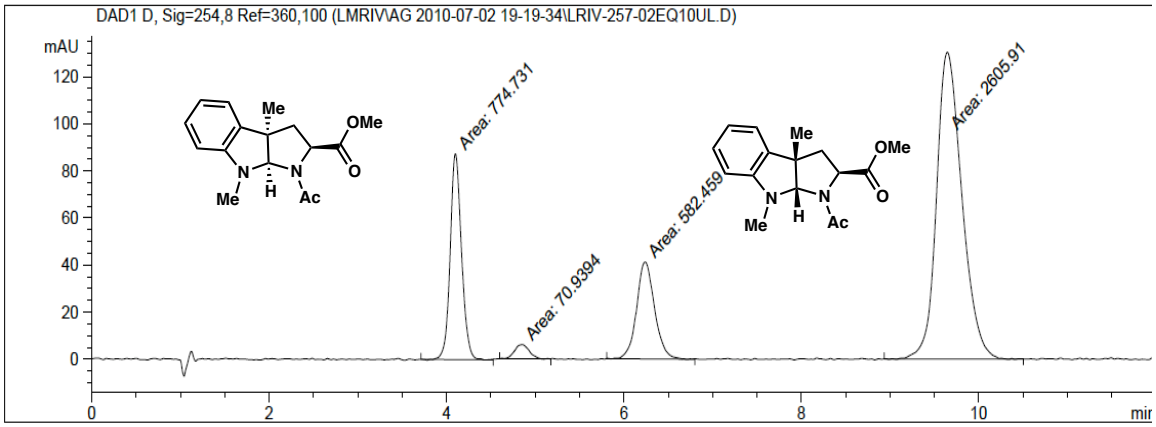
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.021	BB	0.1585	233.11978	22.95946	5.3721
2	4.733	BB	0.2032	229.21661	17.68176	5.2822
3	6.153	BB	0.2451	1949.83508	122.89280	44.9330
4	9.534	BB	0.3471	1927.25183	82.93414	44.4126

91 (**Table 3, entry 2**): enantioenriched, *exo:* 64% ee, *endo*: 83% ee (1.1 equiv BINOL)



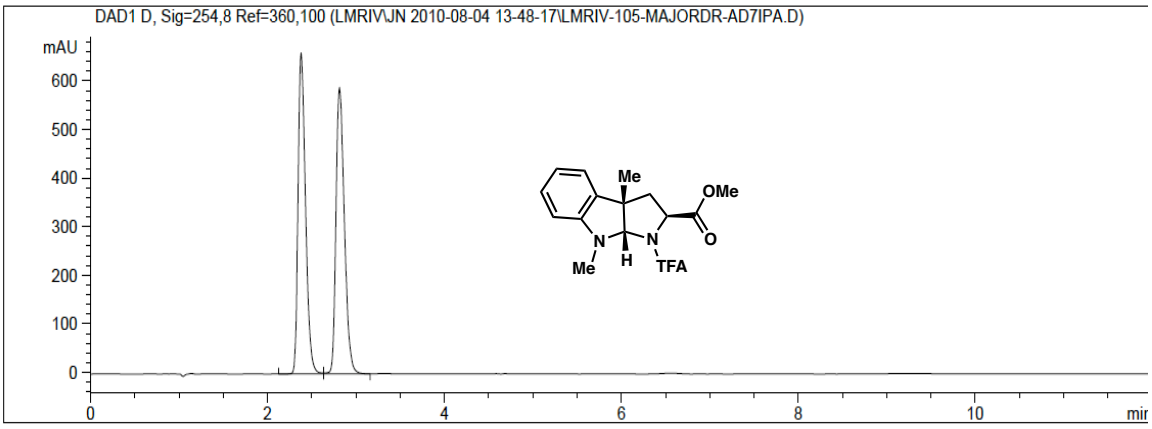
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.934	MF	0.1852	5481.14941	493.18698	20.9406
2	4.658	FM	0.2354	524.30292	37.12406	2.0031
3	6.070	MM	0.2985	3672.91748	205.08722	14.0323
4	9.375	MM	0.5132	1.64964e4	535.76978	63.0240

91 (**Table 3, entry 4**): enantioenriched, *exo:* 63% ee, *endo*: 83% ee (0.2 equiv BINOL)



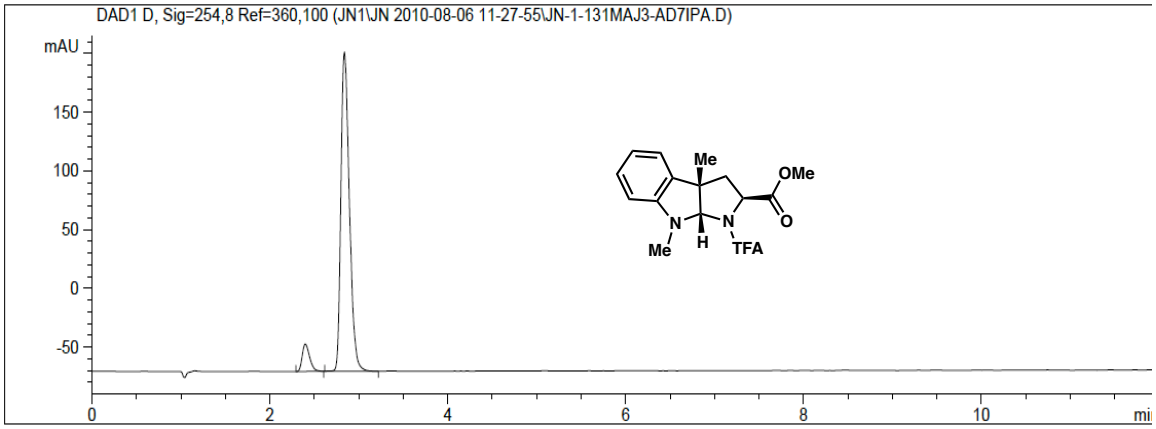
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.100	MM	0.1473	774.73053	87.65621	19.2048
2	4.852	MM	0.1955	70.93945	6.04832	1.7585
3	6.238	MM	0.2351	582.45917	41.28461	14.4386
4	9.647	MM	0.3330	2605.91260	130.42717	64.5981

***exo*-94** (**Table 3, entry 6**): racemic



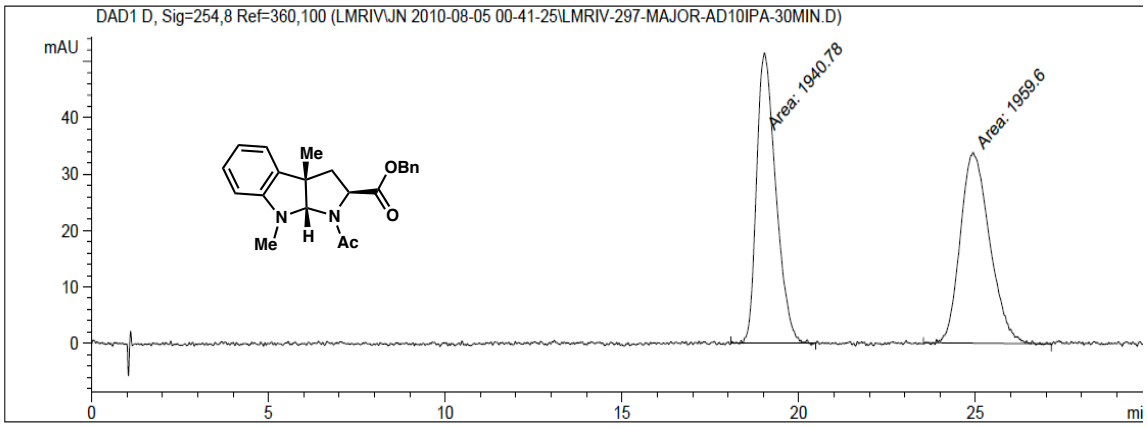
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.381	BV	0.0886	3856.54150	655.60498	49.8096
2	2.815	VB	0.1009	3886.01978	589.71381	50.1904

***exo*-94** (**Table 3, entry 6**): enantioenriched, 86% ee



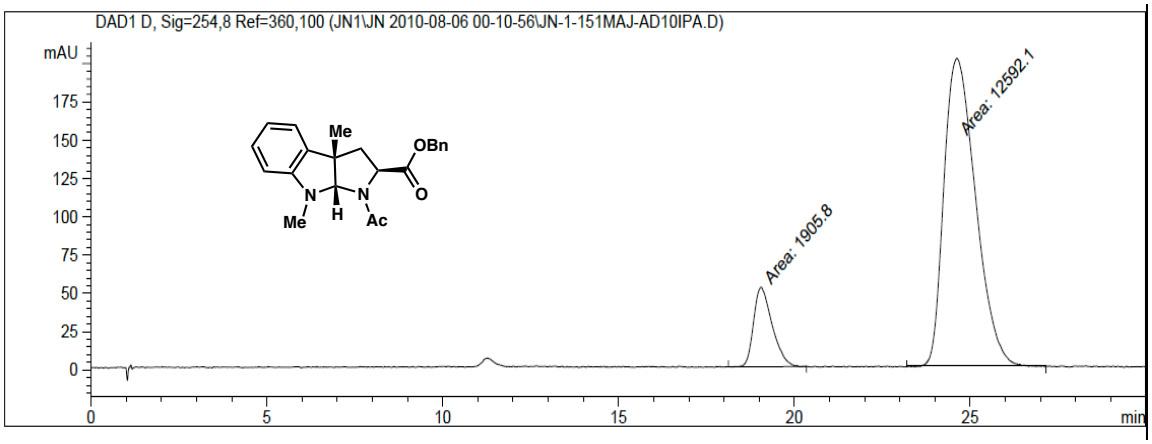
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.399	BB	0.0925	136.26041	23.19655	6.9999
2	2.839	BB	0.1061	1810.34204	270.34299	93.0001

***exo*-95** (**Table 3, entry 7**): racemic



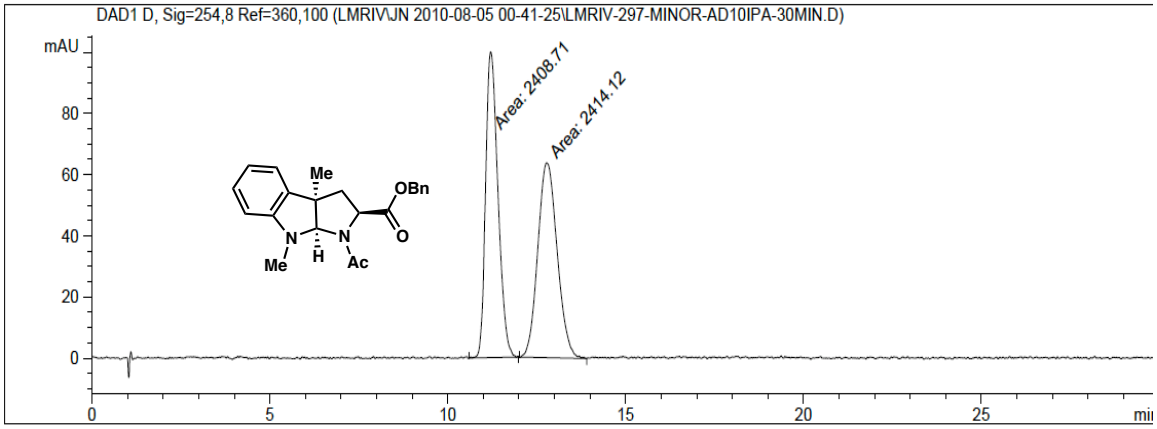
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.033	MM	0.6293	1940.77502	51.40419	49.7587
2	24.937	MM	0.9651	1959.59827	33.84022	50.2413

***exo*-95** (**Table 3, entry 7**): enantioenriched, 74% ee



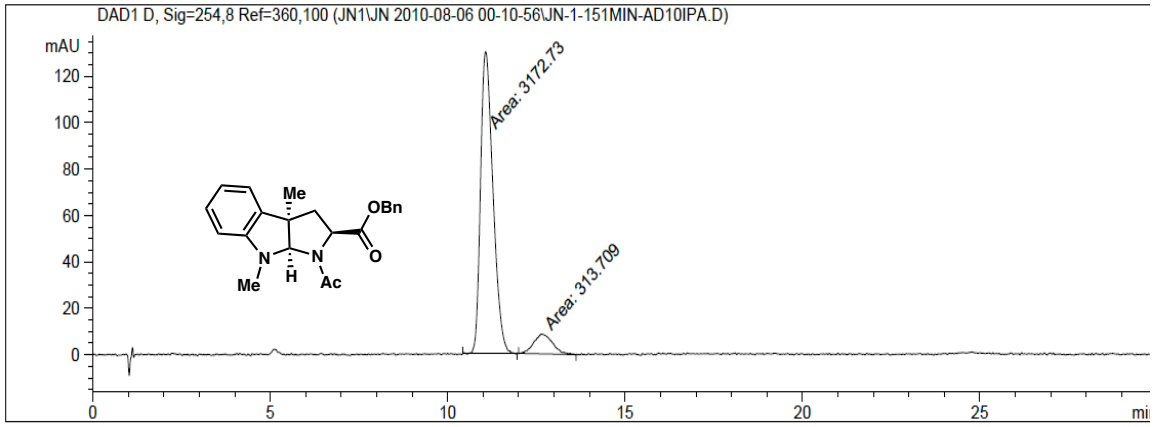
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.055	MM	0.6122	1905.80066	51.88297	13.1454
2	24.623	MM	1.0448	1.25921e4	200.87437	86.8546

***endo*-95 (Table 3, entry 7)**: racemic



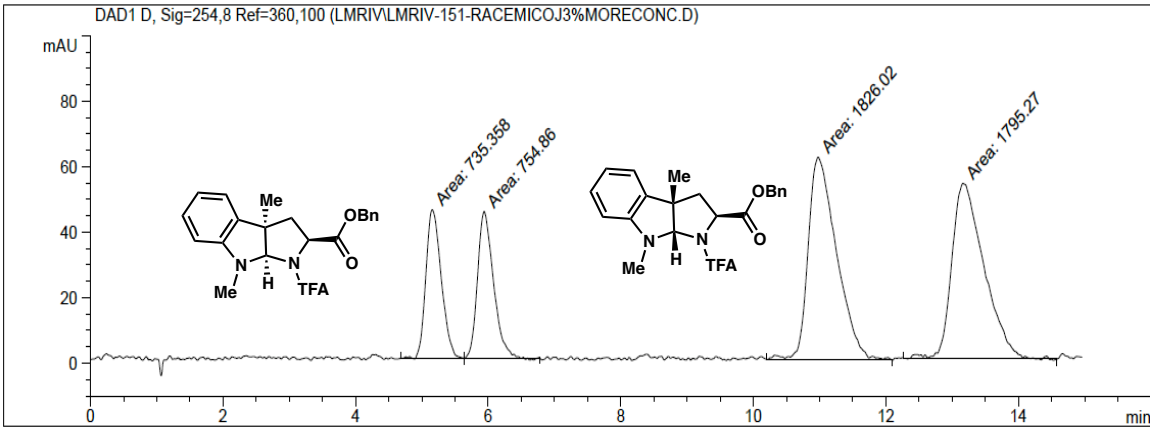
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.210	MM	0.4013	2408.70581	100.04025	49.9439
2	12.782	MM	0.6310	2414.11816	63.76419	50.0561

***endo*-95 (Table 3, entry 7)**: enantioenriched, 82% ee



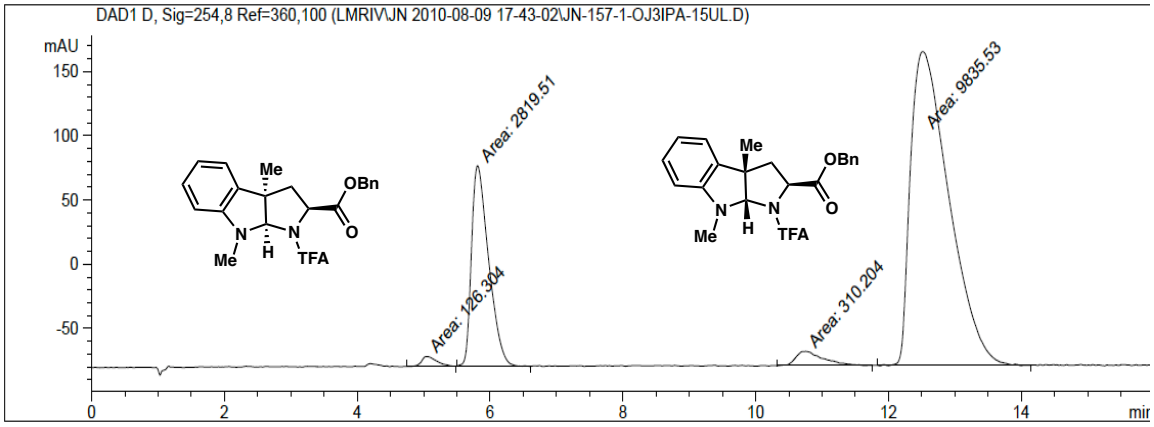
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.074	MM	0.4067	3172.73267	130.02379	91.0020
2	12.646	MM	0.6145	313.70920	8.50807	8.9980

96 (**Table 3, entry 9**): racemic



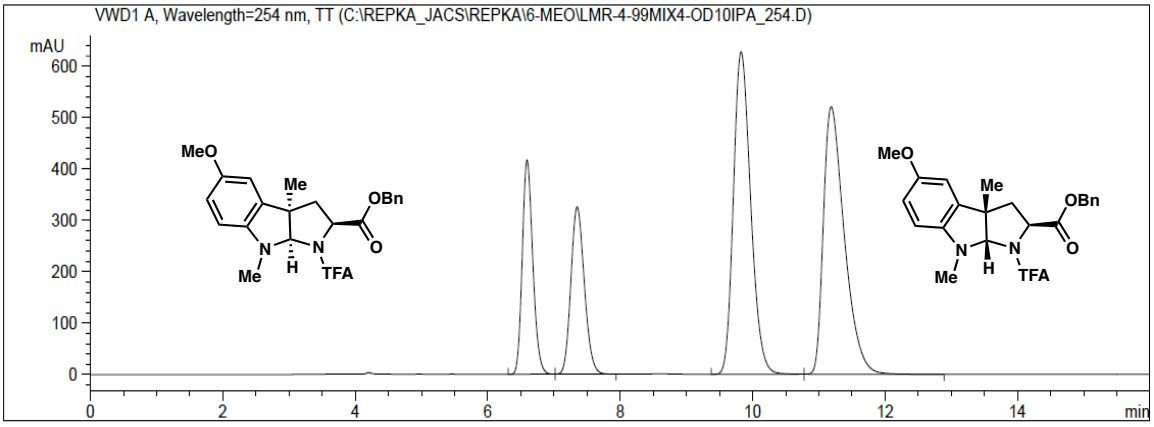
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.156	MF	0.2696	735.35803	45.45393	14.3863
2	5.940	FM	0.2802	754.85999	44.89612	14.7679
3	10.979	MM	0.4932	1826.01990	61.70875	35.7237
4	13.166	MM	0.5603	1795.26794	53.40647	35.1221

96 (**Table 3, entry 9**): enantioenriched, *exo:* 94% ee, *endo*: 91% ee



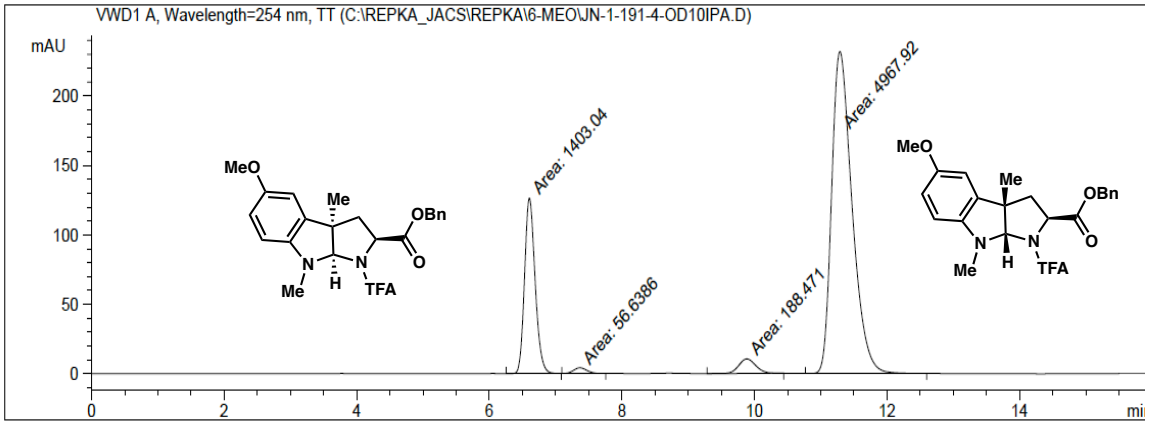
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.044	MM	0.2729	126.30366	7.71386	0.9648
2	5.812	MM	0.3004	2819.51172	156.42670	21.5369
3	10.749	MM	0.4705	310.20364	10.98786	2.3695
4	12.515	MM	0.6705	9835.53320	244.48642	75.1289

98a (Figure 2): racemic



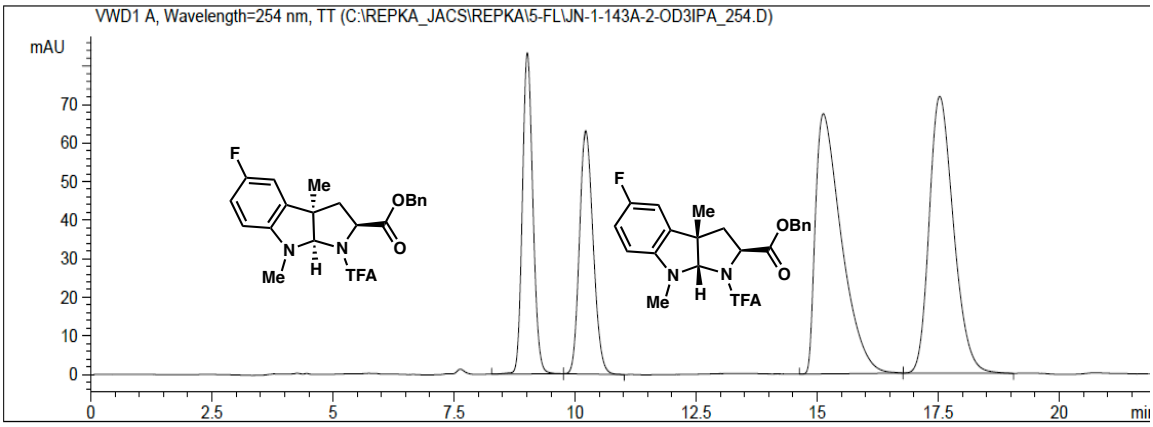
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.594	BB	0.1698	4609.86621	416.95142	14.3772
2	7.350	BB	0.2192	4610.61719	325.26569	14.3795
3	9.826	BB	0.2823	1.13860e4	627.58807	35.5104
4	11.187	BB	0.3325	1.14573e4	520.55212	35.7328

98a (Figure 2): *exo*: 93% ee, *endo*: 92% ee



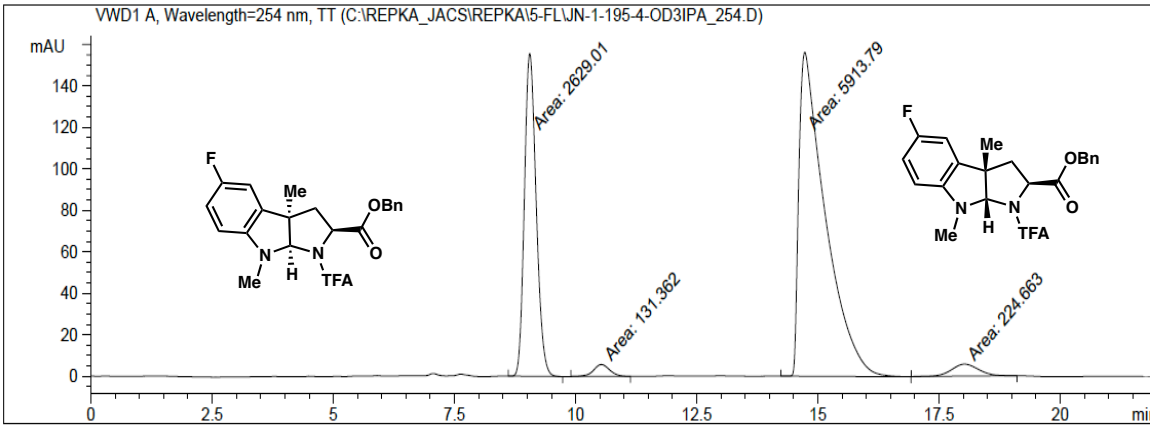
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.605	MM	0.1851	1403.04370	126.31284	21.2066
2	7.366	MM	0.2282	56.63861	4.13736	0.8561
3	9.885	MM	0.3007	188.47099	10.44562	2.8487
4	11.289	MM	0.3574	4967.92139	231.68799	75.0887

98b (Figure 2): racemic



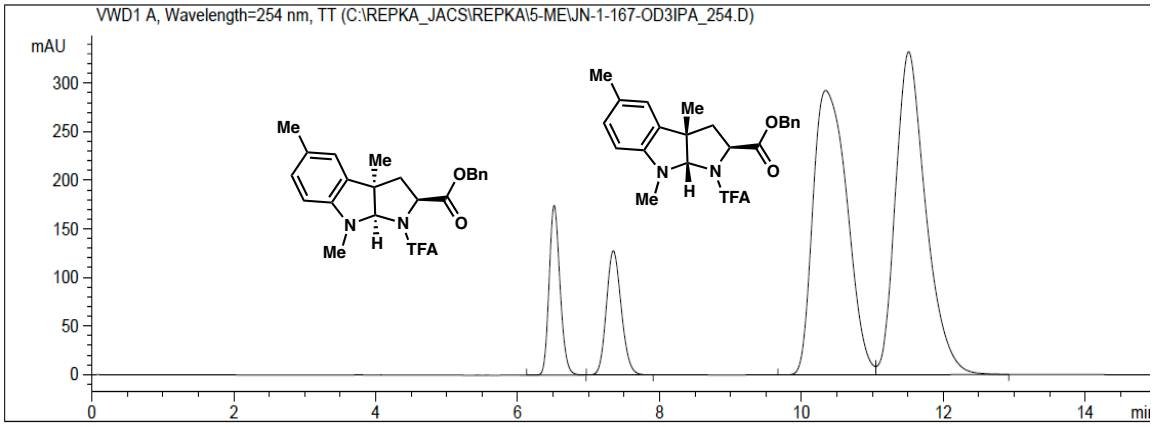
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	9.013	BB	0.2330	1253.27209	83.29908	16.6472
2	10.220	BB	0.3072	1244.32800	63.10659	16.5284
3	15.127	BB	0.5588	2519.96948	67.46533	33.4727
4	17.529	BB	0.5354	2510.85742	71.80063	33.3517

98b (Figure 2): *exo*: 93% ee *endo*: 90% ee



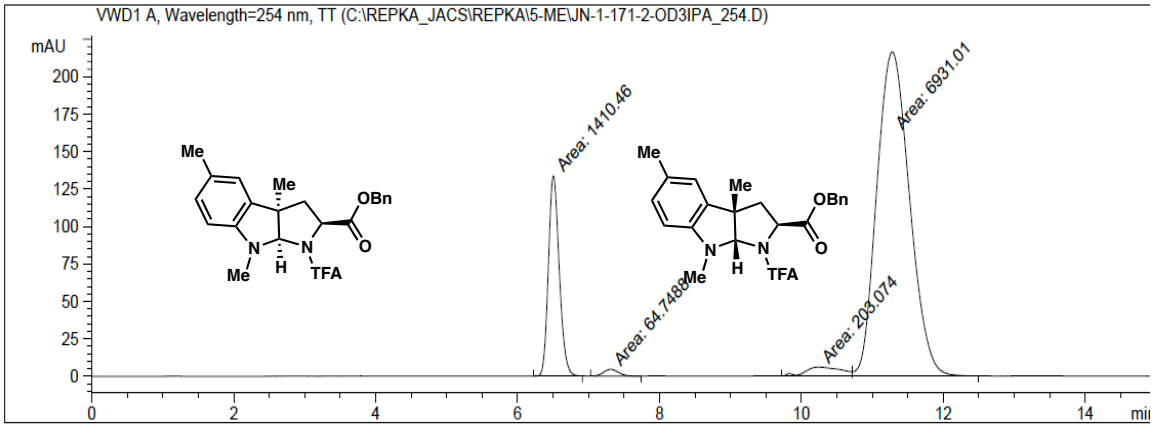
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	9.053	MM	0.2815	2629.00732	155.65556	29.5433
2	10.530	MM	0.3806	131.36226	5.75281	1.4762
3	14.729	MM	0.6305	5913.78809	156.33769	66.4559
4	18.025	MM	0.6446	224.66296	5.80853	2.5246

98c (Figure 2): racemic



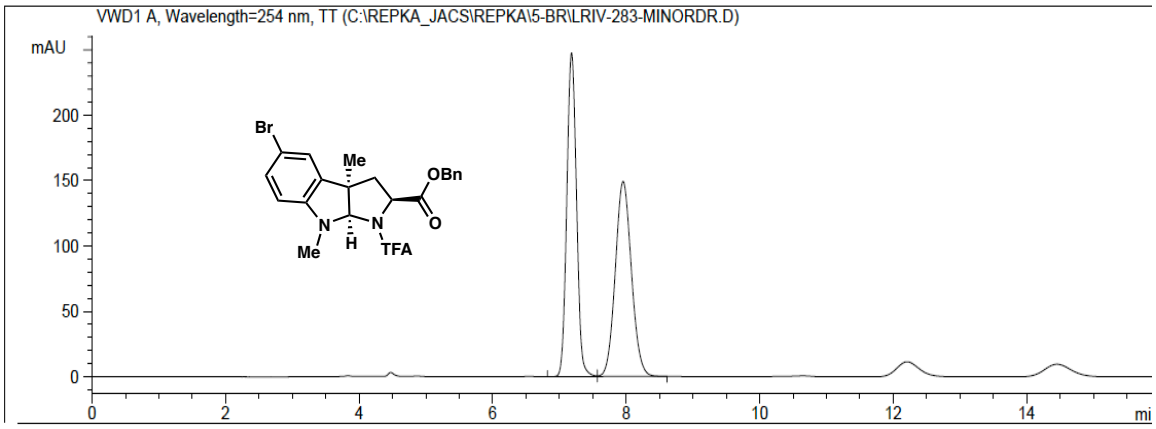
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.515	BB	0.1639	1864.59338	174.59178	7.9727
2	7.349	BB	0.2261	1861.35925	127.72897	7.9589
3	10.343	BV	0.5481	9785.77832	292.62845	41.8426
4	11.512	VV	0.4515	9875.41406	332.30096	42.2258

98c (Figure 2): enantioenriched, *exo:* 94% ee, *endo*: 91% ee



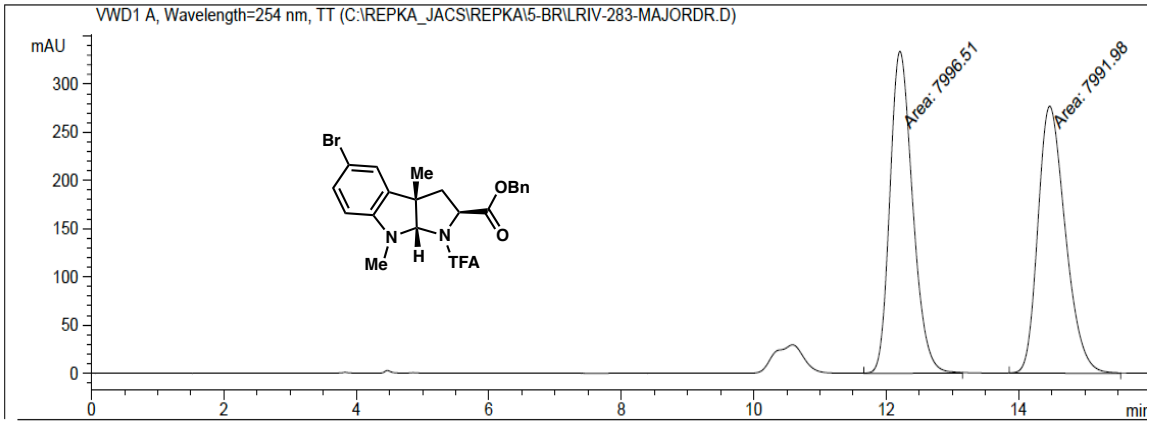
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.505	MM	0.1760	1410.45825	133.56871	16.3830
2	7.313	MM	0.2416	64.74883	4.46749	0.7521
3	10.246	MF	0.5768	203.07445	5.86773	2.3588
4	11.281	FM	0.5342	6931.01367	216.22461	80.5062

***endo*-98d** (Figure 2): racemic



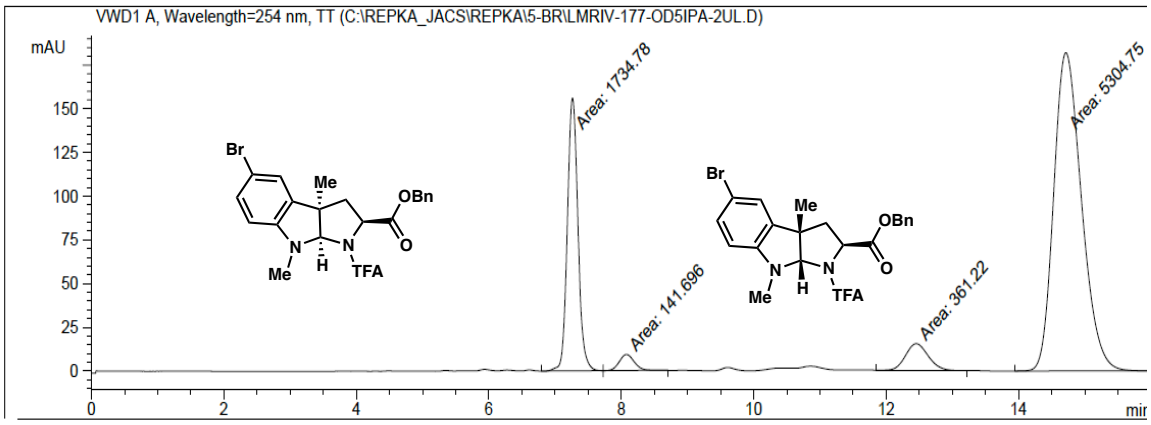
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.181	BV	0.1595	2504.75537	247.61092	50.0224
2	7.954	VB	0.2591	2502.51636	149.14781	49.9776

***exo*-98d** (Figure 2): racemic



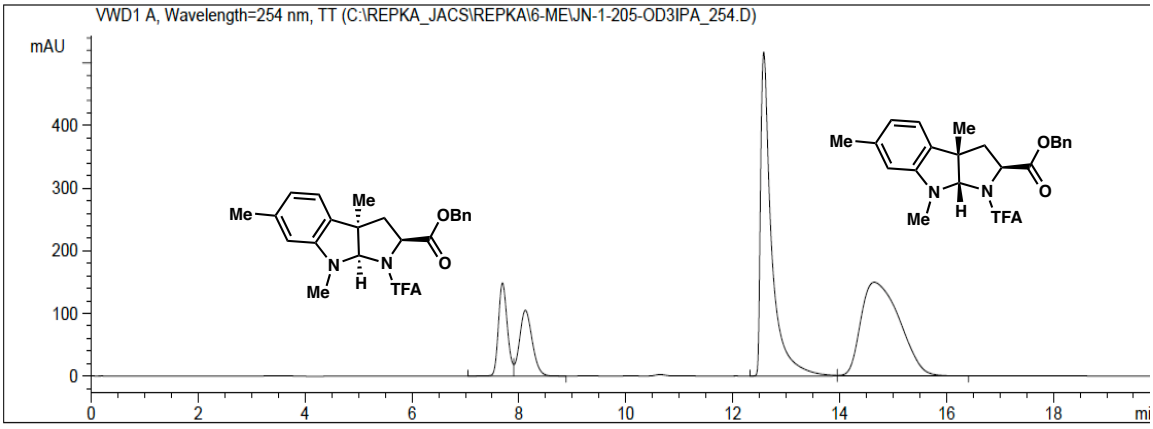
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	12.208	MM	0.3987	7996.50732	334.25320	50.0142
2	14.469	MM	0.4807	7991.97656	277.08136	49.9858

98d (Figure 2): *exo*: 87% ee, *endo:* 85% ee



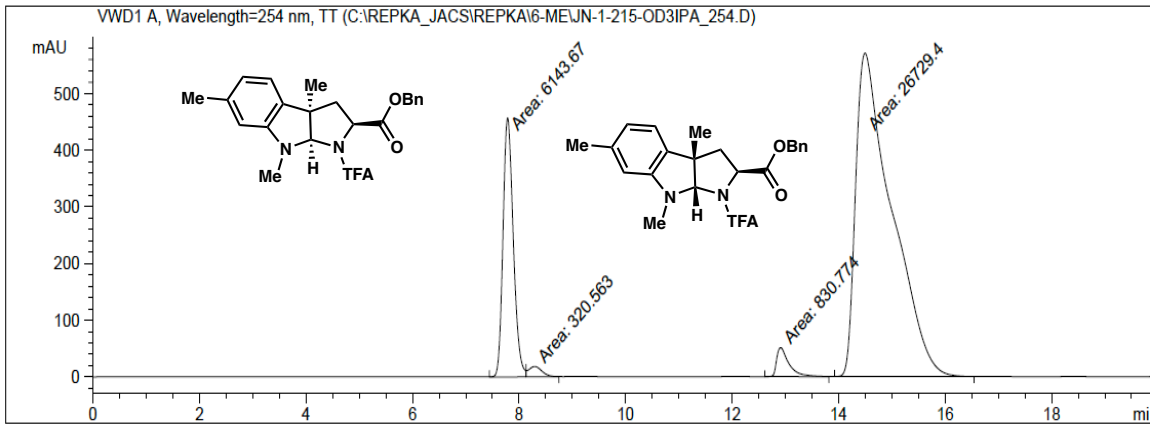
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.263	MF	0.1852	1734.78003	156.08707	23.0002
2	8.076	FM	0.2580	141.69585	9.15505	1.8786
3	12.454	MM	0.3947	361.21967	15.25336	4.7892
4	14.714	MM	0.4855	5304.75488	182.11263	70.3320

98e (Figure 2): racemic



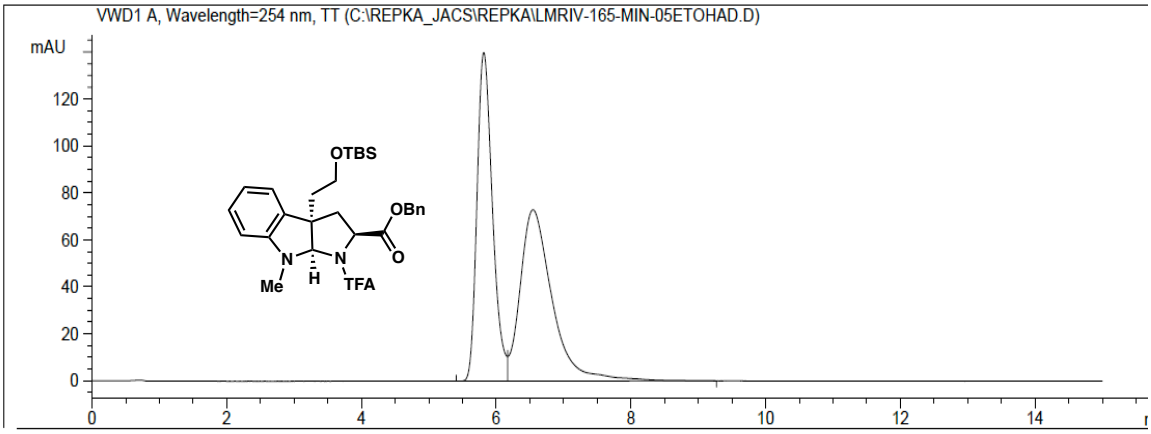
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.694	BV	0.1800	1738.04382	148.72224	9.4448
2	8.122	VB	0.2549	1740.51331	105.22092	9.4582
3	12.583	BV	0.2060	7424.35889	517.51135	40.3450
4	14.649	VB	0.7114	7499.26904	149.61671	40.7521

98e (Figure 2): *exo*: 94% ee, *endo*: 90% ee



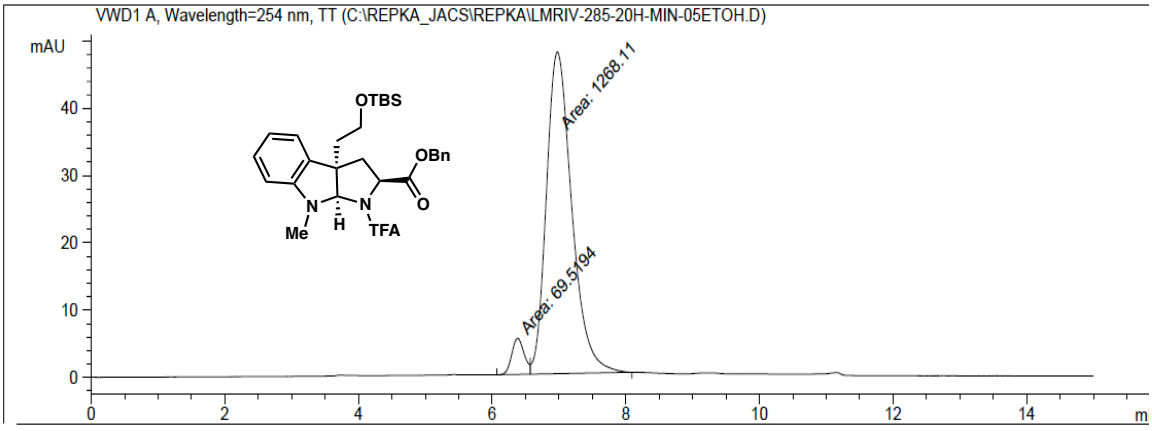
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.785	MF	0.2240	6143.67139	457.11594	18.0567
2	8.294	FM	0.2911	320.56265	18.35141	0.9422
3	12.912	MM	0.2706	830.77399	51.16518	2.4417
4	14.496	MM	0.7807	2.67294e4	570.62366	78.5595

***endo*-98f** (Figure 2): racemic



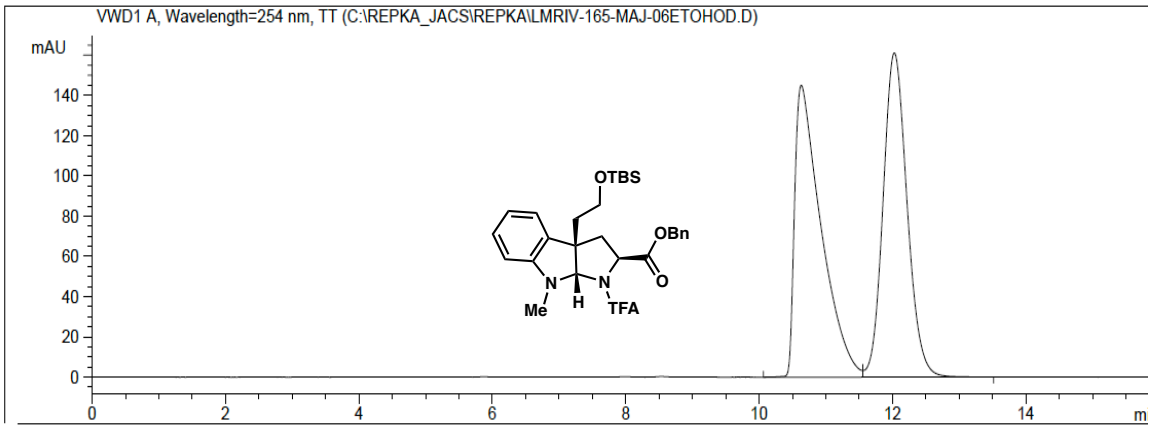
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	5.815	BV	0.2467	2234.77563	139.96280	48.1102
2	6.546	VB	0.4858	2410.33862	72.97266	51.8898

***endo*-98f** (Figure 2): 90% ee



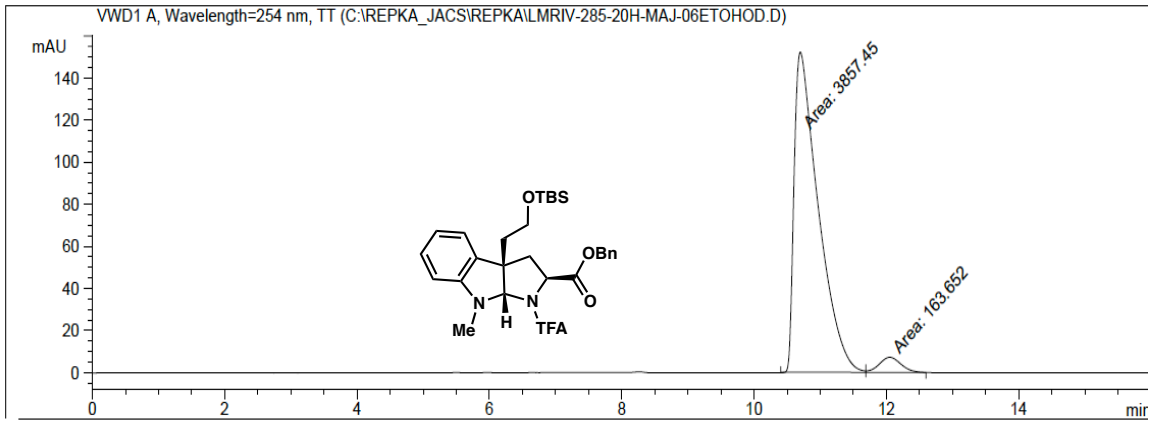
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.380	MF	0.2166	69.51939	5.34894	5.1972
2	6.976	FM	0.4419	1268.11157	47.82830	94.8028

***exo*-98f** (Figure 2): racemic



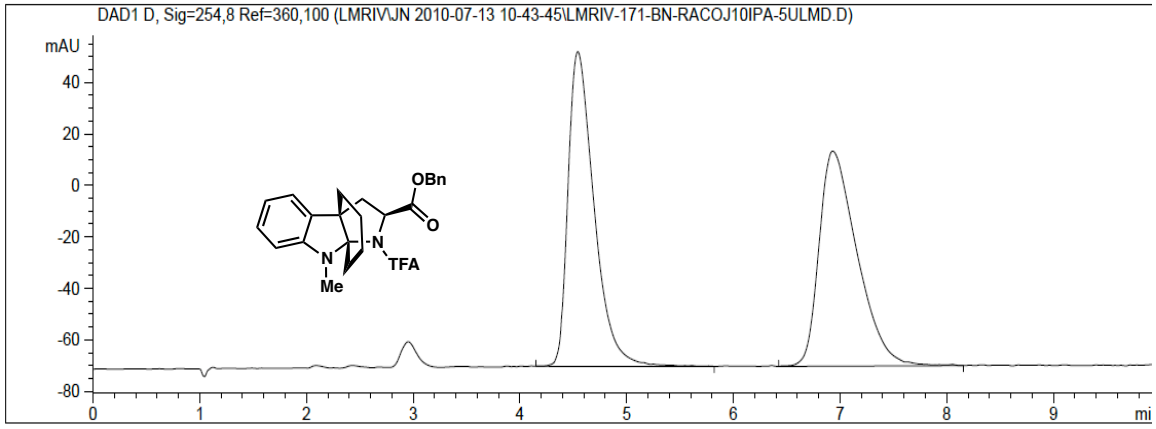
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.632	BV	0.3905	3995.52930	145.07512	49.7976
2	12.028	VB	0.3841	4028.00830	161.10678	50.2024

***exo*-98f** (Figure 2): 92% ee



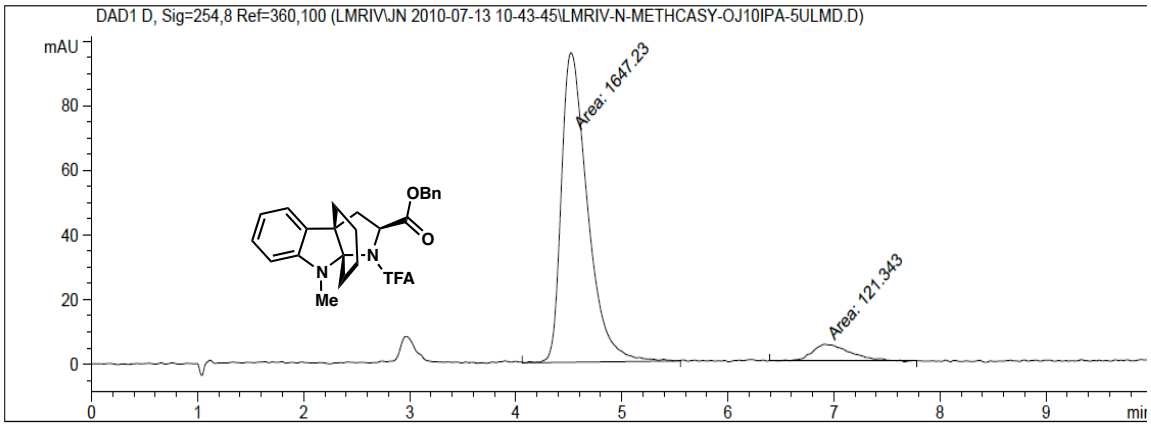
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.700	MF	0.4226	3857.44580	152.13763	95.9302
2	12.052	FM	0.3805	163.65164	7.16747	4.0698

98g (Figure 2): racemic



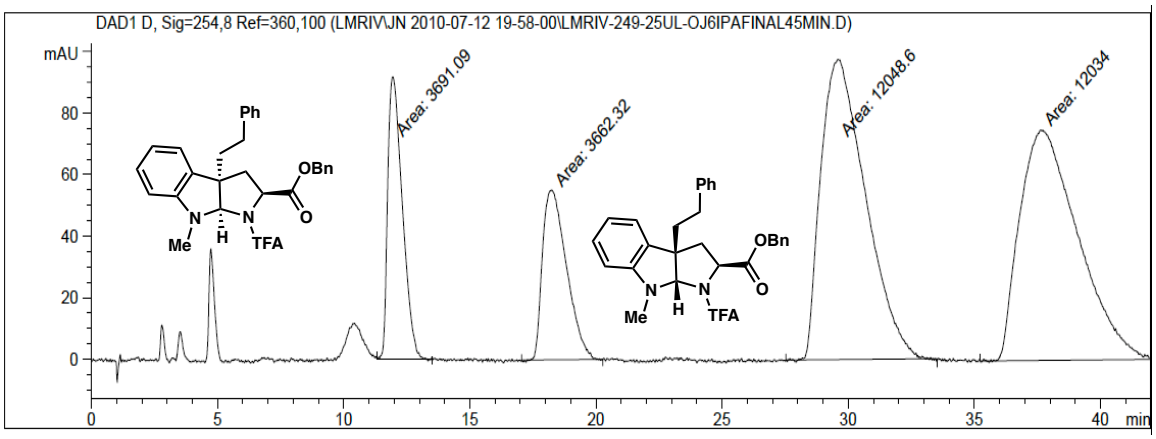
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.543	BB	0.2584	2077.59912	122.17298	50.0580
2	6.933	BB	0.3736	2072.78516	83.50713	49.9420

98g (Figure 2): *exo:* 86% ee



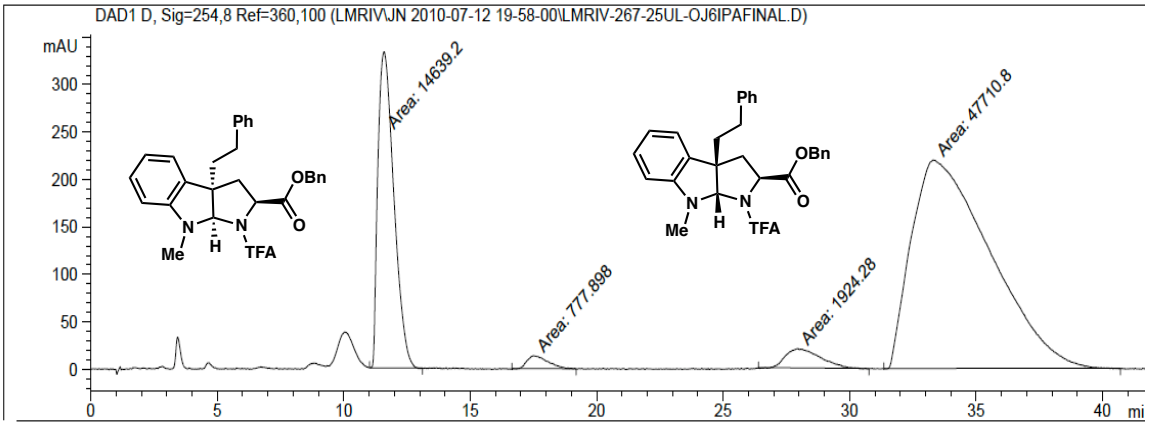
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.522	MM	0.2861	1647.22534	95.95735	93.1389
2	6.911	MM	0.3977	121.34311	5.08583	6.8611

98h (Figure 2): racemic



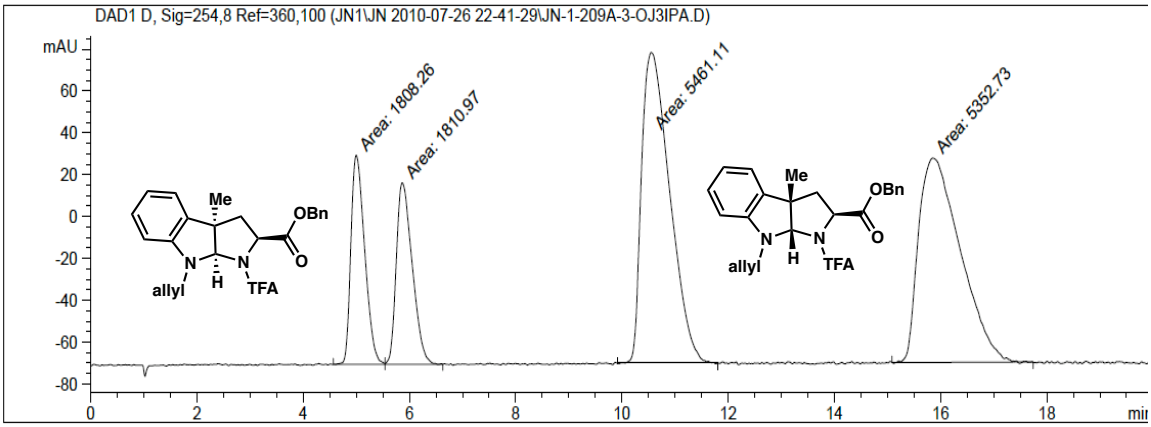
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.947	MM	0.6720	3691.09326	91.53949	11.7416
2	18.252	MM	1.1062	3662.32007	55.18063	11.6501
3	29.587	MM	2.0594	1.20486e4	97.51013	38.3273
4	37.639	MM	2.6782	1.20340e4	74.88902	38.2810

98h (Figure 2): *exo:* 92% ee, *endo*: 90% ee



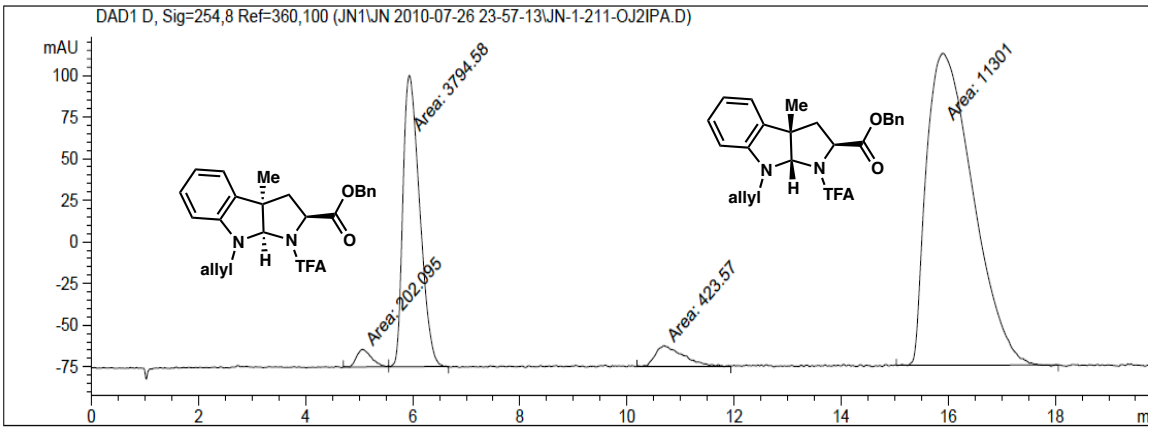
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.596	MM	0.7322	1.46392e4	333.24432	22.5038
2	17.511	MM	0.9481	777.89801	13.67496	1.1958
3	27.957	MM	1.5821	1924.28345	20.27142	2.9581
4	33.312	MM	3.6201	4.77108e4	219.65750	73.3423

72 (Figure 2): racemic



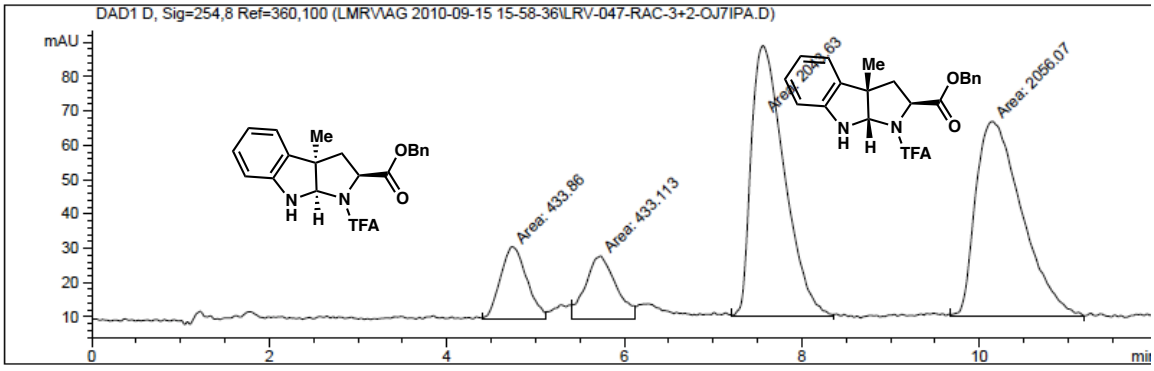
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.000	MF	0.3012	1808.26282	100.06958	12.5286
2	5.866	FM	0.3472	1810.96948	86.92387	12.5474
3	10.557	MM	0.6132	5461.11230	148.42072	37.8375
4	15.854	MM	0.9124	5352.73047	97.77415	37.0866

72 (Figure 2): *exo*: 93% ee, *endo*: 90% ee



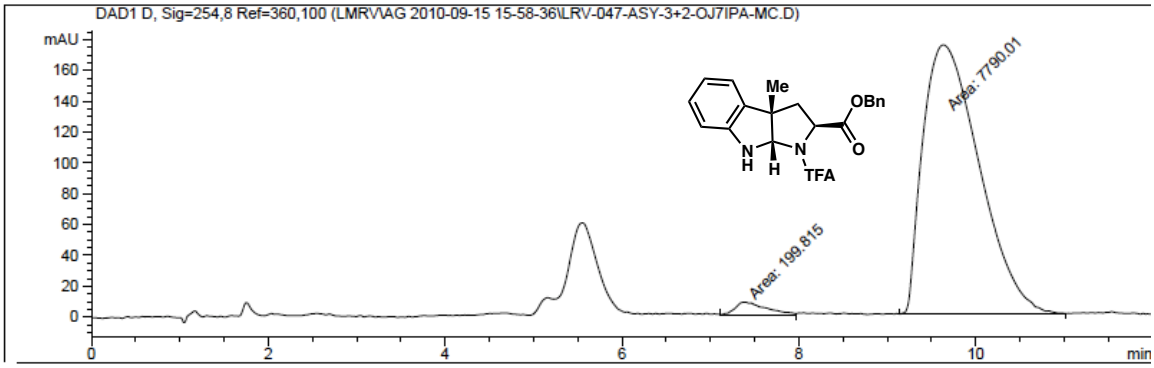
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.064	MF	0.3200	202.09525	10.52417	1.2855
2	5.937	FM	0.3612	3794.57617	175.06740	24.1367
3	10.690	MM	0.5781	423.56973	12.21119	2.6943
4	15.903	MM	1.0047	1.13010e4	187.47484	71.8835

98i (Figure 2): racemic



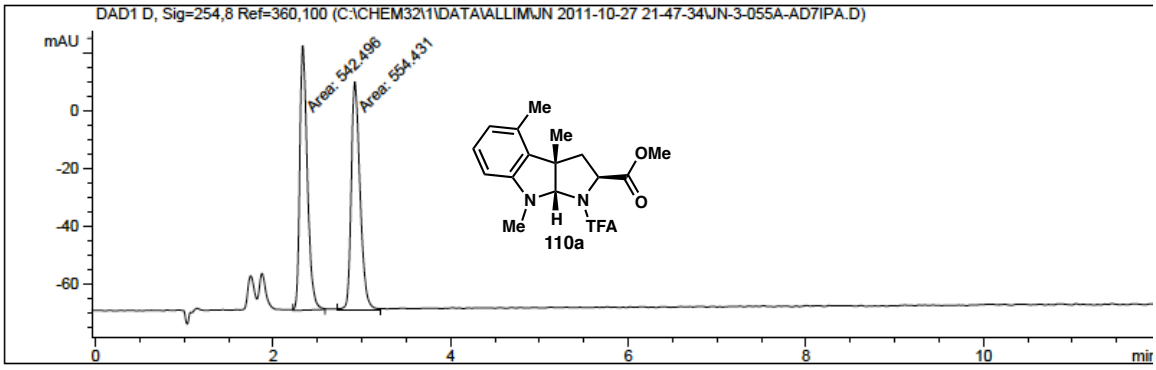
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.737	MM	0.3442	433.85974	21.00586	8.7354
2	5.733	MM	0.3971	433.11276	18.17621	8.7204
3	7.564	MM	0.4321	2043.62988	78.82232	41.1469
4	10.149	MM	0.6038	2056.07129	56.75510	41.3974

98i (Figure 2): enantioenriched, *exo*: 95% ee



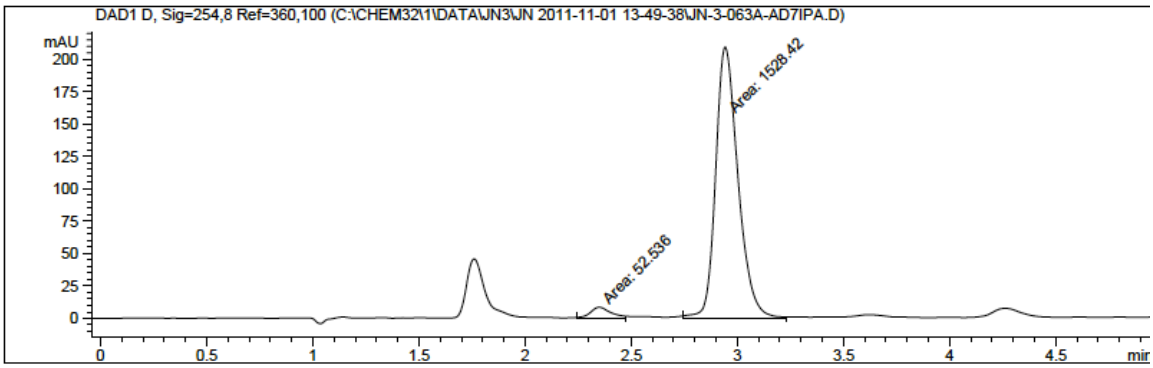
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.393	MM	0.4059	199.81528	8.20531	2.5009
2	9.640	MM	0.7421	7790.00586	174.96088	97.4991

110a (Table 6): racemic



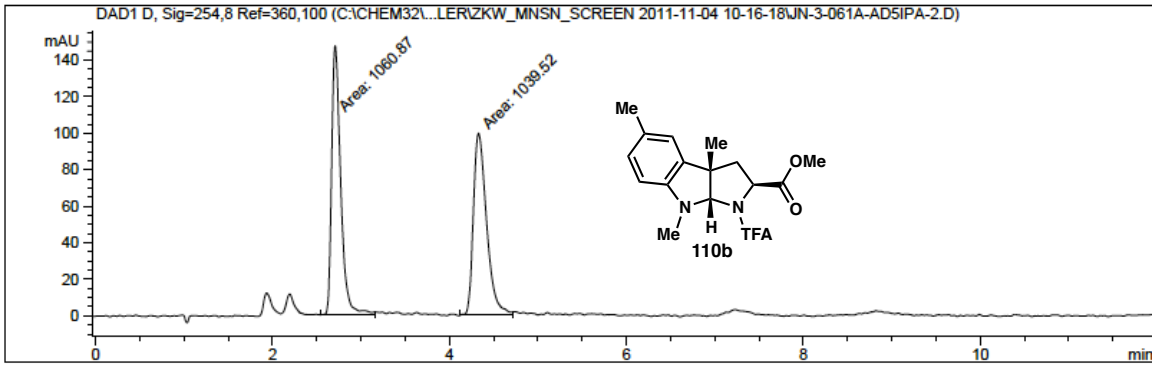
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.336	MM	0.0977	542.49573	92.54591	49.4560
2	2.923	MM	0.1161	554.43109	79.59325	50.5440

110a (Table 6): 93% ee



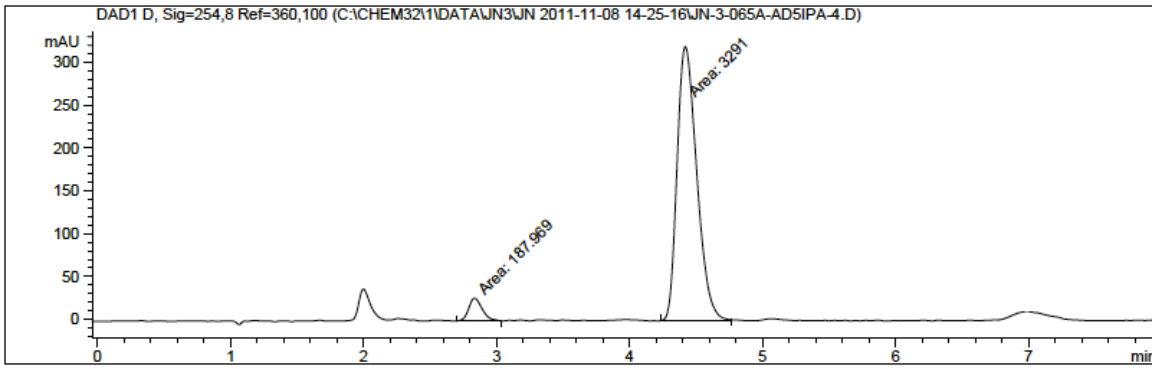
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.349	MM	0.1076	52.53596	8.13525	3.3231
2	2.943	MM	0.1211	1528.41553	210.29921	96.6769

110b (Table 6): racemic



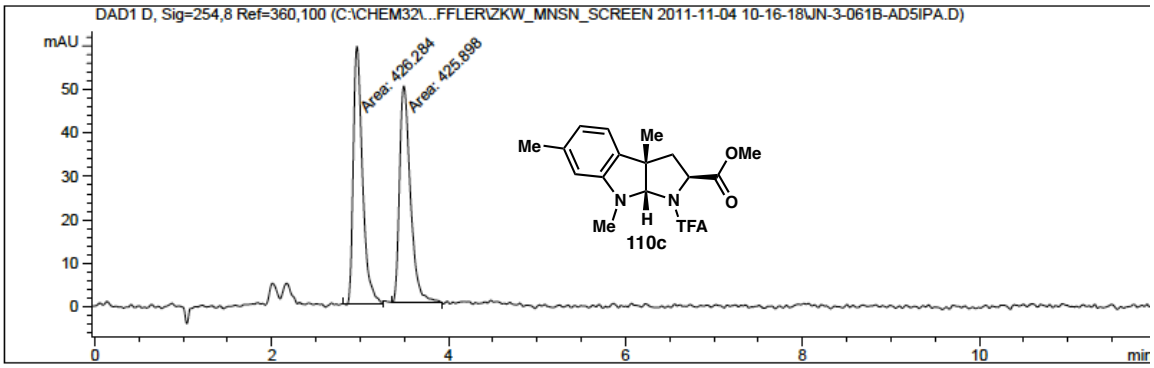
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.710	MM	0.1192	1060.87427	148.35889	50.5083
2	4.330	MM	0.1733	1039.52075	100.00130	49.4917

110b (Table 6): 89% ee



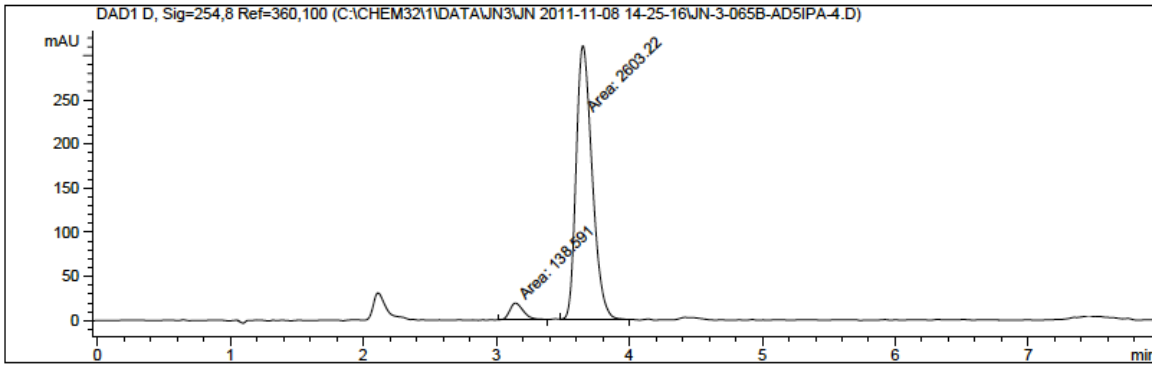
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.835	MM	0.1175	187.96922	26.66648	5.4030
2	4.420	MM	0.1709	3291.00049	320.93707	94.5970

110c (Table 6): racemic



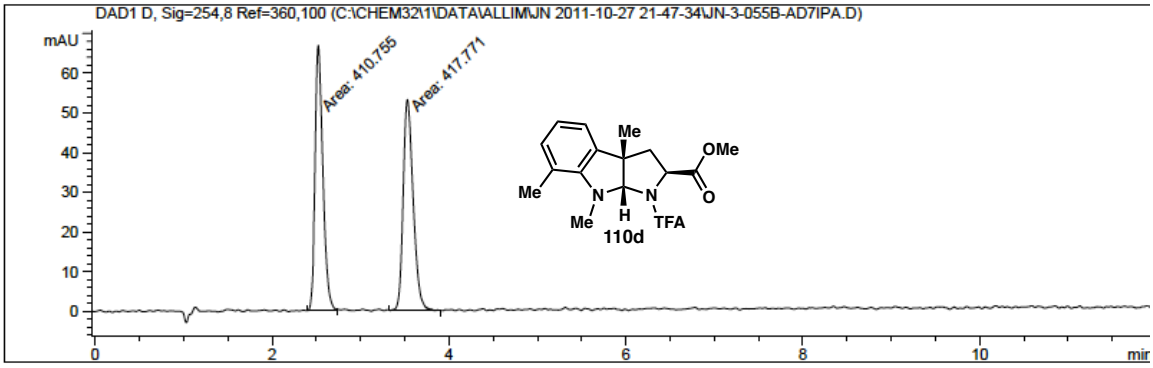
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.963	MM	0.1198	426.28387	59.32737	50.0227
2	3.494	MM	0.1424	425.89764	49.83862	49.9773

110c (Table 6): 90% ee



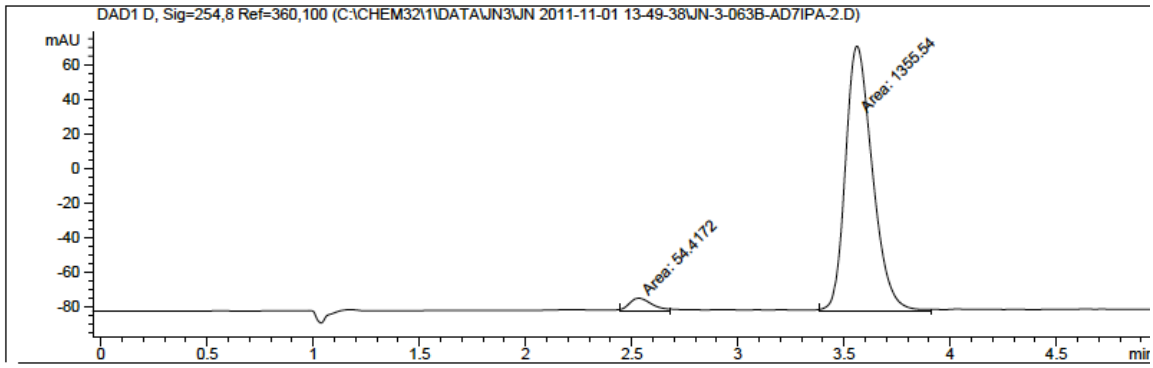
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.146	MM	0.1214	138.59100	19.02013	5.0547
2	3.652	MM	0.1394	2603.21704	311.29327	94.9453

110d (Table 6): racemic



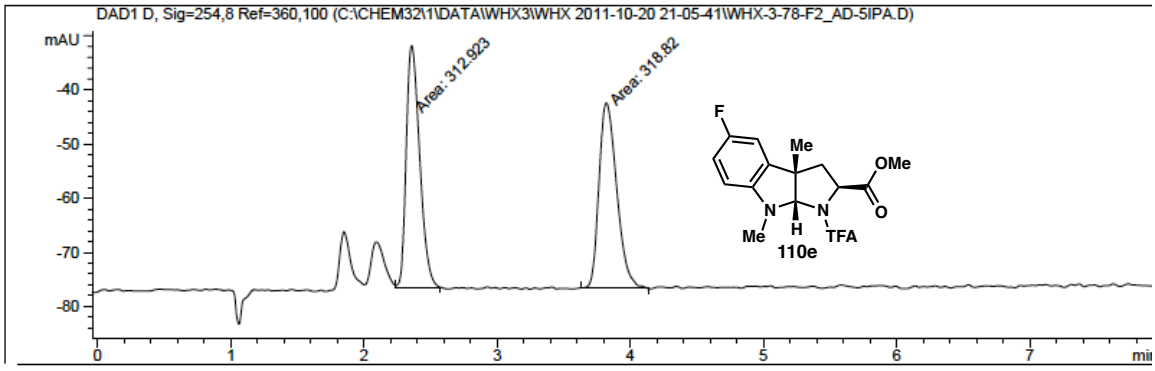
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.523	MM	0.1019	410.75467	67.19356	49.5766
2	3.531	MM	0.1306	417.77090	53.30387	50.4234

110d (Table 6): 93% ee



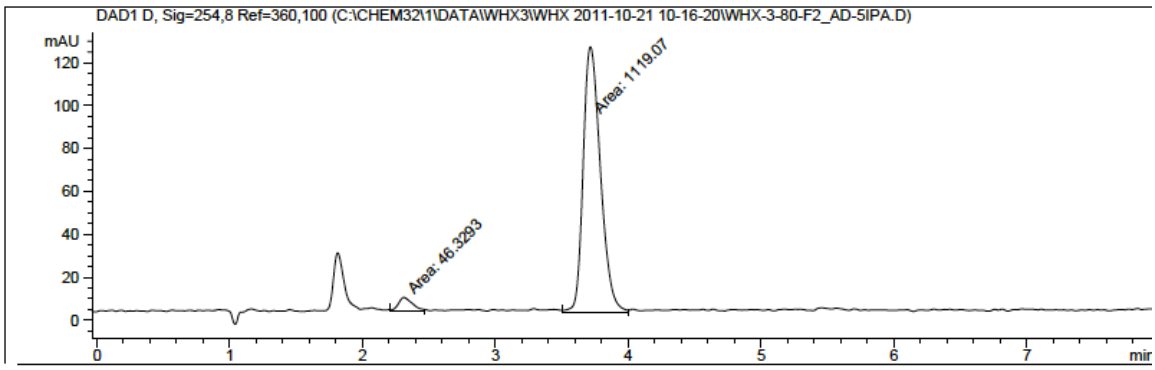
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.533	MM	0.1229	54.41724	7.38052	3.8595
2	3.562	MM	0.1470	1355.53528	153.70358	96.1405

110e (Table 6): racemic



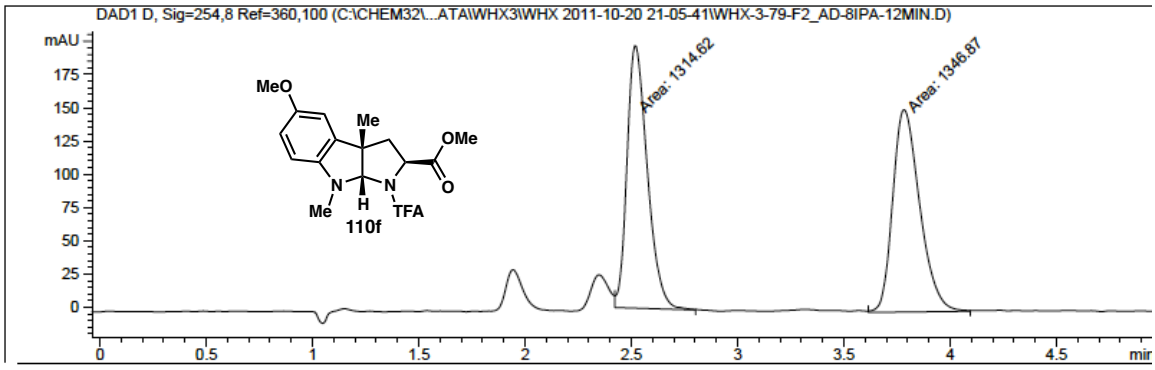
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.360	MM	0.1164	312.92303	44.79716	49.5333
2	3.821	MM	0.1548	318.81989	34.32571	50.4667

110e (Table 6): 92% ee



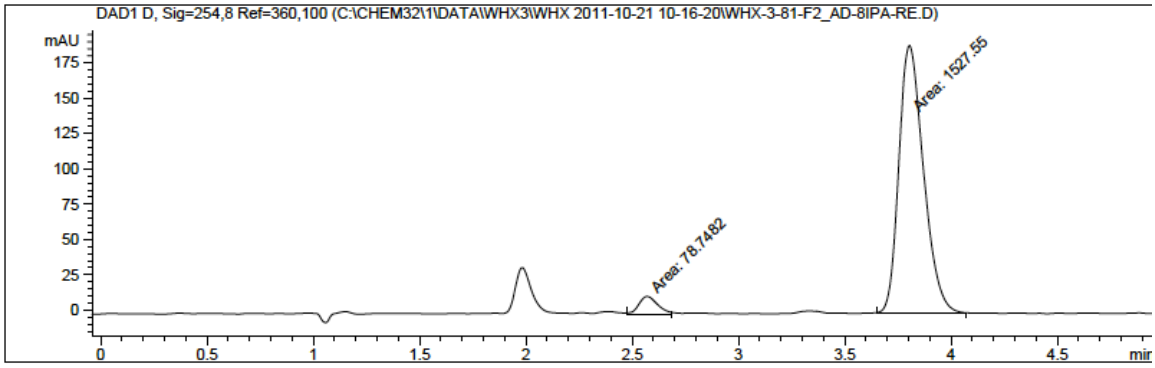
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.311	MM	0.1219	46.32927	6.33424	3.9754
2	3.714	MM	0.1503	1119.06885	124.07474	96.0246

110f (Table 6): racemic



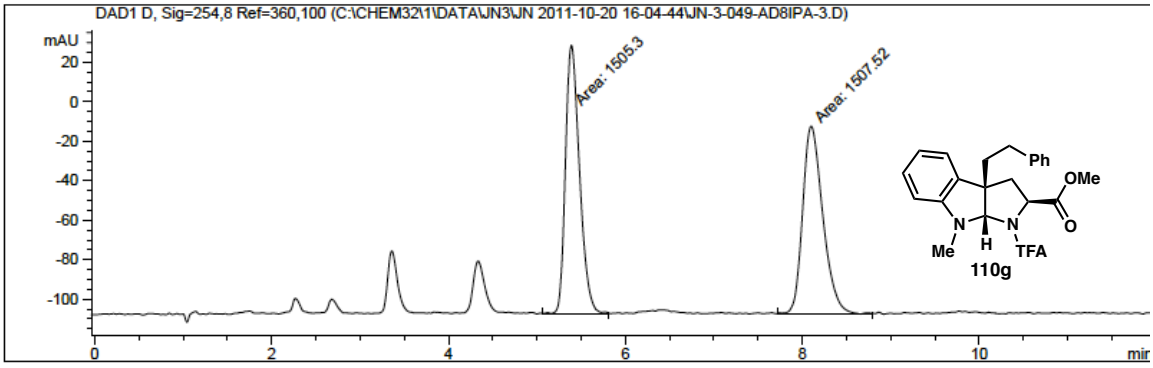
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.519	MM	0.1106	1314.62256	198.18828	49.3942
2	3.783	MM	0.1471	1346.87158	152.55568	50.6058

110f (Table 6): 90% ee



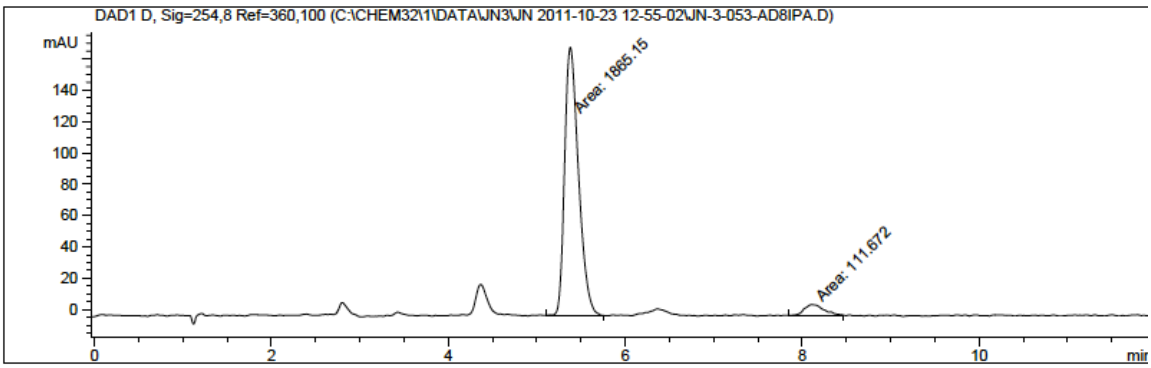
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.571	MM	0.1029	78.74822	12.75990	4.9025
2	3.805	MM	0.1340	1527.54749	190.03099	95.0975

110g (Table 6): racemic



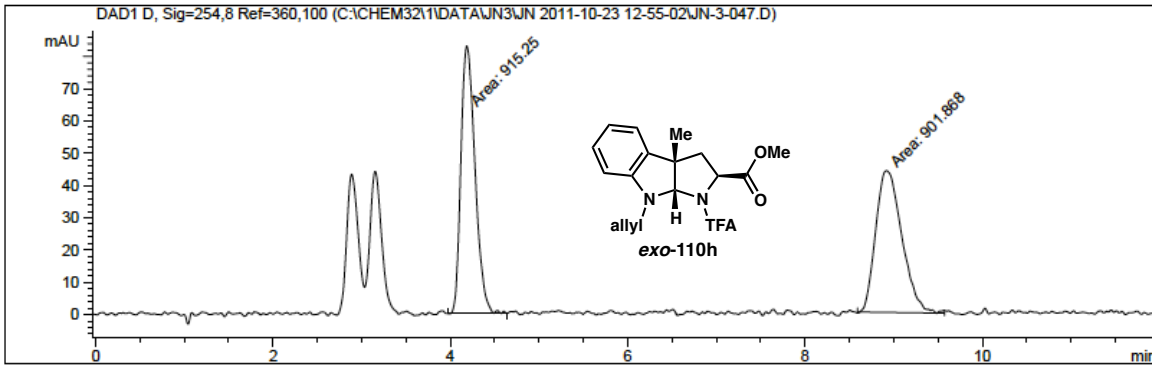
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.390	MM	0.1842	1505.30383	136.19626	49.9633
2	8.101	MM	0.2645	1507.51648	94.98624	50.0367

110g (Table 6): 89% ee



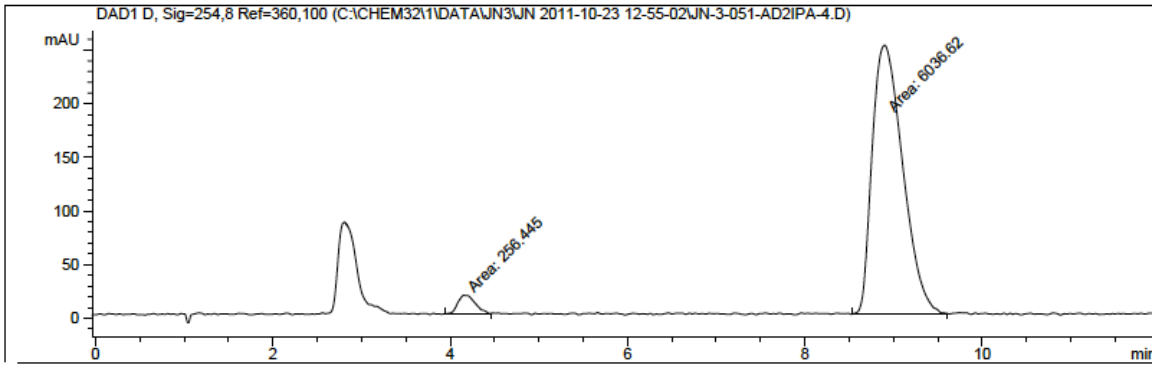
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.379	MM	0.1814	1865.15222	171.37959	94.3509
2	8.117	MM	0.2678	111.67234	6.94881	5.6491

110h (Table 6): racemic



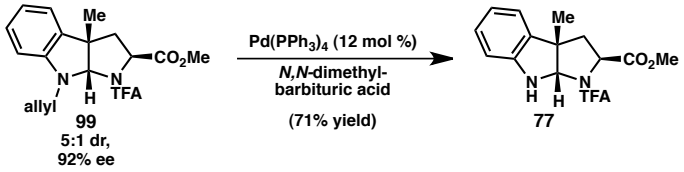
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.186	MM	0.1839	915.25043	82.94954	50.3682
2	8.920	MM	0.3422	901.86816	43.92808	49.6318

110h (Table 6): 92% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.158	MM	0.2383	256.44452	17.93594	4.0750
2	8.897	MM	0.4007	6036.61719	251.06158	95.9250

2.4.6 Pd-catalyzed Deallylation of Pyrroloindoline Methyl Ester 99



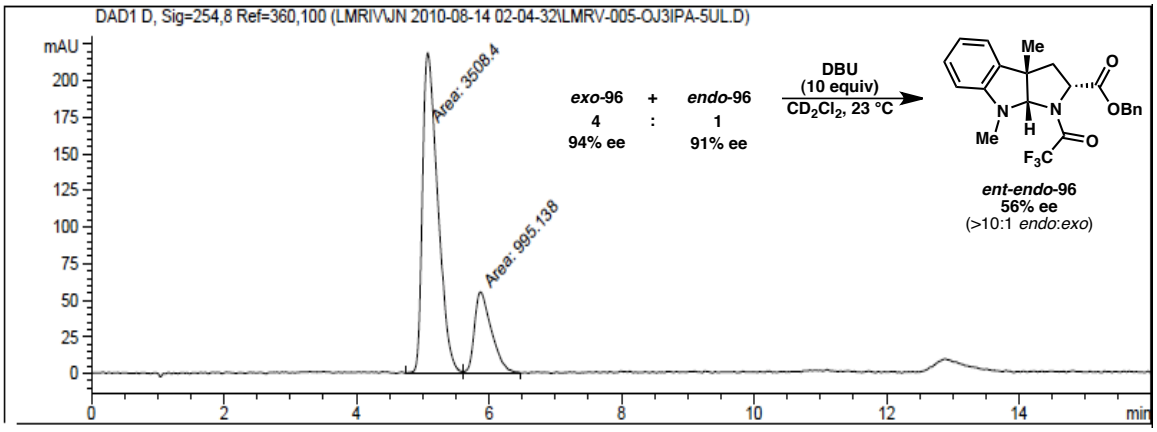
An oven-dried microwave vial was charged with allylpyrroloindoline **99** (55.0 mg, 0.149 mmol, 1.00 equiv), $Pd(PPh_3)_4$ (6.9 mg, 6.0 μmol, 0.040 equiv), and *N,N*-dimethylbarbituric acid (70.0 mg, 0.448 mmol, 3.01 equiv) and then sealed under nitrogen. 1.1 mL DCM was added and the reaction mixture was heated to 35 ºC in an oil bath. Two additional 7.0 mg portions of $Pd(PPh_3)_4$ were added after 34 h and after 75 h. After heating at 35 ºC for 123 h, the reaction was concentrated and the crude residue was diluted in Et_2O, washed with saturated aqueous Na_2CO_3, dried (Na_2SO_4), filtered, and concentrated. The crude residue was subjected to silica gel column chromatography (10:90 EtOAc:hexanes) to yield 34.8 mg (71% yield) of **77** as a colorless oil in an 8:1 mixture of diastereomers (determined by NMR analysis of the pure product). The product was resubjected to identical column conditions to obtain *exo*-**77** in >20:1 dr. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1:1 mixture of rotamers) δ 7.13 (dd, *J* = 7.8, 1.2 Hz, 0.5H), 7.10 (dd, *J* = 7.9, 1.3 Hz, 0.5H), 7.08 (ddd, *J* = 1.3, 0.6, 0.6 Hz, 0.5H), 7.07 (ddd, *J* = 1.3, 0.6, 0.6 Hz, 0.5H), 6.83 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 0.5H), 6.79 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 0.5H), 6.64 (ddd, *J* = 7.8, 0.7, 0.7 Hz, 0.5H), 6.61 (dt, *J* = 7.8, 0.8, 0.8 Hz, 0.5H), 5.64 (app q, *J* = 1.9 Hz, 0.5H), 5.58 (s, 0.5H), 4.62 (ap ddq, *J* = 9.1, 4.4, 1.5 Hz, 0.5H), 4.45 (dd, *J* = 8.5, 7.0 Hz, 0.5H), 3.81 (s, 1.5H), 3.77 (s, 1.5H), 2.75 (dd, *J* = 13.4, 9.1 Hz, 0.5H), 2.59 (ddd, *J* = 13.2, 8.5, 0.5 Hz, 0.5H), 2.37 (dd, *J* = 13.4, 4.4 Hz, 0.5H), 2.19 (dd, *J* = 13.2, 7.0 Hz, 0.5H), 1.49 (s, 1.5H), 1.41 (s, 1.5H).; ^{13}C NMR (125 MHz,

$CDCl_3$; compound exists as a 1:1 mixture of rotamers) δ 172.1, 170.9, 157.6 (q, $J_{C\text{-}F}$ = 37.5 Hz), 156. 7 (q, $J_{C\text{-}F}$ = 38.0 Hz), 146.8, 146.4, 133.14, 133.10, 128.9, 128.7, 122.3, 122.1, 120.2, 119.3, 116.1 (q, $J_{C\text{-}F}$ = 287.1 Hz), 115.7 (q, $J_{C\text{-}F}$ = 286.2 Hz), 109.9, 109.4, 86.4, 84.4 (q, $J_{C\text{-}F}$ = 2.2 Hz), 61.1, 59.5 (q, $J_{C\text{-}F}$ = 3.1 Hz), 54.5, 53.0, 52.6, 50.3, 43.7, 40.3, 24.2, 24.0.; IR (NaCl/thin film): 3387, 2959, 1751, 1693, 1613, 1489, 1469, 1450, 1438, 1359, 1195, 1160, 1104 cm^{-1}; $[\alpha]_D^{25}$ –182.7° (c = 0.50, DCM); HRMS (MM) calc'd for $C_{15}H_{16}F_3N_2O_3$ $[M+H]^+$ 329.1108, found 329.1122.

2.4.7 General Procedure D. Epimerization Studies

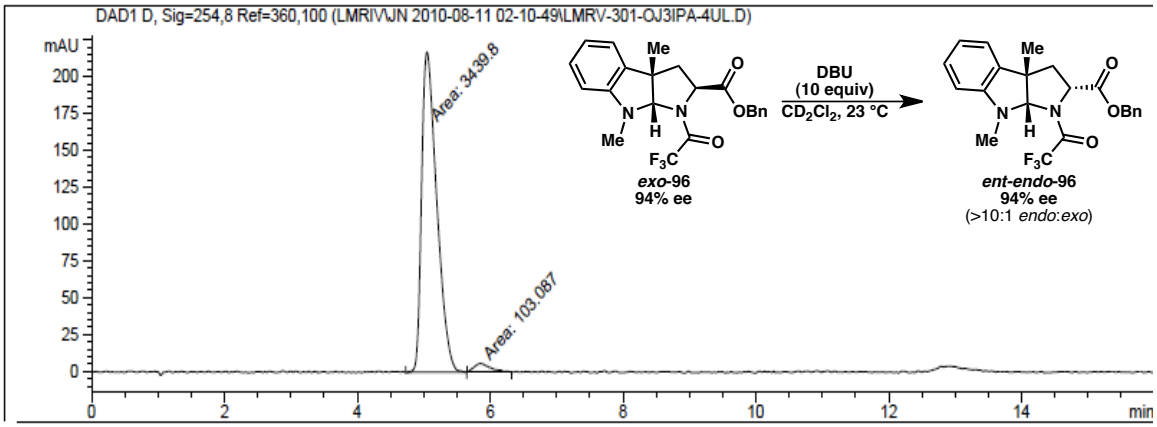
To an NMR tube was added a solution of pyrroloindoline **96** (0.063 mmol, 1.00 equiv) in CD_2Cl_2 (0.46 mL), followed by DBU (0.63 mmol, 10.00 equiv). The reaction was monitored by ^1H NMR until the ratio of diastereomers reached an equilibrium. At this point the reaction was diluted with 3 mL $CHCl_3$ and 25 mL ethyl acetate and washed with saturated $NaHCO_{3(aq)}$ (3 x 15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to give the mixture of pyrroloindoline diastereomers as a pale yellow oil with quantitative recovery of material.

Experiment 1: Treatment of a 4:1 mixture of ***exo*-96** (94% ee) **+ *endo*-96** (91% ee) with DBU (10 equiv) for 65 h to give >10:1 ***ent-endo*-96** (56% ee).



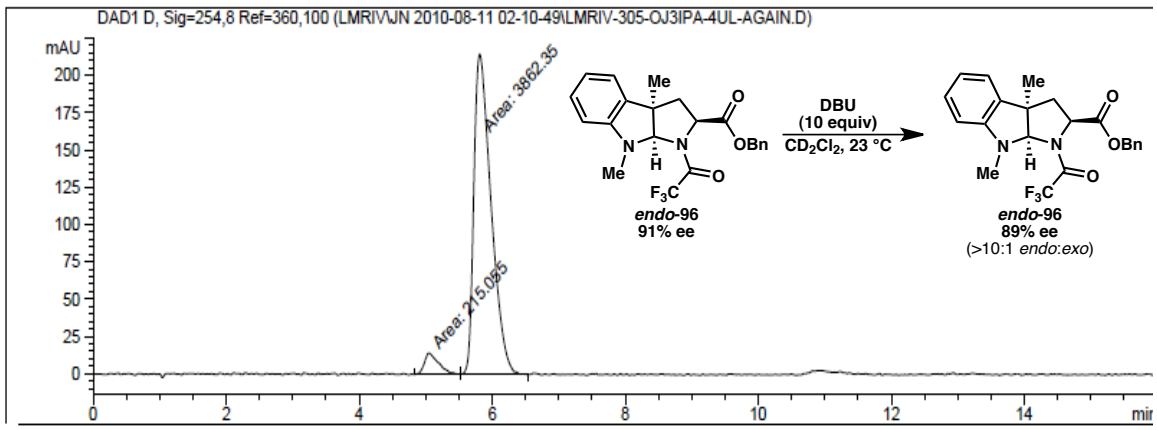
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.078	MM	0.2670	3508.40381	218.96385	77.9032
2	5.872	MM	0.2984	995.13763	55.57482	22.0968

Experiment 2: Treatment of diastereomerically pure ***exo*-96** (94% ee) with DBU (10 equiv) for 96 h to give >10:1 ***ent-endo*-96** (94% ee).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.050	MM	0.2637	3439.80371	217.42592	97.0903
2	5.849	MM	0.2887	103.08688	5.95159	2.9097

Experiment 3: Treatment of diastereomerically pure ***endo*-96** (91% ee) with DBU (10 equiv) for 30 h to return ***endo*-96** (89% ee).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.053	MM	0.2501	215.05467	14.33310	5.2743
2	5.814	MM	0.2994	3862.34961	215.01805	94.7257

2.4.8 Resubjection of Pure Exo and Endo Pyrroloindolines to Reaction Conditions

To an NMR tube was added a solution of pure pyrroloindoline *exo*-**96** (0.073 mmol, 1.00 equiv, 94% ee) in CD_2Cl_2 (297 μL), followed by (*R*)-BINOL (from a 0.0675 M solution in CD_2Cl_2, 0.015 mmol, 0.20 equiv) and $SnCl_4$ (from a 0.72 M solution in CD_2Cl_2, 0.088 mmol, 1.2 equiv). After 4 h at room temperature, the solution was quenched according to general procedure C. The same experiment was performed with pure *endo*-**96** (91% ee), except at a concentration of 0.065 M. In both cases, no epimerization or erosion of ee was observed.

2.4.9 General Procedure E. in situ Monitoring of the Formal (3 + 2) Cycloaddition by ^{1}H NMR.

In the glovebox, a 1 M solution of 1,3-dimethylindole, a 1 M solution of benzyl trifluoroacetamidoacrylate (with 0.3 equiv 1,4-diethylbenzene as an internal standard), a 0.72 M solution of $SnCl_4$, and a 0.0675 M solution of (*R*)-BINOL in CD_2Cl_2 were made. To an oven-dried NMR tube equipped with a teflon-lined cap were added 90 μL of the indole solution, μL of the acrylate + internal standard solution, 267 μL of the (*R*)-BINOL solution, and 186 μL of CD_2Cl_2. A ^{1}H NMR spectrum was taken (1 scan) to determine the initial ratio of substrates, (*R*)-BINOL, and internal standard. Immediately before beginning the collection of kinetics data, $SnCl_4$ was added via a microsyringe through the teflon cap of the NMR tube. The tube was inverted once, then quickly inserted into the instrument. The concentration of acrylate over the course of the reaction was determined by integrating its resonance at 6.3 ppm, then normalizing by the internal standard's resonance at 2.74 ppm.

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