CHAPTER 2

Formal (3 + 2) Cycloaddition Approach to Pyrroloindolines[†]

2.1 INTRODUCTION

As discussed in Chapter 1, many approaches have recently been reported for the direct, enantioselective, catalytic construction of pyrrolindolines from indole precursors. However, when we initially began our efforts in this field only two reports of this type had been disclosed, the iminium catalysis and allylic alkylation approaches from the groups of MacMillan and Trost. This chapter describes the development of a new approach to pyrroloindolines involving 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 is the only direct, enantioselective approach that incorporates the necessary C2-stereocenter for advancement to diketopiperazine natural products. Mechanistic studies will be discussed that confirmed an asymmetric protonation as the enantiodetermining step and ultimately led to the development of a

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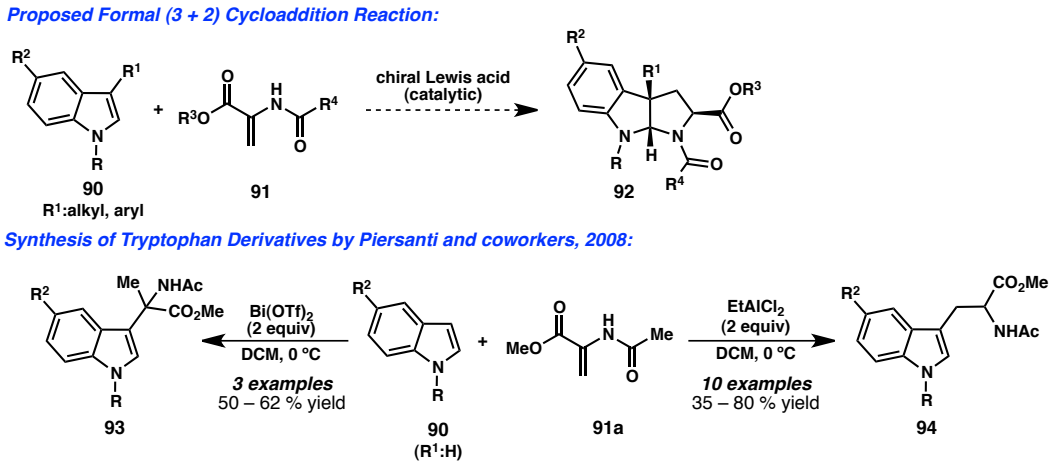
tandem conjugate addition/enantioselective protonation reaction for the synthesis of tryptophan derivatives (Chapter 3).

2.1.1 Design of the Cycloaddition Approach

The majority of catalytic, asymmetric indole functionalization approaches to prepare pyrroloindolines, including the seminal reports of MacMillan[1] and Trost,[2] involve the electrophilic substitution of tryptamine substrates. In our effort to provide a complementary approach to pyrroloindolines, we became interested in the possibility of a formal (3 + 2) cycloaddition reaction between 3-substituted indoles (**90**) and 2-amidoacrylates (**91**) that constitutes a formal (3 + 2) cycloaddition (Scheme 2.1.1). Successful realization of the proposed transformation could allow rapid access to a variety of substitution patterns and the pyrroloindoline-2-carboxylate products (**92**) formed should be suitable precursors for elaboration to diketopiperazine natural products (e.g. chaetocin (**3**, Figure 1.1.1)).

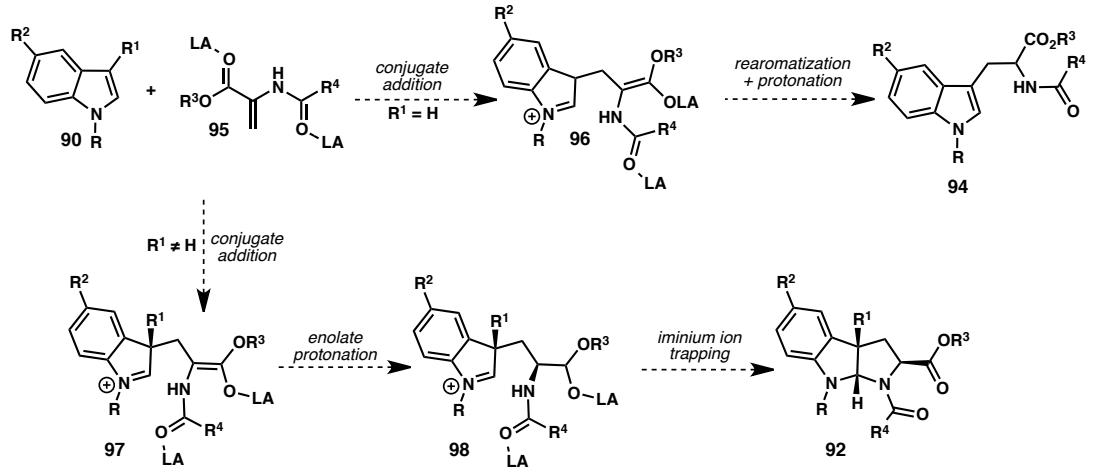
Scheme 2.1.1. Our proposed reaction and precedent in tryptophan synthesis.



Although the potential for reaction between 3-substituted indoles and weak electrophiles such as amidoacrylates was unclear at the outset of this project, we were

particularly encouraged by the recent findings of Piersanti and coworkers reported in 2008.[3] These authors disclosed that Lewis acids promote the condensation of C3-unsubstituted indoles (**90**, R^1:H) and methyl 2-acetamidoacrylate (**91a**) to afford Friedel–Crafts alkylation products as racemates (Scheme 2.1.1). Interestingly, the regioselectivity of addition to **91a** strongy depends on the choice of Lewis acid; whereas hard, oxaphilic Lewis acids such as $EtAlCl_2$ afford tryptophan derivatives (**94**), softer, more azaphilic Lewis acids such as $Bi(OTf)_3$ result in reaction of the acrylate via the imine tautomer to generate quaternary amides (**93**).

*Scheme 2.1.2. Proposed mechanisms of **92** and **94** formation.*



Mechanistically, Piersanti's reaction to prepare tryptophan **94** is proposed to occur by conjugate addition at C3 of the indole to generate transient enolate **96**, followed by rearomatization and protonation (Scheme 2.1.2). We envisioned that in the case of 3-substituted indoles, the initial conjugate addition would still occur; however, instead of rearomatization, enolate protonation and cyclization of the pendant amide nitrogen to the transiently generated iminium ion **98** could provide the desired pyrroloindoline product (**92**) in a single operation. The mechanism for the Friedel–Crafts alkylation has not been

thoroughly investigated, but notably this reaction requires two equivalents of Lewis acid. By ^{1}H NMR, Piersanti and coworkers found that subjection of methyl 2-acetamidoacrylate **91a** to 1 equivalent of $EtAlCl_2$ resulted in broadening of signals from a vinyl proton and the amide proton and methyl substituents, whereas subjection to two equivalents resulted in complete broadening of the acrylate signals. These experiments suggest that the reaction is second-order in the Lewis acid and proceeds via doubly activated enolate **95**.

The requirement of superstoichiometric Lewis acid in the Friedel–Crafts reaction suggested that the development of the formal (3 + 2) cycloaddition reaction using a catalytic Lewis acid would be challenging; however, we were encouraged by the general reactivity of amidoacrylates observed in the tryptophan synthesis as well as the potential for straightforward screening given the commercial availability of all reagents.

2.2 DEVELOPMENT OF THE FORMAL CYCLOADDITION REACTION[4]

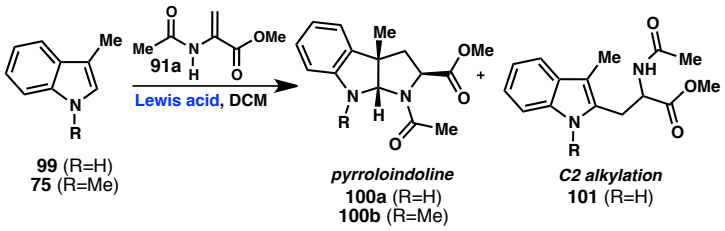
2.2.1 Identification of an Effective Lewis Acid

Our studies began with the reaction between 3-methylindole (**99**) and methyl 2-acetamidoacrylate (**91a**). A screen of Lewis acids revealed that use of two equivalents $EtAlCl_2$ delivered the desired pyrroloindoline (**100a**) as the major product in 3:1 dr favoring the *exo* diastereomer, although the C2 Friedel–Crafts alkylation product (**101**) was also observed (Table 2.2.1, entry 2). Consistent with Piersanti and coworkers' findings in the synthesis of tryptophan derivatives, no reaction occurred in the presence of stoichiometric $EtAlCl_2$ (entry 1); however, 1.0 equivalent of $SnCl_4$ was found to promote the reaction with comparable 6:1 selectivity for pyrroloindoline formation over

alkylation (entry 3). Fortunately, methylation of the indole nitrogen increased the regioselectivity for the pyrroloindoline product (entry 8). Attempted reactions with catalytic loadings identified that this reaction requires stoichiometric quantities of $SnCl_4$. Interestingly, the yield of pyrroloindoline is dramatically reduced using substoichiometric quantities of $SnCl_4$, with no product formed when 50 mol % is employed (entry 9).

Under our initially optimized conditions for this transformation, exposure of 1,3-dimethylindole (**75**) and methyl 2-acetamidoacrylate (**91a**) to 1.2 equivalents $SnCl_4$ in dichloroethane gave the desired pyrroloindoline **100b** in 64% yield as a 6:1 mixture of *exo* and *endo* diastereomers (entry 10).

Table 2.2.1. Initial Lewis acid screen.



Entry	Lewis Acid (equiv)	Substrate	Temperature (°C)	Pyrroloindoline: C-2 alkylation	dr[a]
1	$EtAlCl_2$ (1)	**99**	23	nr	--
2	$EtAlCl_2$ (2)	**99**	8	8:1	3:1
3	$SnCl_4$ (1)	**99**	23	6:1	9:1
4	$MgClO_4$ (1)	**99**	23	nr	--
5	$Sc(OTf)_2$ (2)	**99**	23	>20:1	5:1
6	$Cu(OTf)_2$ (2)	**99**	23	decomposition	--
7	$Zn(OTf)_2$ (2)	**99**	23	nr	--
8	$SnCl_4$ (1)	**75**	23	>20:1[b]	11:1
9	$SnCl_4$ (0.5)	**75**	23	nr	--
10[c]	$SnCl_4$ (1.2)	**75**	23	>20:1 (64)[d]	6:1

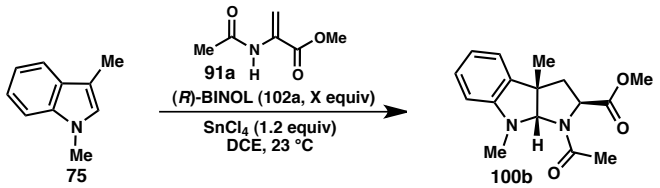
[a] Determined by analysis of the crude ^1H NMR with comparison to reported spectra.[4] [b] Complete conversion to **100b** by crude ^1H NMR. [c] Reaction run in DCE. [d] Isolated yield of **100b**. nr: no reaction.

2.2.2 Identification of Enantioselective Conditions and Optimization

In light of our preliminary results with $SnCl_4$, we initiated studies targeting an asymmetric variant of the formal (3 + 2) cycloaddition reaction. A screen of a variety of

chiral ligands previously reported to be used in conjunction with $SnCl_4$ revealed that use of (*R*)-BINOL provides **100b** in promising enantioselectivity. Thus, treatment of 1,3-dimethylindole (**75**) and methyl 2-acetamidoacrylate (**91a**) with a 1.1:1 mixture of (*R*)-BINOL and $SnCl_4$ provided pyrroloindoline **100b** in 86% yield as a 4:1 mixture of diastereomers, with the *exo* diastereomer formed in 64% ee (Table 2.2.2, entry 2).

Table 2.2.2. (R)-BINOL loading optimization studies.



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

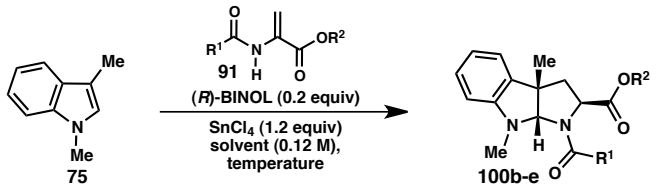
[a] Isolated yield of combined diastereomers. [b] Determined by ^{1}H NMR analysis of crude reaction mixture. [c] Determined by chiral stationary phase SFC. [d] ee of *exo*/*endo* diastereomers. [e] Reaction run for 30 h. [f] Reaction run for 3.5 h. [g] 1.0 equiv of $SnCl_4$ was used. [h] Reaction run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

Somewhat surprisingly, side-by-side reactions of 1,3-dimethylindole (**75**) and methyl 2-acetamidoacrylate (**91a**) combined in the presence and absence of stoichiometric BINOL, under otherwise identical conditions, revealed that BINOL accelerates the rate of the reaction and provides **100b** in improved yield.[5] Based on these observations, it was hypothesized that similar enantioselectivities might be accessible using only catalytic quantities of (*R*)-BINOL. Gratifyingly, treatment of 1,3-dimethylindole (**75**) and methyl 2-acetamidoacrylate (**91a**) with 1.2 equivalents $SnCl_4$ and 20 mol % (*R*)-BINOL furnished the desired pyrroloindoline **100b** in 94% yield as a 5:1 mixture of diastereomers, favoring the *exo* diastereomer in 63% ee (Table 2.2.2, entry 4).

Remarkably, moderate levels of enantioselectivity are observed even when the reaction is conducted with 5 mol % (*R*)-BINOL (entry 6).

In our initial effort to improve the enantioselectivity, we first evaluated the effect of temperature. Unlike many transformations that proceed optimally at lower temperature, reduced ee and dr are observed for the formal (3 + 2) cycloaddition under these conditions (Table 2.2.3, entries 3-4). Alternatively, conducting the reaction above room temperature did not significantly alter the selectivity (entry 5). Notably, similar temperature effects have been reported in a few instances involving Lewis acid•BINOL complexes.[6]

Table 2.2.3. Enantioselectivity optimization studies.



Entry	R^1, R^2	pdt	Temperature (°C) (Time (h))	Solvent	Yield (%)[a]	dr[b]	ee (%)[c,d]
1	Me, Me (**91a**)	**100b**	23 (4)	DCE	94	5:1	63/83
2[e]	Me, Me (**91a**)	**100b**	8 (24)	DCE	88[f]	4:1	66/nd
3[e]	Me, Me (**91a**)	**100b**	–40 (24)	DCM	69[f]	3:1	39/nd
4[e]	Me, Me (**91a**)	**100b**	–78 (24)	DCM	26[f]	2:1	21/nd
5[e]	Me, Me (**91a**)	**100b**	40 (0.5)	DCE	97[f]	5:1	66/nd
6	CF_3, Me (**91b**)	**100c**	23 (4)	DCE	77	6:1	86/nd
7	Me, Bn (**91c**)	**100d**	23 (4)	DCE	81	2:1	74/82
8	CF_3, Bn (**91d**)	**100e**	23 (4)	DCE	81	3:1	91/90
9	CF_3, Bn (**91d**)	**100e**	23 (5.5)	DCM	86	4:1	94/91
10	CF_3, Bn (**91d**)	**100e**	23 (4)	$CHCl_3$	58	3:1	88/89
11	CF_3, Bn (**91d**)	**100e**	23 (3.5)	CCl_4	0	--	--

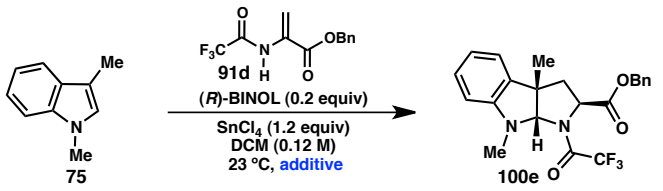
[a] Isolated yield of combined diastereomers. [b] Determined by ^{1}H NMR analysis of crude reaction mixture. [c] Determined by chiral stationary phase SFC or HPLC. [d] ee of *exo*/*endo* diastereomers. [e] 1.0 equiv of $SnCl_4$ and 1.1 equiv (*R*)-BINOL was used. [f] Approximate conversion to **100b** based on ratio with acrylate in crude ^{1}H NMR. nd= not determined.

More promising effects were found by varying acrylate substitution. Utilization of methyl 2-trifluoroacetamidoacrylate (**91b**) and benzyl 2-acetamidoacrylate (**91c**) provided pyrroloindoline products **100c** and **100d** in enhanced enantioselectivities, with

the *exo* diastereomers formed in 86% and 74% ee, respectively (Table 2.2.3, entries 6-7). Fortunately, these effects were additive; reaction of benzyl 2-trifluoroacetamidoacrylate (**91d**) afforded pyrroloindoline **100e** 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 are optimal and switching from DCE to DCM afforded **100e** in 86% yield and 94% ee for the *exo* diastereomer (entry 9).

With these optimized reaction conditions in hand, we reevaluated the parameters of the formal (3 + 2) cycloaddition reaction and confirmed that a Lewis acid is required for the transformation; exposure of 1,3-dimethylindole (**75**) and **91d** to Brønsted acids, including (*R*)-BINOL, HCl, and Ph_2PO_2H (Table 2.2.4, entries 1-3) gave no reaction. Several water and acid scavenging additives were also screened but no significant change in enantioselectivity was observed in their presence (entries 4, 5 and 7).

Table 2.2.4. Additive screen.



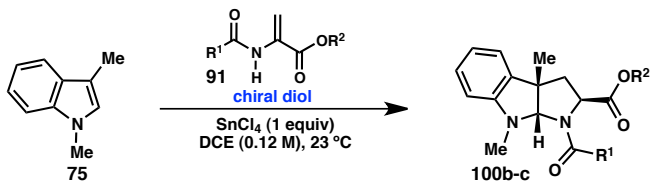
Entry	Additive (equiv)	Time (h)	Yield (%)[a]	dr[b]	ee (%)[c,d]
1	[e]	4	0	--	--
2	HCl (1.2)[e]	7	0	--	--
3	Ph_2PO_2H (1.2)[e]	7	0	--	--
4[f]	molecular sieves	4	70	4:1	93:89
5[f]	MgO (1)	4.5	72	4:1	93:91
6	2,6-lutidine (1)	6	0	--	--
7	2,6-lutidine (0.2)	5	53	6:1	94:89

[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.

Although (*R*)-BINOL ultimately proved to afford the highest enantioselectivities, various BINOL derivatives as well as other chiral diols were also evaluated in the course

of efforts to determine optimal conditions and to investigate the mechanism of this transformation. (*R*)-2'-methoxy-[1,1'-binaphthalen]-2-ol (**102b**) promoted **100b** formation in a reduced 40% ee, suggestive of an important role for the hydroxyl protons in the enantiodetermining step (Table 2.2.5, entry 2). Furthermore, sterically hindered BINOL derivatives **102c**-**e** provided **100b** as a racemate, but with good diastereoselectivity (entries 3-5). 6,6'-dibromo-BINOL (**102f**), which is sterically similar to BINOL but more electron deficient, afforded pyrroloindoline **100c** in slightly reduced ee (entry 7) and non-BINOL-derived chiral diols, TADDOL (**103**) and hydrobenzoin (**104**), gave **100c** in 0 and 46% ee, respectively (entries 8 and 9).

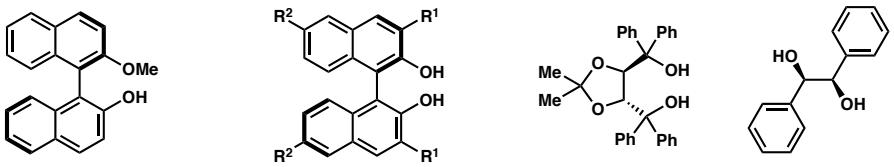
Table 2.2.5. Screen of chiral diols.



Entry	Diol (equiv)	R^1, R^2	Product	dr[a]	ee (%)[b,c]
1	**102a** (1.1)	Me, Me (**91a**)	**100b**	4:1	64
2	**102b** (1.1)	Me, Me (**91a**)	**100b**	3:1	40
3	**102c** (1.1)	Me, Me (**91a**)	**100b**	6:1	0
4	**102d** (1.1)	Me, Me (**91a**)	**100b**	>10:1	0
5	**102e** (1.1)	Me, Me (**91a**)	**100b**	7:1	0
6[d]	**102a** (0.2)	CF_3, Me (**91b**)	**100c**	6:1	86
7	**102f** (0.2)	CF_3, Me (**91b**)	**100c**	8:1	81
8	**13** (0.2)	CF_3, Me (**91b**)	**100c**	10:1	0
9	**14** (0.2)	CF_3, Me (**91b**)	**100c**	8:1	46

[a] Determined by ^{1}H NMR analysis of crude reaction mixture. [b] Determined by chiral stationary phase SFC or HPLC. [c] ee of *exo* diastereomer. [d] Reaction run with 1.2 equiv $SnCl_4$.

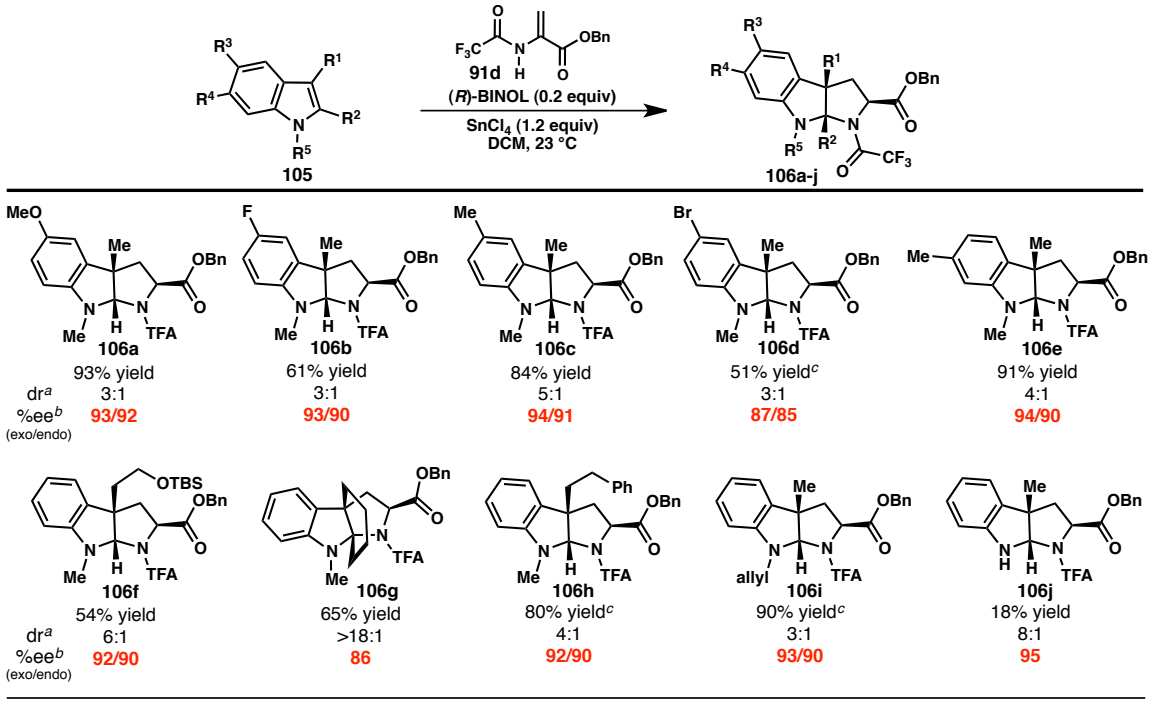
Figure 2.2.1. Chiral diols.



102b **102a** (R^1, R^2: H) **102e** (R^1: anthryl, R^2: H) **103** **104**
102c (R^1: mesityl, R^2: H) **102f** (R^1: H, R^2: Br)
102d (R^1: $SiPh_3$, R^2: H)

2.2.3 Substrate Scope of Pyrroloindoline Synthesis

Scheme 2.2.1. Substrate scope.

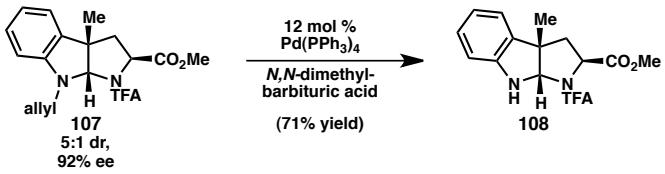


[a] Determined by ^{1}H NMR analysis of mixture. [b] Determined by chiral SFC or HPLC analysis. [c] 1.6 equiv $SnCl_4$ was employed.

The enantioselective formal (3 + 2) cycloaddition with benzyl 2-trifluoroacetamidoacrylate (**91d**) is general for a range of indole substrates. Indoles substituted at C5 with either electron-donating or electron-withdrawing groups are tolerated in this reaction, although electron-poor indoles react at a slower rate (Scheme 2.2.1, **106a**-**e**). Indoles substituted at C3 with functionalized alkyl groups reacted in moderate to good yields with high enantioselectivity (**106f** and **106h**). Notably, the reaction of *N*-methyltetrahydrocarbazole proceeded with >18:1 diastereoselectivity, delivering the *exo* diastereomer **106g** in 86% ee. In a single step, this reaction generates the aza-propellane core of the natural products minfiensine,[7] echitamine,[8] and vincorine.[9] Consistent with our preliminary findings, *N*-alkylation is important to the reactivity;

subjection of 3-methylindole to identical conditions provided pyrroloindoline **106j** in only 18% yield albeit with excellent enantioselectivity. However, *N*-allyl-3-methylindole (**105i**) was successfully employed as a substrate to afford pyrroloindoline **106i**. The combination of $Pd(PPh_3)_4$ and *N,N*-dimethylbarbituric acid have been shown to smoothly convert related methyl ester **107** to the deallylated product **108** (Scheme 2.2.2);[10] this finding is particularly useful in the context of total synthesis as many pyrroloindoline natural products do not bear substitution on nitrogen.

*Scheme 2.2.2. Pd-catalyzed deallylation of pyrroloindoline methyl ester **107**.*

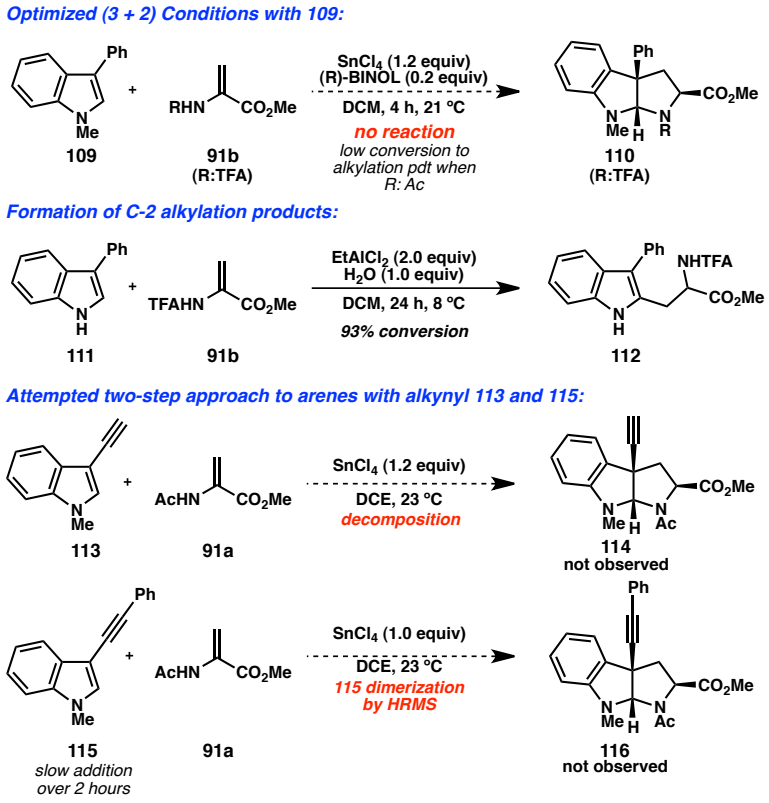


Although many substrates are well-tolerated in the formal (3 + 2) cycloadditon reaction, this transformation proved challenging for more sterically encumbered substrates. 3a-Indolylpyrroloindolines constitute a large number of pyrroloindoline natural products and thus, we were also very interested in accessing arylpyrroloindolines using the formal (3 + 2) cycloaddition methodology. However, subjection of 1-methyl-3-phenylindole (**109**) to our standard conditions with methyl 2-trifluoroacetamidoacrylate (**91b**) resulted in no reaction whereas exposure to methyl 2-acetamidoacrylate (**91a)** gave low conversion to the corresponding C2-alkylation product (Scheme 2.2.3). Clean conversion to C2-alkylation product **112** has also been observed for 3-phenylindole (**111**) in the presence of $EtAlCl_2$.

Alternatively, we also envisioned a two-step approach to generate indolylpyrroloindolines through initial formation of 3a-alkynylpyrroloindolines and a

subsequent Larock annulation; however, subjection of 1-methyl-3-ethynylindole (**113**) and **91a** to $SnCl_4$ gave decomposition and subjection of 1-methyl-3-(phenylethynyl)indole (**115**) and **91a** to $SnCl_4$ resulted in dimerization of the indole, even when **115** was added slowly to the reaction mixture over 2 hours.

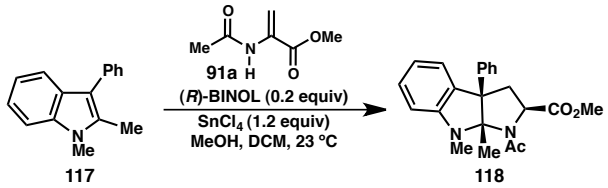
Scheme 2.2.3. Unsuccessful approaches to arylpyrroloindolines.



In a final effort to access arylpyrroloindolines, we employed 1,3-dimethyl-3-phenylindole (**117**) as the substrate to ensure complete selectivity for pyrroloindoline formation by prohibiting Friedel–Crafts alkylation. Although exposure of **117** and **91a** to standard conditions gave only trace conversion to phenylpyrroloindoline **118** (Table 2.2.6, entry 1), addition of 0.20 equiv MeOH cleanly afforded **118** in 40% yield as a single diastereomer in 91% ee (entry 4). Unfortunately, prolonged reaction times and

increased $SnCl_4$ loading did not substantially improve yield (entries 5 and 7) and inconsistent ees varying from 84 – 91% were obtained for the reaction (entries 4-6).

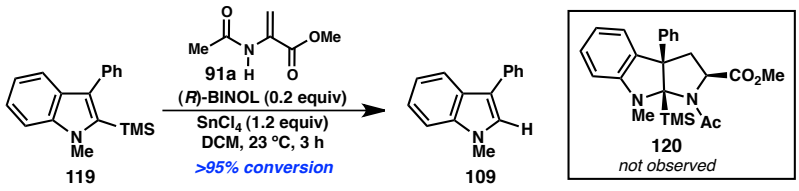
*Table 2.2.6. Methanol-promoted synthesis of phenylpyrroloindoline **118**.*



Entry	Scale (mmol)	MeOH (equiv)	Concentration (M)	Time (h)	117:118[a]	Yield[b] (%)	dr[a]	ee (%)[c,d]
1[e]	0.15	--	0.12	13	17:1	nd	nd	--
2[e]	0.15	0.2[f]	0.12	13	2:1	nd	>20:1	--
3[e]	0.15	1.0[f]	0.12	13	>20:1	--	--	--
4	0.20	0.20[g]	0.11	12.5	nd	40	>20:1	91
5	0.20	0.20[g]	0.11	64	nd	47	>20:1	88
6	0.19	0.20[g]	0.11	12	1:2	38	>20:1	84
7[h]	0.19	0.20[g]	0.11	12	1:2	45	>20:1	81

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield. [c] Determined by chiral SFC analysis. [d] ee of *exo* diastereomer. [e] Reaction conducted with (*R*/*S*)-BINOL. [f] neat MeOH was added to the reaction. [g] MeOH was added from a stock solution in DCM. [h] Reaction run with 1.6 equiv $SnCl_4$. nd: not determined.

*Scheme 2.2.4. Subjection of 2-trimethylsilylindole **119** to cycloaddition conditions.*[‡]

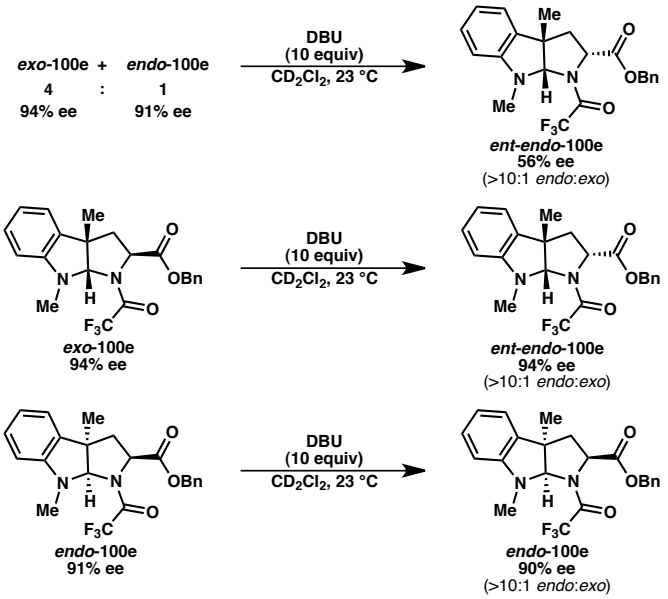


When we first discovered this transformation, no other direct enantioselective approaches to arylpyrroloindolines had been reported. Most natural products are unsubstituted at C2a and thus, we elected to pursue this transformation using 2-(trimethylsilyl)indole **119**, which could undergo desilylation in a second step following cycloaddition to generate C2-unsubstituted pyrroloindolines; however, we found that protodesilylation occurs readily in the presence of $SnCl_4$ to give 1-methyl-2-phenylindole

(**109**, *Scheme 2.2.4*).[‡] At this point, no further work is being conducted to extend this pyrroloindoline methodology to sterically encumbered substrates. However, these challenges ultimately provided inspiration for the development of a second approach to pyrroloindolines within our laboratory involving the Cu-catalyzed arylation of tryptamine[11] and tryptophan derivatives[12] using aryl iodonium salts.

2.3 MECHANISTIC CONSIDERATIONS

Scheme 2.3.1. Epimerization studies.

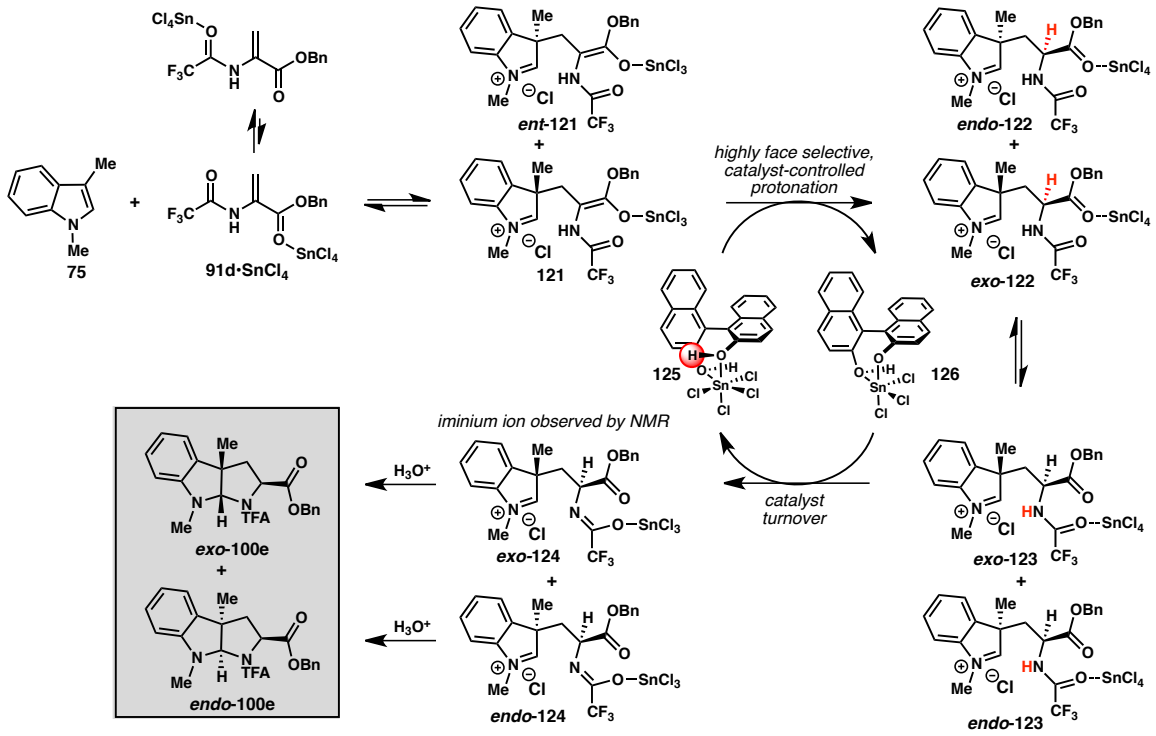


The formal (3 + 2) cycloaddition reaction favors formation of the *exo* pyrroloindoline product. Previous studies regarding pyrroloindolines have revealed that the *exo* diastereomer is the kinetic product and the *endo* diastereomer is thermodynamically favored.[13] With the objective of accessing the *endo* diastereomer, we carried out epimerization studies on the product mixture resulting from the formal (3 + 2) cycloaddition of 1,3-dimethylindole (**75**) and benzyl 2-trifluoroacetamidoacrylate (**91d**)

[‡] This reaction was completed by Dr. Paola Romanato, a former postdoctoral scholar in the Reisman lab.

(Scheme 2.3.1). In the presence of excess DBU, the 4:1 mixture of *exo* and *endo* diastereomers (94% and 91% ee) was cleanly converted to the *endo* diastereomer. Surprisingly, the *endo* diastereomer was recovered in 56% ee, favoring the opposite enantiomer. These results indicate that the diastereomers formed in the formal (3 + 2) cycloaddition reaction are of opposite enantiomeric series. Calculations given this assumption predict an enantioselectivity of 58% ee. This result was confirmed by control experiments involving exposure of the pure *exo* diastereomer to DBU; exposure of 94% ee *exo*-**100e** to the epimerization conditions returned *ent-endo*-**100e** in 94% ee.

Scheme 2.3.2. Proposed mechanism for stereoselective cycloaddition reaction.



Current efforts are focused on understanding the mechanism of BINOL•$SnCl_4$ catalyzed pyrroloindoline formation. However, one possible scenario consistent with the experimental data is shown in Scheme 2.3.2. In this mechanism, it is proposed that $SnCl_4$-promoted conjugate addition of the indole to the acrylate proceeds reversibly to afford a

racemic mixture of enolates **121** and *ent*-**121**. In the second step, an irreversible, highly face-selective, catalyst controlled protonation would serve to resolve the two enantiomers into diastereomeric iminium ions *exo*-**122** and *endo*-**122**. In this mechanistic hypothesis, the diastereoselectivity depends on the relative rates of protonation of **121** and *ent*-**121**. Subsequent catalyst turnover by deprotonation of the amide followed by cyclization upon workup would deliver *exo*-**100e** and *endo*-**100e.**

It is proposed that $SnCl_4$•BINOL complex **125** serves as a chiral proton source to set the absolute stereochemistry of *exo*-**100e** and *endo*-**100e** by protonation of enolates **121** and *ent*-**121**. Enantioselective protonations promoted by (*R*)-BINOL•$SnCl_4$ complexes are well documented based on extensive studies by Yamamoto and coworkers. In these reports, it is suggested that (*R*)-BINOL•$SnCl_4$ serves as a chiral Lewis acid-assisted Brønsted acid (LBA) to effect protonation.[14] In the Yamamoto examples, use of a less reactive stoichiometric achiral phenol is required to turnover the catalyst.[14b] In the formation of pyrroloindolines **100e**, the active catalyst **125** might be regenerated from **126** by protonation with the amide proton of *exo*-**123** and *endo*-**123**, thereby affording **124**. These protonated iminium species are stable under the reaction conditions as identified by ^{1}H NMR and undergo cyclization to afford *exo*-**100e** and *endo*-**100e** during the work-up. Notably, resubjection of *exo*-**100e** to the reaction conditions cleanly regenerates iminium **124** without any erosion of ee, thus confirming the irreversibility of the protonation step.

2.4 CONCLUDING REMARKS

In summary, we have established a unique strategy for the direct prepararation of enantioenriched pyrroloindolines by an (*R*)-BINOL•$SnCl_4$-catalyzed formal (3 + 2)

cycloaddition reaction. The transformation requires an equivalent of $SnCl_4$ but addition of (*R*)-BINOL creates such a large rate acceleration that the reaction can be completed with catalytic loadings of BINOL in excellent enantioselectivity. The method allows access to a variety of pyrroloindolines including new structural motifs such as aza-propellanes (**106g**). Although the reaction proceeds poorly with more sterically encumbered substrates, we have found that additional of catalytic MeOH greatly improves reactivity and enables access to phenylpyrroloindoline product **118**.

The formal (3 + 2) cycloaddition reaction has been exploited both in the development of new methodology and in total synthesis. Mechanistic studies of this reaction showed that the reaction occurs via a highly face-selective catalyst-controlled protonation and that cyclization of the resultant iminium intermediate only occurs upon work-up; these observations have respectively led to the development of a tandem conjugate addition/enantioselective protonation reaction (Chapter 3) and to the generation of indoline products by in situ iminium reduction.[§,15] In addition, synthetic efforts using this reaction have culminated in the efficient total syntheses of two diketopiperazine-containing pyrroloindoline natural products lansai B[16] and nocardioazine A.[17,**] 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 methodology, and the synthesis of pyrroloindoline alkaloid natural products.

[§] This transformation was developed by Jane Ni, a graduate student in the Reisman lab.

[**] Research directed toward these natural products has been conducted by Haoxuan Wang, a graduate student in the Reisman lab.

2.5 EXPERIMENTAL SECTION

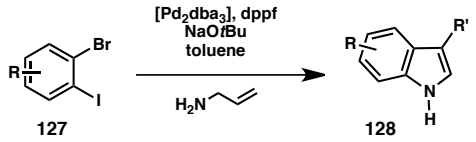
2.5.1 Materials and Methods

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, 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'-dibromo-BINOL (**102f**),[18] (*R*)-2'-methoxy-[1,1'-binaphthalen]-2-ol (**102b**)[19], TADDOL (**103**),[20] 3-phenylindole (**111**),[21] and 1-methyl-3-phenylindole (**109**)[22] were prepared according to literature procedures. 1-methyl-3-(phenylethynyl)indole (**115**),[23] (*R*)-3,3'-dianthryl-BINOL (**102e**),[24] (*R*)-3,3'-dimesityl-BINOL (**102c**)[25] and (*R*)-3,3'-di(triphenylsilyl)-BINOL (**102d**)[26] are known and were prepared by procedures adapted from the literature. 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.[27] 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. ^{1}H 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.

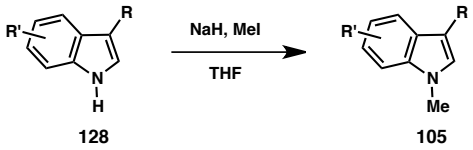
2.5.2 Substrate Synthesis

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



Procedure was adapted from Jørgensen *et al*.[28] 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.

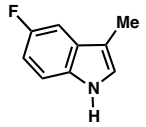
General Procedure B. *N*-methylation of indole derivatives.



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

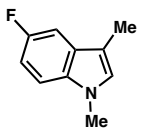
concentrated under reduced pressure. The crude residue was purified by flash chromatography.

5-Fluoro-3-methyl-1*H*-indole (128b).



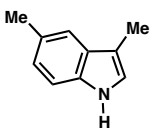
Prepared from 3.75 mmol of 2-bromo-4-fluoro-1-iodobenzene, 0.63 mol % [Pd_2dba_3] and 2.5 mol % dppf using general procedure A. The product was purified by flash chromatography (10% ethyl acetate/hexanes) to yield 5-fluoro-3-methyl-1*H*-indole (**128b**, 0.22 g, 38% yield). Spectral data matches that reported in the literature.[28]

5-Fluoro-1,3-dimethyl-1*H*-indole (105b).



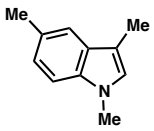
Prepared from 1.07 mmol of 5-fluoro-3-methyl-1*H*-indole using general procedure B. The product was purified by flash chromatography (3% ethyl acetate/hexanes) to yield **105b** (0.97 g, 55% yield) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.13 (m, 2H), 7.00 – 6.92 (m, 1H), 6.86 (s, 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 (128c).



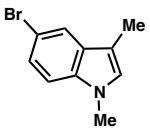
Prepared from 2.88 mmol of 2-bromo-1-iodo-4-methylbenzene,[29] 2.5 mol % [Pd_2dba_3] and 10 mol % dppf using general procedure A. The product was purified by flash chromatography (5→13% ethyl acetate/hexanes) to yield 3,5-dimethyl-1*H*-indole (**128c**, 0.11 g, 14% yield). Spectral data matches that reported in the literature.[28]

1,3,5-trimethyl-1*H*-indole (105c).



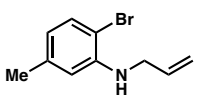
Prepared from 0.70 mmol of 3,5-dimethyl-1*H*-indole using general procedure B. The product was purified by flash chromatography (2% ethyl acetate/hexanes) to yield **105c** (0.048 g, 43% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 1H), 7.18 (d, *J* = 8.3 Hz, 1H), 7.05 (dd, *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 (105d).



Prepared from 0.95 mmol of 5-bromo-3-methyl-1*H*-indole[30] using general procedure B. The product was purified by flash chromatography (5% ethyl acetate/hexanes) to yield **105d** (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.

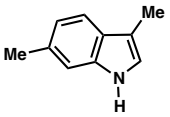
***N*-allyl-2-bromo-5-methylaniline (129).**



Procedure was adapted from Sørensen and Pombo-Villar.[31] 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 hours. 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 (**129**, 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.

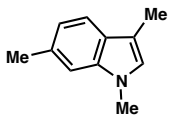
3,6-dimethyl-1*H*-indole (128e).



Procedure was adapted from Sørensen and Pombo-Villar.[31] A solution of *N*-allyl-2-bromo-5-methylaniline (**129**, 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 16h. The reaction was cooled to room temperature, saturated $NaHCO_{3\ (aq)}$ solution and 100 mL water were 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 (5→10% ethyl acetate/hexanes) to yield 3,6-dimethyl-1*H*-indole (**128e**, 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* =

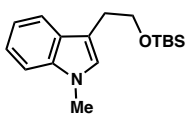
2.1 Hz, 1.1 Hz, 1H), 2.45 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 131.6, 126.2, 120.9, 120.8, 118.5, 111.6, 110.9, 21.7, 9.7. IR (NaCl/thin film): 3409, 2922, 1452, 1329, 1086, 908, 803, 733 cm^{-1}. HRMS (MM: ESI–APCI) calc'd for $[M+H]^+$ 146.0964, found 146.0970.

1,3,6-trimethyl-1*H*-indole (105e).



Prepared from 0.70 mmol of 3,6-dimethyl-1*H*-indole (**128e**) using general procedure B. The product was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield **105e** (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.

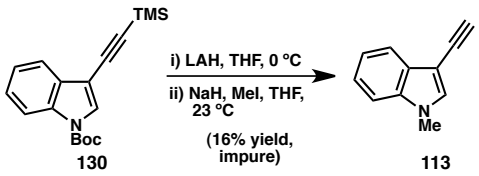
1-methyl-3-*t*-butyldimethylsiloxyethyl-1*H*-indole (105f).



Prepared from 2.66 mmol of 3-*t*-butyldimethylsiloxyethyl-1*H*-indole[32] using general procedure B. The product was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield **105f** (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):

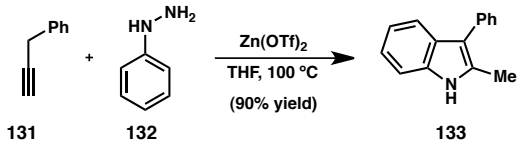
3056, 2954, 2929, 2857, 1472, 1251, 1095, 836, 737 cm^{-1}; HRMS (ESI) calc'd for $[M+H]^+$ 290.1940, found 290.1933.

1-methyl-3-ethynylindole (113).



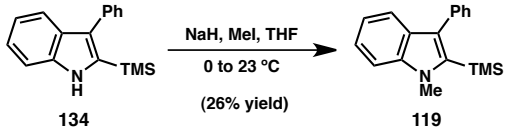
To a solution of 1-Boc-3-(trimethylsilylethynyl)indole[33] (**130**, 290 mg, 0.930 mmol, 1.00 equiv) in 4.6 mL THF cooled to 0 ºC in an ice bath was added LAH (2 M in THF, 1.1 mL, 2.2 mmol, 2.4 equiv). After 2 h stirring at 0 ºC, the reaction mixture was subjected to a standard Fieser workup. The crude residue was then dried under hi-vacuum, then redissolved in 4.6 mL THF. NaH (60 wt % dispersion in oil, 56 mg, 1.4 mmol, 1.5 equiv) was then added and the reaction was then cooled to 0 ºC in an ice bath, followed by addition of MeI (116 μL, 1.86 mmol, 2.00 equiv). The reaction mixture was then allowed to warm to room temperature and stirred for 3 hours, then cooled to 0 ºC. MeOH was added to quench the reaction, followed by dilution with H_2O, and extraction with DCM (3 x). The combined organic layers were then dried (Na_2SO_4) and concentrated. The crude oil was subjected to silica gel column chromatography (0:100 to 5:95 EtOAc:hexanes) to yield 23.1 mg (16% yield containing impurities) of 1-methyl-3-ethynlindole (**113**) and 47.8 mg (23% yield) of a compound that is likely 1-methyl-3-((trimethylsilyl)ethynyl)indole. The ^1H NMR shifts observed for **113** vary slightly from the literature[34] and are thus listed herein. ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 – 7.72 (m, 1H), 7.33 – 7.23 (m, 3H), 7.20 (ddd, J = 8.0, 6.4, 1.8 Hz, 1H), 3.75 (s, 3H), 3.21 (s, 1H).

2-methyl-3-phenylindole (133).



2-methyl-3-phenylindole (**133)** was prepared by a procedure adapted from Beller and coworkers.[35] A flame-dried 25 mL Schlenk tube was charged with $Zn(OTf)_2$ (0.546 g, 1.50 mmol, 1.00 equiv) and flushed with argon. 4 mL THF, phenylhydrazine (**132**, 191 μL, 1.95 mmol, 1.30 equiv), and 3-phenyl-1-propyne (**131**, 187 μL, 1.50 mmol, 1.00 equiv) were added in that order and the Schlenk tube was then sealed and heated to 100 ºC. After stirring at 100 ºC for 25.5 hours, the reaction mixture was allowed to cool to room temperature, and concentrated. The crude residue was purified by silica gel column chromatography to yield 282 mg (90% yield) of 2-methyl-3-phenylindole (**133**). Spectral data were in agreement with the literature.[21]

1-methyl-3-phenyl-2-(trimethylsilyl)indole (119).



A solution of 3-phenyl-2-(trimethylsilyl)indole[36] (**134**, 228 mg, 0.859 mmol, 1.00 equiv) in 20 mL THF was cooled to 0 ºC in an ice bath under argon, followed by addition of NaH (60 wt % dispersion in oil, 41 mg, 1.7 mmol, 2.0 equiv). After stirring 15 minutes at 0 ºC, MeI (107 μL, 1.72 mmol, 2.00 equiv) was added and the reaction was allowed to warm to room temperature. After stirring 20 hours at room temperature, the reaction mixture was cooled to 0 ºC and quenched with saturated aqueous NH_4Cl then diluted with Et_2O. The organic layer was washed (saturated aqueous $NaHCO_3$ then brine), dried

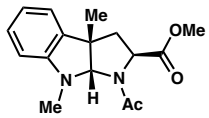
(Na_2SO_4), filtered, and concentrated. The crude residue was purified by column chromatography to yield 63 mg (26% yield) of 1-methyl-3-phenyl-2-(trimethylsilyl)indole (**119**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.35 (m, 7H), 7.30 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.10 (ddd, *J* = 7.9, 6.8, 1.1 Hz, 1H), 3.94 (s, 3H), 0.22 (s, 9H).

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

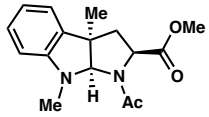
To a flame-dried flask was added indole (0.20 mmol, 1.00 equiv), acrylate (0.20 mmol, 1.00 equiv), and (*R*)-BINOL (0.04 mmol, 0.20 equiv). The flask was charged with DCM (1.5 mL), followed by addition of $SnCl_4$ (0.24 mmol, 1.20 equiv unless specifically indicated, 1 M in DCM), then stirred at room 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.

2.5.4 Pyrroloindoline Products under General Procedure C

Pyrroloindoline 100b.



(a) *exo* diastereomer



(b) *endo* diastereomer

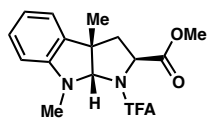
Screen varying (*R*)–BINOL loading. All reactions were run at room temperature for 3 h in DCE with 1,3-dimethyl-1*H*-indole[37] (**75**, 0.2 mmol, 1 equiv), methyl 2-acetamidoacrylate[38] (**91a**, 0.2 mmol, 1 equiv) and $SnCl_4$ (1.2 equiv, 1 M in DCM) Purified by flash chromatography (0→50% ethyl acetate/hexanes). 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).

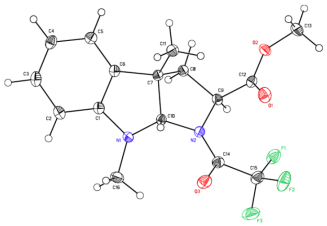
Exo diastereomer: pale yellow oil. t_R(major) = 9.5 min t_R(minor) = 6.2 min. ^{1}H NMR (400 MHz, $CDCl_3$; compound exists as a 1:1 mixture of rotamers) δ 7.10 – 7.01 (m, 1H), 6.95 (d, *J* = 7.3 Hz, 0.5H), 6.91 (d, *J* = 7.3 Hz, 0.5H), 6.68 (t, *J* = 7.4 Hz, 0.5H), 6.62 (t, *J* = 7.4 Hz, 0.5H), 6.43 (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.

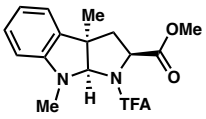
Endo diastereomer: bright yellow oil. t_R(major) = 4.0 min t_R(minor) = 4.7 min. ^1H NMR (400 MHz, $CDCl_3$; compound exists as a 3:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.11 (t, *J* = 7.6 Hz, 1H§), 7.06 (t, *J* = 7.8 Hz, 1H*), 7.01 (d, *J* = 7.1 Hz, 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 100c.





(a) *exo* diastereomer



(b) *endo* diastereomer

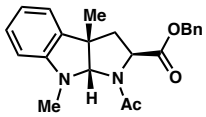
Prepared from 1,3-dimethyl-1*H*-indole **75** and methyl 2-trifluoroacetamidoacrylate[39] **91b** using general procedure C (with DCE as the solvent). The reaction was allowed to run for 4 h. The crude residue was purified by flash chromatography (20→35% ethyl acetate/hexanes) to yield 53.0 mg (77% yield) of **100c** 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§,

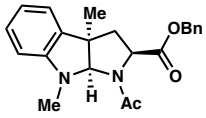
118.7*, 116.1* (q, $J_{C\text{-}F}$ = 288.4 Hz), 109.4[§], 108.0*, 93.3*, 91.7[§], 61.3[§], 60.3*, 53.0*, 52.6[§], 49.2*[§], 44.0*, 40.6[§], 36.8*, 34.4[§], 23.5*, 22.8[§]; IR (NaCl/thin film): 2959, 1751, 1696, 1610, 1490, 1435, 1204, 1155, 988, 744 cm^{-1}; melting point: 105.5 – 107.5 °C; $[\alpha]_D^{25}$ = –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 100d.



(a) *exo* diastereomer



(b) *endo* diastereomer

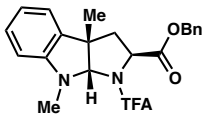
Prepared from 1,3-dimethyl-1*H*-indole **75** and benzyl 2-acetamidoacrylate[40] **91c** using general procedure C (with DCE as the solvent). The reaction was allowed to run for 4 h. The product **100d** was formed in a 2:1 ratio of diastereomers (determined by ^{1}H NMR analysis of the crude reaction 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§,

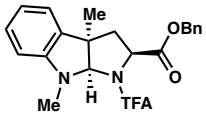
49.7*, 43.8*, 41.4§, 36.5*, 34.3§, 23.0§, 22.7*, 22.7*, 22.4§; IR (NaCl/thin film): 3032, 2962, 2877, 1745, 1661, 1609, 1489, 1390, 1175, 1117, 744 cm^{-1}; $[\alpha]_D^{25}$ = –66.9° (*c* = 0.98, DCM). HRMS (ESI) calc'd for $[M+H]^+$ 365.1865, found 365.1875.

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 100e.



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



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

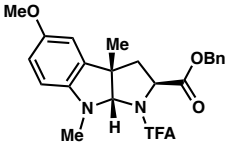
Prepared from 1,3-dimethyl-1*H*-indole (**75**, 0.15 mmol) and benzyl 2-trifluoroacetamidoacrylate[41] (**91d**, 0.15 mmol) using general procedure C. The reaction was allowed to run for 5.5 h. The crude residue was purified by flash chromatography (5→8% ethyl acetate/hexanes) to yield 54 mg (86% yield) of **100e** 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, $J_{C\text{-}F}$ =

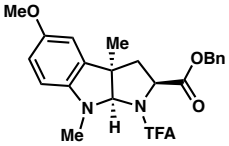
288.6 Hz)*, 109.3[§], 107.8*, 93.1*, 91.6[§], 67.8*, 67.1[§], 61.2[§], 60.2 (q, $J_{C\text{-}F}$ = 2.44 Hz)*, 52.9[§], 49.0*, 43.6*, 40.2[§], 36.5*, 34.2[§], 23.1*, 22.5[§]; IR (NaCl/thin film): 3034, 2966, 1747, 1695, 1610, 1490, 1456, 1432, 1188, 1156, 745 cm^{-1}; $[\alpha]_D^{25}$ –90.1° (c = 1.11, 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 106a.



(a) *exo* diastereomer



(b) *endo* diastereomer

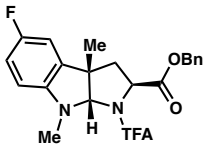
Prepared from 5-methoxy-1,3-dimethyl-1*H*-indole[42] and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 4 h. The crude residue was purified by flash chromatography (5→10% ethyl acetate/hexanes) to yield 83.1 mg (93% yield) of **106a** in a 3:1 ratio 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*,

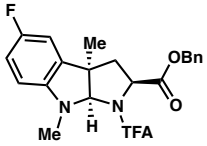
36.9[§], 23.5[§], 23.4*; IR (NaCl/thin film): 2963, 2833, 1748, 1694, 1497, 1432, 1156, 1030, 991, 754 cm^{-1}; $[\alpha]_D^{25}$ = –78.1° (*c* 1.07, DCM); HRMS (ESI) calc'd for $[M+H]^+$ 449.1683, found 449.1676.

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 106b.



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



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

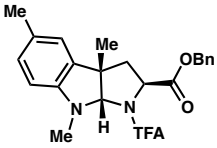
Prepared from 5-fluoro-1,3-dimethyl-1*H*-indole **105b** and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 5.5 h. The crude residue was purified by flash chromatography (5→12% ethyl acetate/hexanes) to yield 53.0 mg (61% yield) of **106b** in a 3:1 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*,

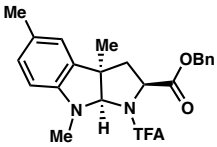
92.2[§], 68.2*, 67.5[§], 61.3[§], 60.3*, 53.2[§], 49.2*, 43.7*, 40.1[§], 37.6*, 35.6[§], 23.3*, 22.9[§]; IR (NaCl/thin film): 2966, 1748, 1698, 1495, 1434, 1350, 1270, 1157, 994, 843 cm^{-1}; $[\alpha]_D^{25}$ = –81.7° (*c* 1.14, DCM); HRMS (ESI) calc'd for $[M+H]^+$ 437.1483, found 437.1476.

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 106c.



(a) *exo* diastereomer



(b) *endo* diastereomer

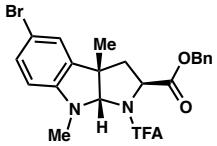
Prepared from 5-methyl-1,3-dimethyl-1*H*-indole (**105c**) and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 4 h. The crude residue was purified by flash chromatography (5→15% ethyl acetate/hexanes) to yield 72.9 mg (84% yield) of **106c** in a 5:1 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,

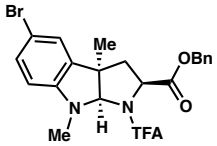
1194, 1153, 992, 754 cm^{-1}; $[\alpha]_D^{25}$ = –87.1° (*c* 0.90, DCM); HRMS (APCI) calc'd for $[M+H]^+$ 433.1734, found 433.1713.

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 106d.



(a) *exo* diastereomer



(b) *endo* diastereomer

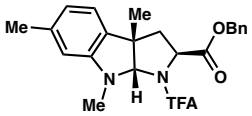
Prepared from 5-bromo-1,3-dimethyl-1*H*-indole (**105d)** and benzyl 2-trifluoroacetamidoacrylate using general procedure C, in DCE with 1.6 equivalents $SnCl_4$. The reaction was allowed to run for 57 h. The crude residue was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield 50 mg (51% yield) of **106d** 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):

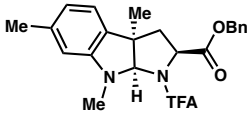
3034, 2965, 2931, 1747, 1698, 1602, 1489, 1205, 1154, 806, 751 cm^{-1}; $[\alpha]_D^{25}$ –86.4° (c = 0.60, DCM); HRMS (FAB+) calc'd for $[M+H]^+$ 498.0589, found 498.0576.

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, $J_{C\text{-}F}$ = 37.0 Hz)*, 149.4*, 134.4*, 134.2*, 131.8*, 131.4§, 125.5*, 124.9§, 116.1(q, $J_{C\text{-}F}$ = 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 106e.



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



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

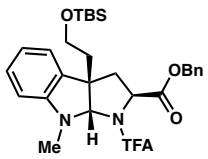
Prepared from 6-methyl-1,3-dimethyl-1*H*-indole (**105e**) and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 6 h. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield 78.3 mg (91% yield) of **106e** in a 4:1 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*,

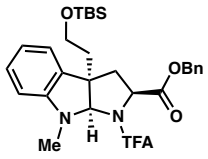
92.0[§], 68.1*, 67.4[§], 61.5[§], 60.5*, 52.9[§], 49.0*, 43.9*, 40.4[§], 36.8*, 34.7[§], 23.5*, 23.0[§], 21.7*[§]; IR (NaCl/thin film): 2964, 1748, 1697, 1616, 1499, 1456, 1423, 1160, 1004, 752 cm^{-1}; $[\alpha]_D^{25}$ = –85.6º (*c* 0.93, DCM); HRMS (EI+) calc'd for $M^{+\bullet}$ 432.1661, found 432.1663.

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 106f.



(a) *exo* diastereomer



(b) *endo* diastereomer

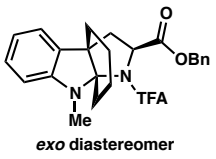
Prepared from 1-methyl-3-*t*-butyldimethylsiloxyethyl-1*H*-indole (**105f**) and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 20 h. The crude residue was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield 61 mg (54% yield) of **106f** 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*§,

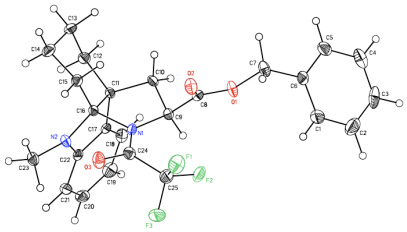
119.9[§], 118.4*, 116.0 (q, $J_{C\text{-}F}$ = 288.0 Hz)*, 110.0[§], 108*, 90.8*, 89.5[§], 67.9*, 67.3[§], 60.5[§], 59.6*, 56.4[§], 52.3*, 43.5*, 39.9[§], 39.1[§], 39.0*, 36.4*, 35.7[§], 25.8*, 18.1[§], -5.6*[§]; IR (NaCl/thin film): 3035, 2955, 2930, 2857, 2884, 1750, 1694, 1492, 1432, 1257, 1201, 1158, 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 106g.



exo diastereomer

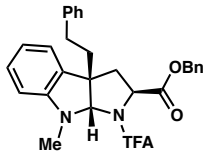


Prepared from 9-methyl-2,3,4,9-tetrahydro-1*H*-carbazole[43] and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 11 h. The crude residue was purified by flash chromatography (5→20% ethyl acetate/hexanes) to yield 60 mg (65% yield) of **106g** in a >18:1 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).

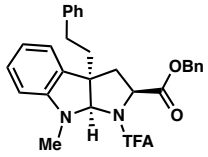
Exo diastereomer: pale yellow oil. The oil was crystallized from ethyl acetate/hexanes to give crystals suitable for single crystal X-ray diffraction. The enantiomeric excess was determined to be 86% by chiral SFC analysis (OJ-H, 2.5 mL/min, 6% IPA in hexanes, λ = 254 nm): t_R(major) = 4.5 min t_R(minor) = 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 106h.



(a) *exo* diastereomer



(b) *endo* diastereomer

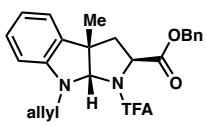
Prepared from 3-phenethyl-1-methyl-1*H*-indole[44] and benzyl 2-trifluoroacetamidoacrylate using general procedure C, with 1.6 equivalents $SnCl_4$. The reaction was allowed to run for 9.5 h. The crude residue was purified by flash chromatography (5→20% ethyl acetate/hexanes) to yield 81 mg (80% yield) of **106h** 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§,

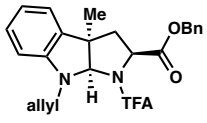
128.7*, 128.4*, 128.2*, 126.0*[§], 122.3[§], 121.9*, 120.1[§], 118.9*, 116.0 (q, $J_{C\text{-}F}$ = 288.4 Hz)*, 109.7[§], 108.3*, 90.4*, 89.2[§], 68.1*, 67.4[§], 60.7[§], 59.5*, 57.5[§], 53.7*, 43.5*, 40.0[§], 39.0*, 38.6[§], 36.9*, 35.1[§], 31.9*[§] ; IR (NaCl/thin film): 3030, 2921, 2852, 1747, 1694, 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. ^1H 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 106i.



(a) ***exo*** diastereomer



(b) ***endo*** diastereomer

Prepared from 1-allyl-3-methyl-1*H*-indole[45] 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 **106i** 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).

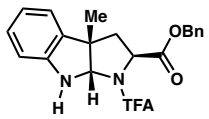
Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 93% by chiral SFC analysis (OJ-H, 2.5 mL/min, 6% IPA in CO_2, λ = 254 nm): t_R(major) = 5.7 min t_R(minor) = 4.3 min. ^{1}H NMR (400 MHz, $CDCl_3$; compound exists as a 5.7:1 mixture of rotamers, the major rotamer is denoted 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 106j.



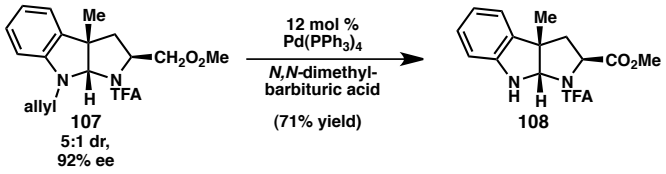
exo diastereomer

Prepared from 3-methyl-1*H*-indole (0.15 mmol) and benzyl 2-trifluoroacetamidoacrylate (**91d**, 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 **106j** 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.

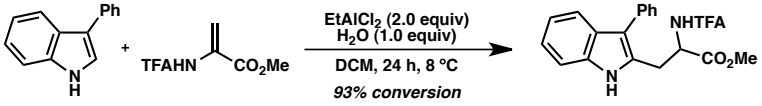
2.5.5 Pd-catalyzed Deallylaton of Pyrroloindoline Methyl Ester 107



An oven-dried microwave vial was charged with allylpyrroloindoline **107** (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) 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 hours and after 75 hours. After heating at 35 ºC for 123 hours, 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 **108** 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*-**108** in >20:1 dr. ^1H 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.

*2.5.6 Preparation of Methyl 3-(3-phenyl-1*H*-indol-2-yl)-2-(2,2,2-trifluoroacetamido)propanoate (112)*

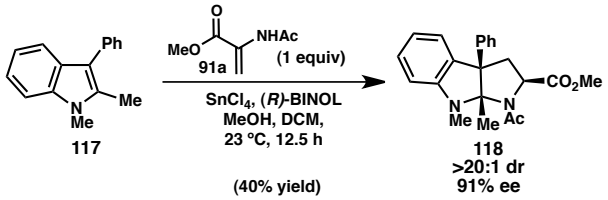


111 91b 112

A flame-dried flask was charged with 3-phenylindole (**111**, 13.6 mg, 70.0 μmol, 1.00 equiv) and trifluoromethyl 2-acetamidoacrylate (**91b**, 13.8 mg, 70.0 μmol, 1.00 equiv). 0.3 mL DCM was then added and the solution was cooled to 0 ºC. $EtAlCl_2$ (1 M in hexanes, 0.14 mL, 2.0 mmol, 2.0 equiv) was then added dropwise, followed by 1.0 μL H_2O (63 μmol, 0.90 equiv). The reaction was then stirred in a cold room at 8 ºC for 24 hours. By crude ^{1}H NMR, 93% conversion of **91b** was observed to cleanly afford methyl

3-(3-phenyl-1*H*-indol-2-yl)-2-(2,2,2-trifluoroacetamido)propanoate (**112**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (br s, 1H), 7.60 (dddd, *J* = 7.9, 1.3, 0.7, 07 Hz, 1H), 7.51 – 7.42 (m, 4H), 7.40 – 7.31 (m, 2H), 7.24 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.13 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 6.82 (br d, *J* = 7.5 Hz, 1H), 4.81 (dt, *J* = 7.4, 5.5 Hz, 1H), 3.64 – 3.45 (m, 5H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 157.0 (q, $J_{C\text{-}F}$ = 38.1 Hz), 135.6, 134.1, 129.7, 128.8, 128.0, 127.6, 126.6, 122.7, 120.2, 119.3, 117.5, 115.3 (q, $J_{C\text{-}F}$ = 287.5 Hz), 110.8, 53.1, 52.5, 28.3.; FTIR (NaCl/thin film): 3377, 3058, 2918, 2848, 1718, 1604, 1541, 1499, 1459, 1438, 1329, 1267, 1214, 1171 cm^{-1}; HRMS (ESI) calc'd for $C_{20}H_{16}F_3N_2O_3$ $[M\text{-}H]^-$ 389.1119, found 389.1114.

2.5.7 Preparation of Phenylpyrroloindoline 118

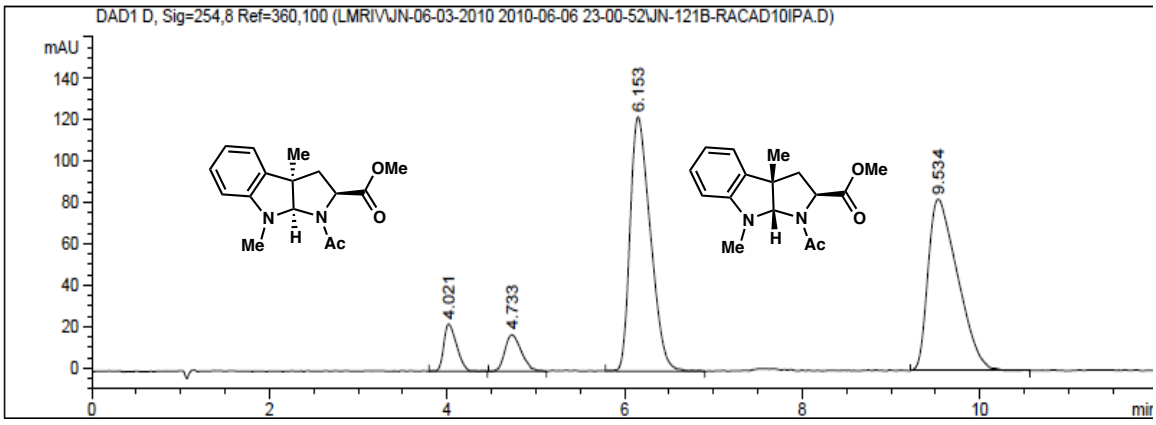


A 10 mL flame-dried flask was charged with (*R*)-BINOL (11.4 mg, 39.9 μmol, 0.20 equiv), methyl 2-acetamidoacrylate (**91a**, 28.6 mg, 0.200 mmol, 1.00 equiv), and 1,2-dimethyl-3-phenylindole[46] (**117**, 44.2 mg, 0.200 mmol, 1.00 equiv). MeOH (40 μmol, 0.20 equiv) was then added as a solution in 1.5 mL DCM (from a stock solution of 16 μL MeOH in 15 mL DCM), followed by $SnCl_4$ (1 M solution in DCM, 240 μL, 0.240 mmol, 1.20 equiv). After stirring in the dark 12.5 hours, the orange reaction mixture was diluted with 4 mL MeCN and 5 mL EtOAc, then washed with 10 mL of 0.1 M HCl in brine. The aqueous layer was extracted with 5 mL EtOAc and the combined organic layers were washed with 10 mL 1 M aqueous NaOH. The aqueous layer was extracted with 5 mL

EtOAc and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified by silica gel column chromatography (0:100 to 40:60 EtOAc:hexanes) to yield 29 mg (40% yield) of 3a-phenylpyrroloindoline **118** as a pale yellow oil. The enantiomeric excess was determined to be 91% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO_2, λ = 235 nm): t_R(major) = 4.4 min, t_R(minor) = 3.5 min. ^{1}H NMR (300 MHz, $CDCl_3$, compound exists as a 1.9:1 mixture of rotamers, the major rotamer is designated by *, minor rotamer designated by §) δ 7.30 – 7.15 (m, 4H*, 4H§), 6.98 – 6.79 (m, 3H*, 4H§), 6.75 (d, J = 8.1 Hz, 1H§), 6.68 (ddd, J = 7.4, 7.4, 1.0 Hz, 1H*), 6.54 (d, J = 7.9 Hz, 1H*), 4.31 – 4.16 (m, 1H*, 1H§), 3.82 (s, 3H*), 3.77 (s, 3H§), 3.09 (s, 3H*), 3.02 (s, 3H§), 3.01 – 2.80 (m, 2H*, 2H§), 2.17 (s, 3H§), 1.76 (s, 3H*), 1.47 (s, 3H*), 1.35 (s, 3H§).; ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 1.9:1 mixture of rotamers) δ 173.9, 173.7, 170.5, 170.4, 151.0, 150.2, 140.2, 139.5, 134.2, 132.8, 129.2, 129.1, 128.4, 128.3, 127.3, 127.23, 127.16, 126.9, 123.5, 122.9, 120.9, 117.8, 111.0, 106.6, 94.1, 91.0, 64.8, 61.2, 60.2, 59.3, 52.7, 52.1, 35.34, 34.28, 32.2, 31.5, 23.6, 22.7, 19.5, 17.6.; FTIR (NaCl/thin film): 3002, 2950, 1747, 1662, 1607, 1491, 1447, 1385, 1343, 1212, 1200, 1165, 1111, 1102 cm^{-1}; $[\alpha]_D^{25}$ = –122.7° (c = 0.98, $CHCl_3$). HRMS (ESI) calc'd for $C_{22}H_{25}N_2O_3$ $[M+H]^+$ 365.1860, found 365.1867.

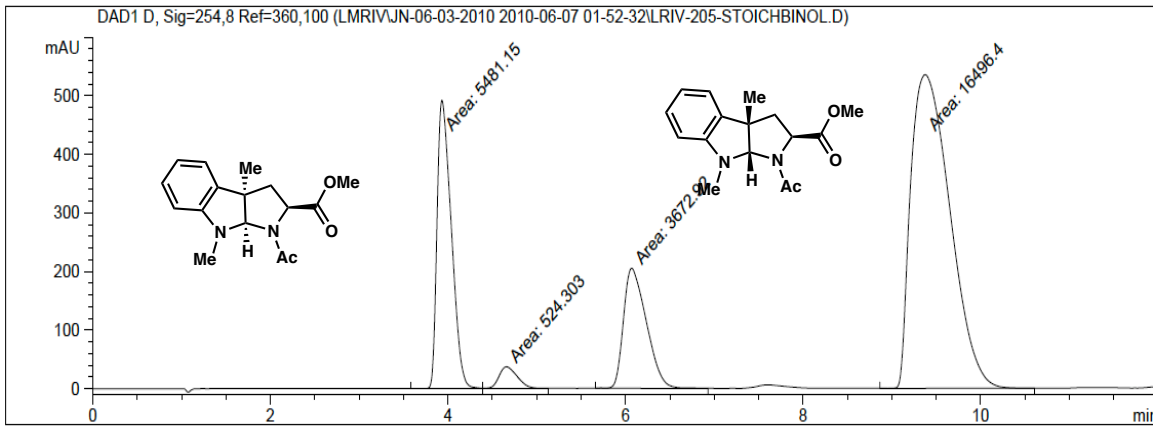
2.5.8 SFC and HPLC Traces for Racemic and Enantioenriched Products.

100b: racemic



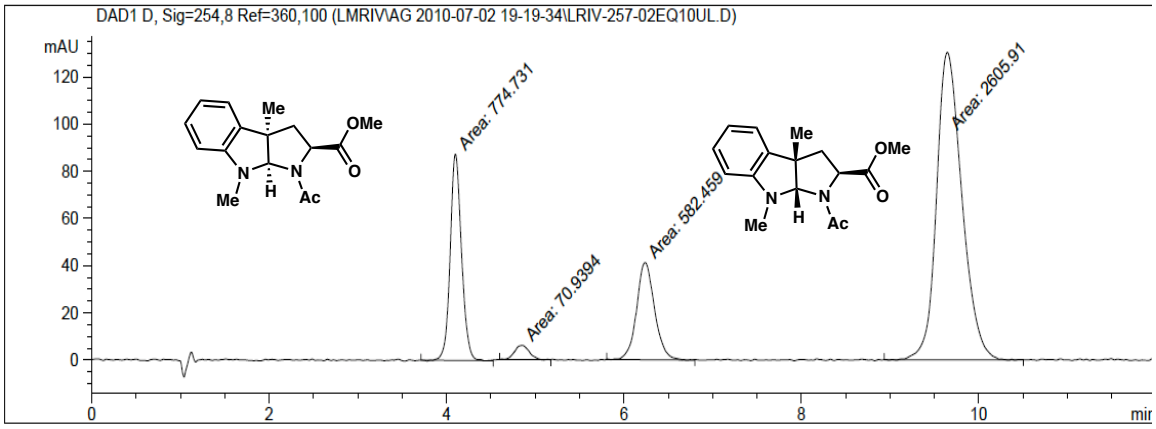
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.021	BB	0.1585	233.11978	22.95946	5.3721
2	4.733	BB	0.2032	229.21661	17.68176	5.2822
3	6.153	BB	0.2451	1949.83508	122.89280	44.9330
4	9.534	BB	0.3471	1927.25183	82.93414	44.4126

100b (Table 2.2.2, **entry 2**): enantioenriched, *exo:* 64% ee, *endo*: 83% ee (1.1 equiv BINOL)



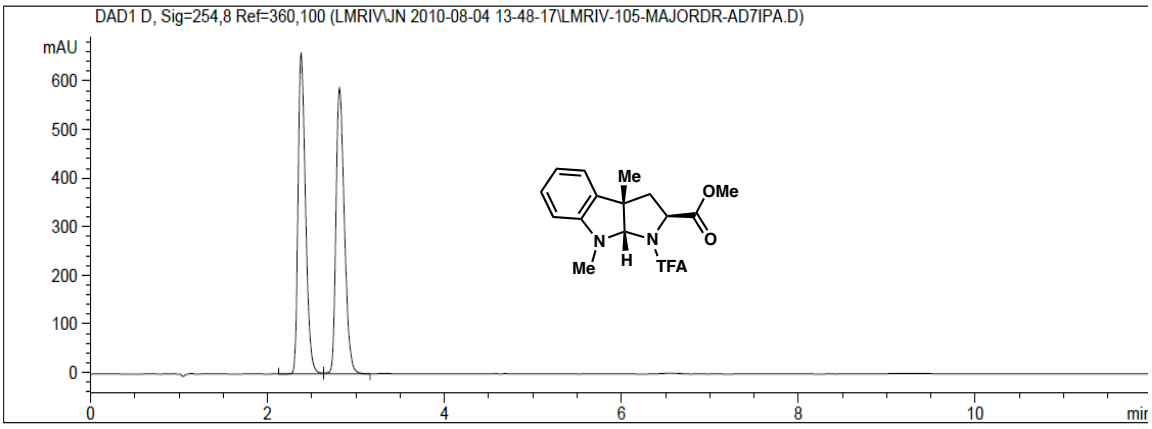
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.934	MF	0.1852	5481.14941	493.18698	20.9406
2	4.658	FM	0.2354	524.30292	37.12406	2.0031
3	6.070	MM	0.2985	3672.91748	205.08722	14.0323
4	9.375	MM	0.5132	1.64964e4	535.76978	63.0240

100b (Table 2.2.2, **entry 4**): enantioenriched, *exo:* 63% ee, *endo*: 83% ee (0.2 equiv BINOL)



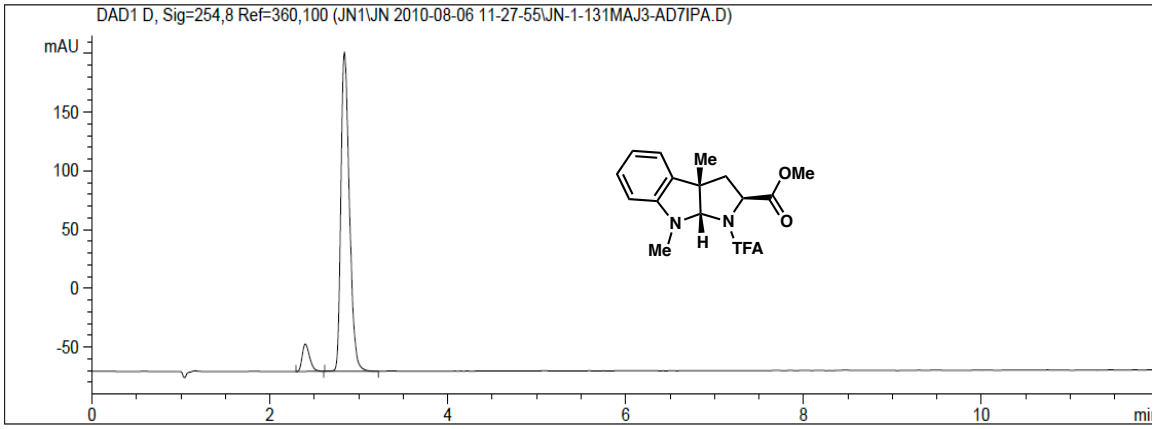
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.100	MM	0.1473	774.73053	87.65621	19.2048
2	4.852	MM	0.1955	70.93945	6.04832	1.7585
3	6.238	MM	0.2351	582.45917	41.28461	14.4386
4	9.647	MM	0.3330	2605.91260	130.42717	64.5981

***exo*-100c** (Table 2.2.3, **entry 6**): racemic



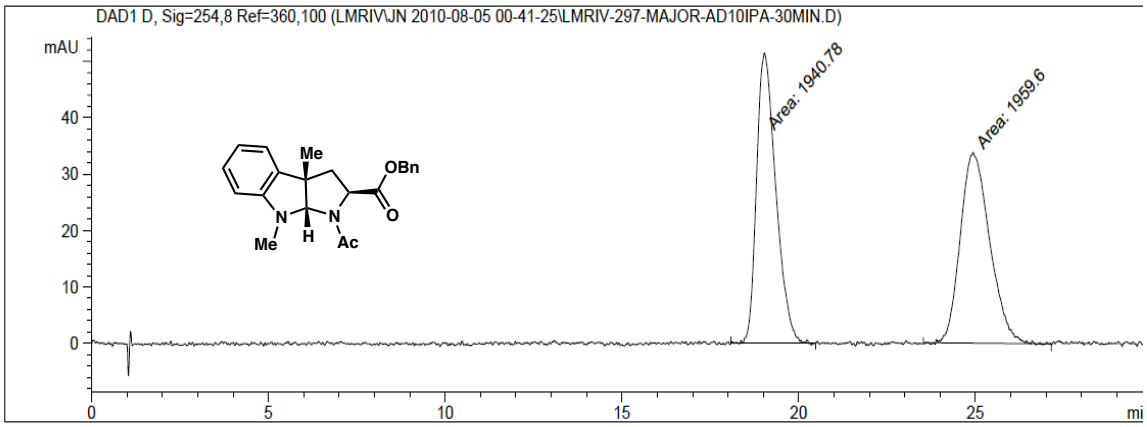
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.381	BV	0.0886	3856.54150	655.60498	49.8096
2	2.815	VB	0.1009	3886.01978	589.71381	50.1904

***exo*-100c** (Table 2.2.3, **entry 6**): enantioenriched, 86% ee



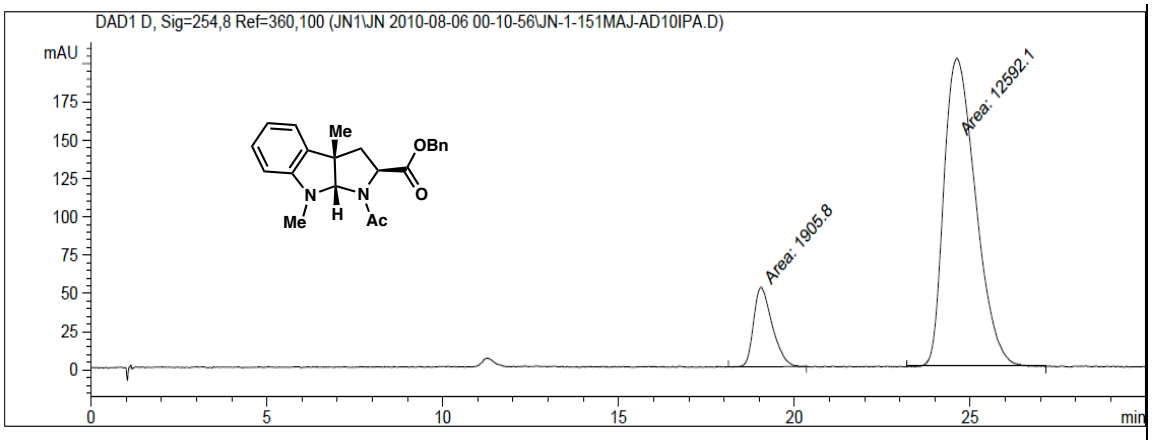
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.399	BB	0.0925	136.26041	23.19655	6.9999
2	2.839	BB	0.1061	1810.34204	270.34299	93.0001

***exo*-100d** (Table 2.2.3, **entry 7**): racemic



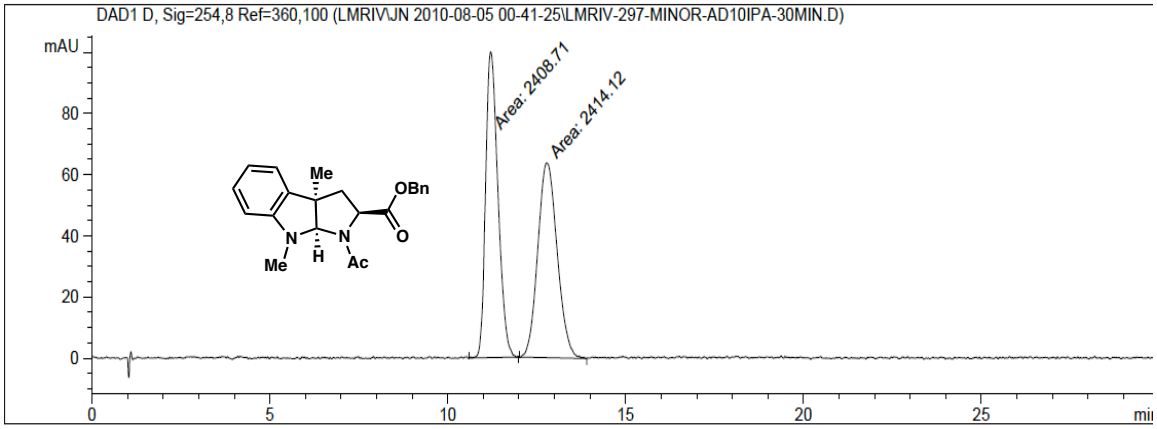
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.033	MM	0.6293	1940.77502	51.40419	49.7587
2	24.937	MM	0.9651	1959.59827	33.84022	50.2413

***exo*-100d** (Table 2.2.3, **entry 7**): enantioenriched, 74% ee



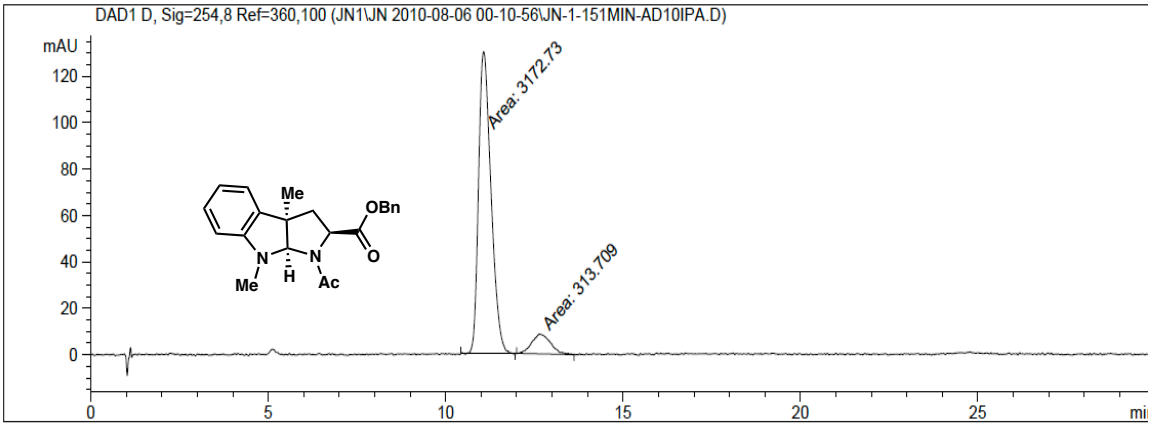
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.055	MM	0.6122	1905.80066	51.88297	13.1454
2	24.623	MM	1.0448	1.25921e4	200.87437	86.8546

***endo*-100d** (Table 2.2.3, **entry 7**): racemic



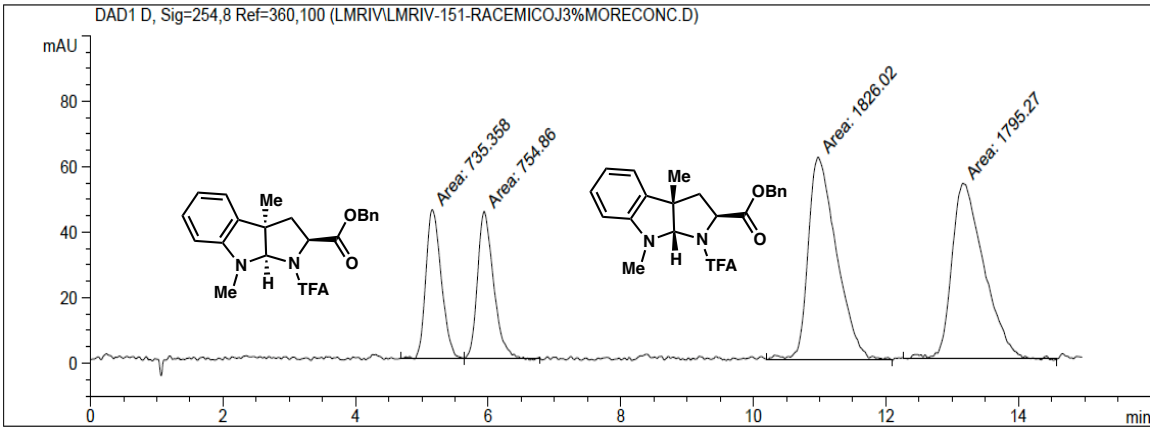
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.210	MM	0.4013	2408.70581	100.04025	49.9439
2	12.782	MM	0.6310	2414.11816	63.76419	50.0561

***endo*-100d** (Table 2.2.3, **entry 7**): enantioenriched, 82% ee



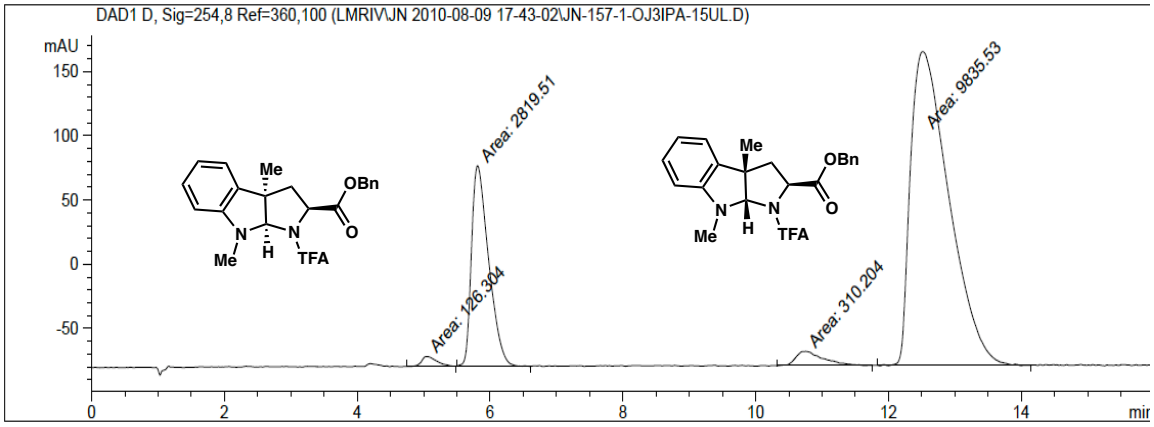
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.074	MM	0.4067	3172.73267	130.02379	91.0020
2	12.646	MM	0.6145	313.70920	8.50807	8.9980

100e (Table 2.2.3, **entry 9**): racemic



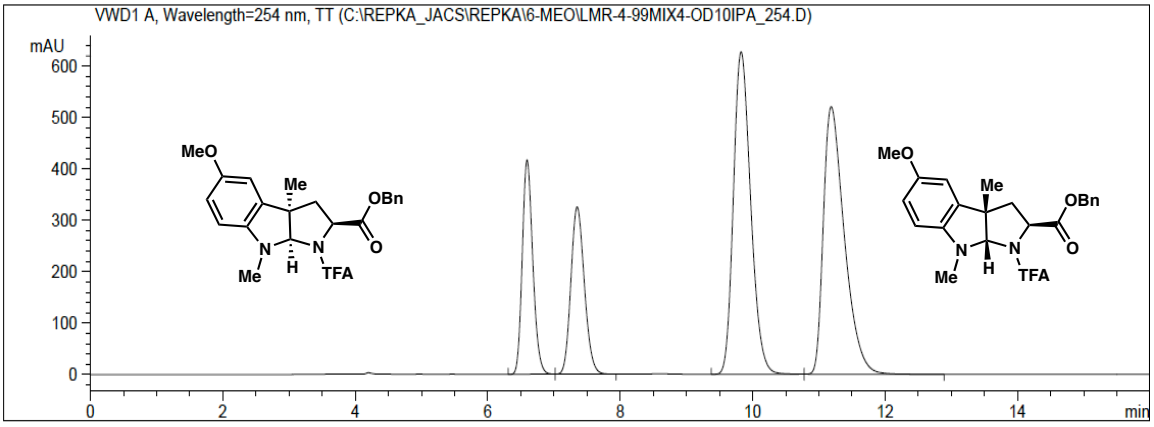
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.156	MF	0.2696	735.35803	45.45393	14.3863
2	5.940	FM	0.2802	754.85999	44.89612	14.7679
3	10.979	MM	0.4932	1826.01990	61.70875	35.7237
4	13.166	MM	0.5603	1795.26794	53.40647	35.1221

100e (Table 2.2.3, **entry 9**): enantioenriched, *exo:* 94% ee, *endo*: 91% ee



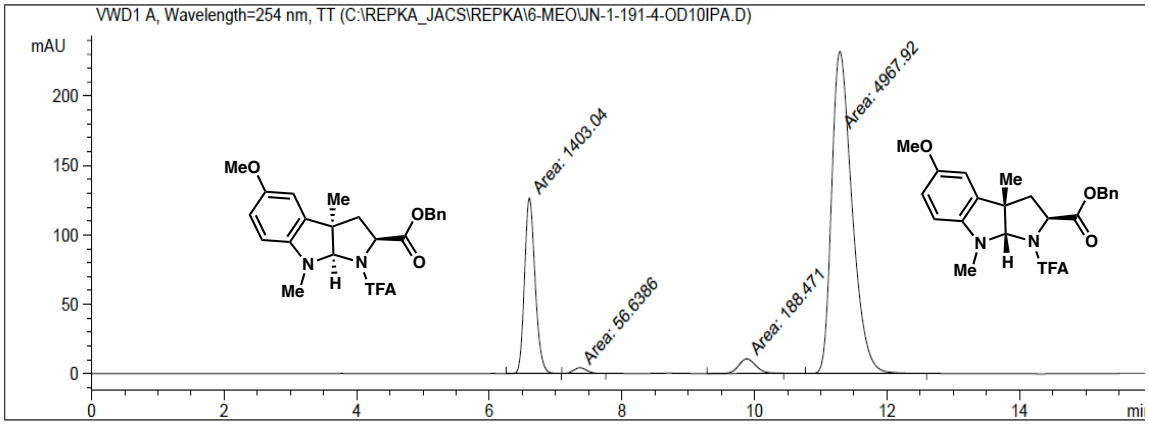
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.044	MM	0.2729	126.30366	7.71386	0.9648
2	5.812	MM	0.3004	2819.51172	156.42670	21.5369
3	10.749	MM	0.4705	310.20364	10.98786	2.3695
4	12.515	MM	0.6705	9835.53320	244.48642	75.1289

106a (Scheme 2.2.1): racemic



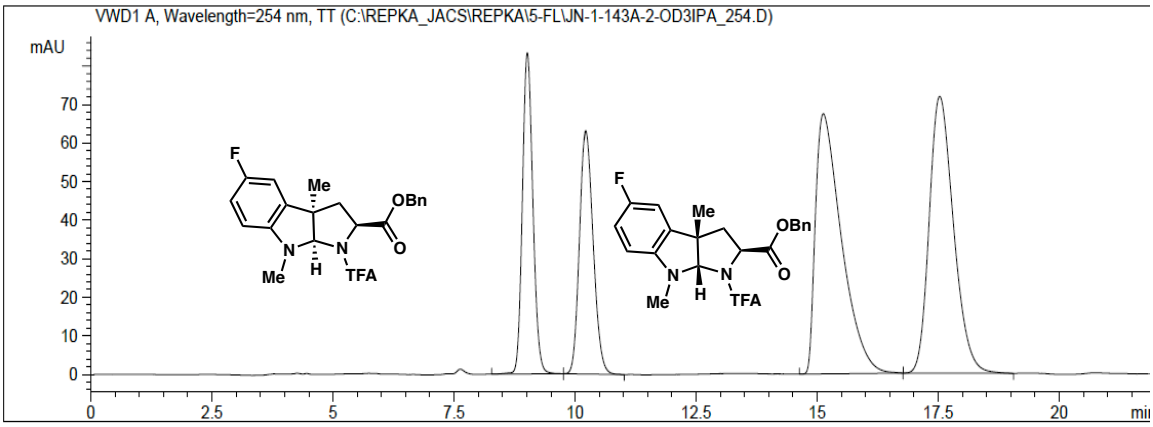
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.594	BB	0.1698	4609.86621	416.95142	14.3772
2	7.350	BB	0.2192	4610.61719	325.26569	14.3795
3	9.826	BB	0.2823	1.13860e4	627.58807	35.5104
4	11.187	BB	0.3325	1.14573e4	520.55212	35.7328

106a (Scheme 2.2.1): *exo*: 93% ee, *endo*: 92% ee



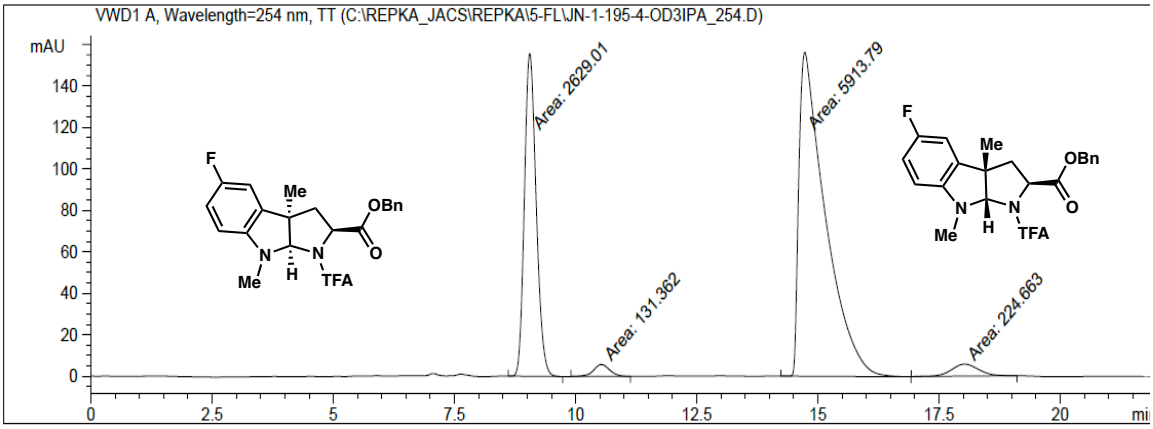
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.605	MM	0.1851	1403.04370	126.31284	21.2066
2	7.366	MM	0.2282	56.63861	4.13736	0.8561
3	9.885	MM	0.3007	188.47099	10.44562	2.8487
4	11.289	MM	0.3574	4967.92139	231.68799	75.0887

106b (Scheme 2.2.1): racemic



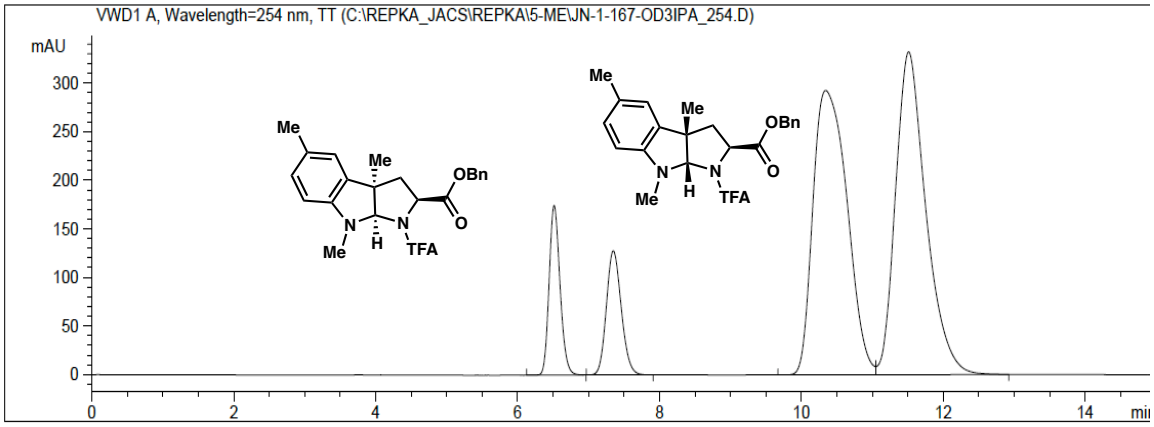
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	9.013	BB	0.2330	1253.27209	83.29908	16.6472
2	10.220	BB	0.3072	1244.32800	63.10659	16.5284
3	15.127	BB	0.5588	2519.96948	67.46533	33.4727
4	17.529	BB	0.5354	2510.85742	71.80063	33.3517

106b (Scheme 2.2.1): *exo*: 93% ee *endo*: 90% ee



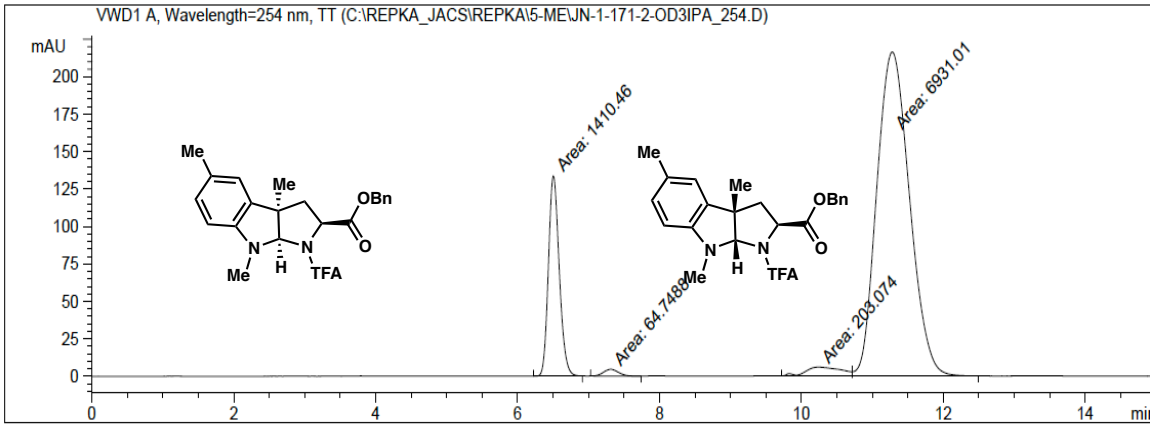
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	9.053	MM	0.2815	2629.00732	155.65556	29.5433
2	10.530	MM	0.3806	131.36226	5.75281	1.4762
3	14.729	MM	0.6305	5913.78809	156.33769	66.4559
4	18.025	MM	0.6446	224.66296	5.80853	2.5246

106c (Scheme 2.2.1): racemic



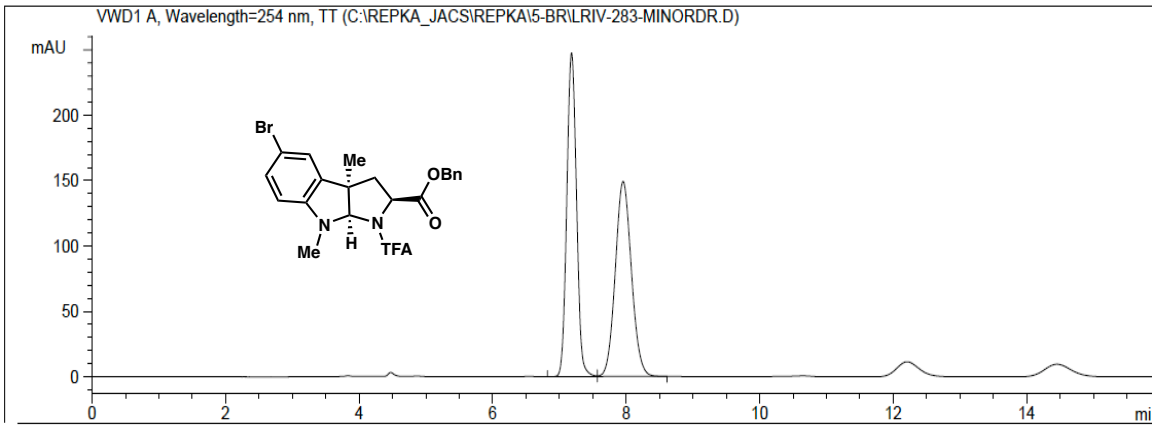
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.515	BB	0.1639	1864.59338	174.59178	7.9727
2	7.349	BB	0.2261	1861.35925	127.72897	7.9589
3	10.343	BV	0.5481	9785.77832	292.62845	41.8426
4	11.512	VV	0.4515	9875.41406	332.30096	42.2258

106c (Scheme 2.2.1): enantioenriched, *exo:* 94% ee, *endo*: 91% ee



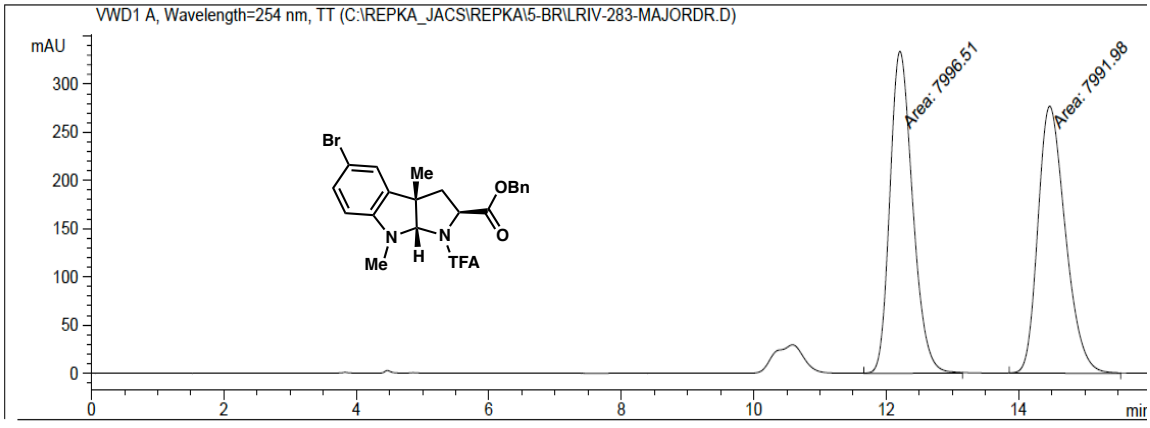
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.505	MM	0.1760	1410.45825	133.56871	16.3830
2	7.313	MM	0.2416	64.74883	4.46749	0.7521
3	10.246	MF	0.5768	203.07445	5.86773	2.3588
4	11.281	FM	0.5342	6931.01367	216.22461	80.5062

***endo*-106d** (Scheme 2.2.1): racemic



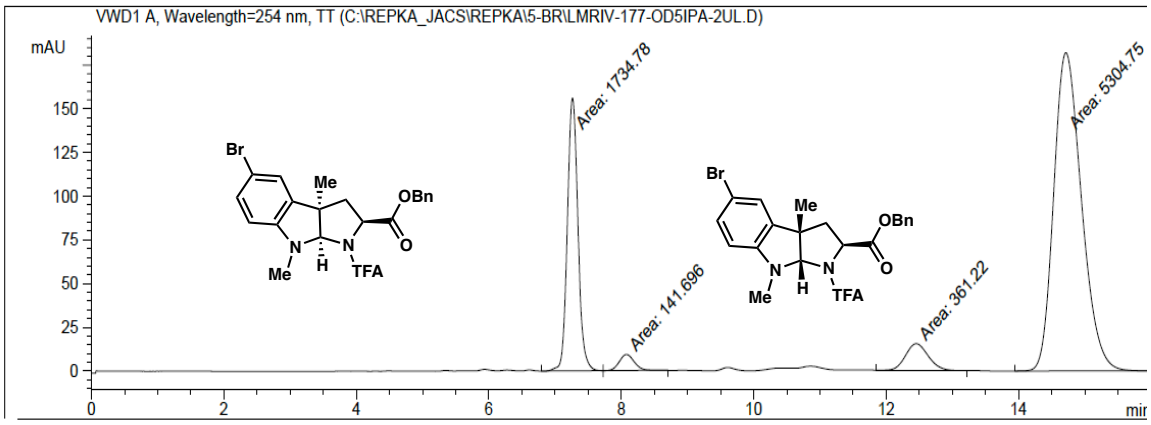
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.181	BV	0.1595	2504.75537	247.61092	50.0224
2	7.954	VB	0.2591	2502.51636	149.14781	49.9776

***exo*-106d** (Scheme 2.2.1): racemic



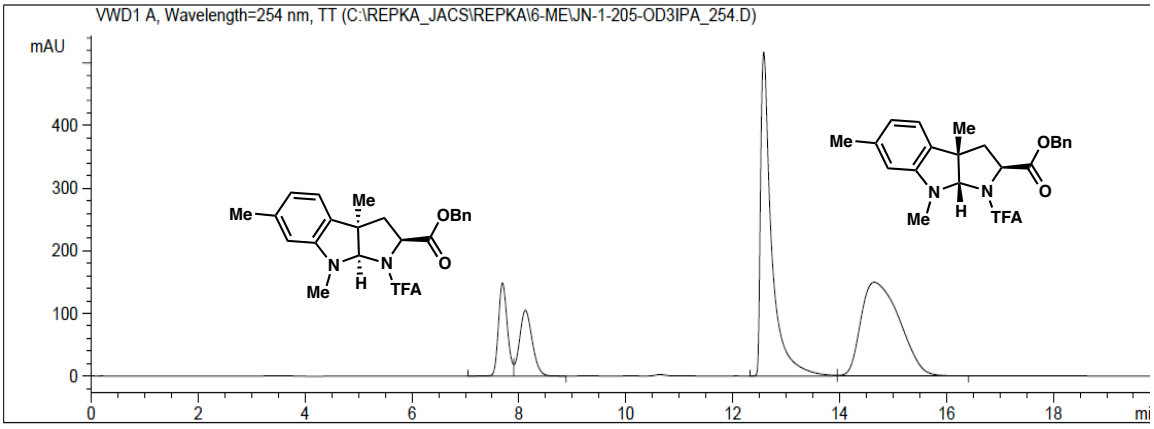
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	12.208	MM	0.3987	7996.50732	334.25320	50.0142
2	14.469	MM	0.4807	7991.97656	277.08136	49.9858

106d (Scheme 2.2.1): *exo*: 87% ee, *endo:* 85% ee



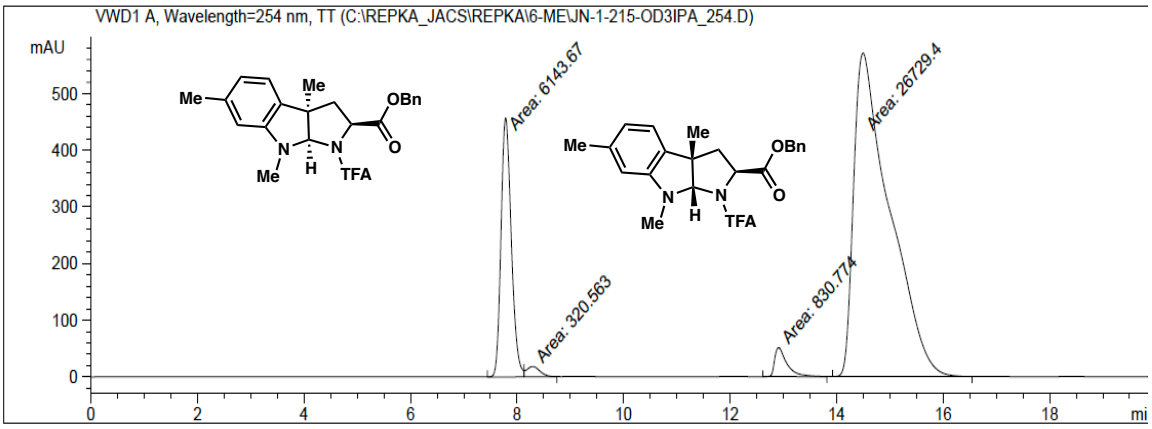
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.263	MF	0.1852	1734.78003	156.08707	23.0002
2	8.076	FM	0.2580	141.69585	9.15505	1.8786
3	12.454	MM	0.3947	361.21967	15.25336	4.7892
4	14.714	MM	0.4855	5304.75488	182.11263	70.3320

106e (Scheme 2.2.1): racemic



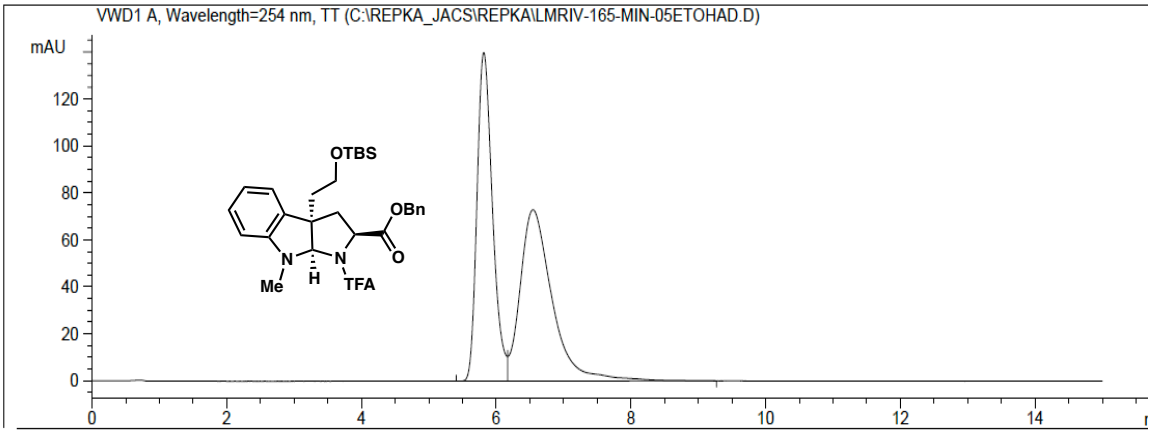
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.694	BV	0.1800	1738.04382	148.72224	9.4448
2	8.122	VB	0.2549	1740.51331	105.22092	9.4582
3	12.583	BV	0.2060	7424.35889	517.51135	40.3450
4	14.649	VB	0.7114	7499.26904	149.61671	40.7521

106e (Scheme 2.2.1): *exo*: 94% ee, *endo*: 90% ee



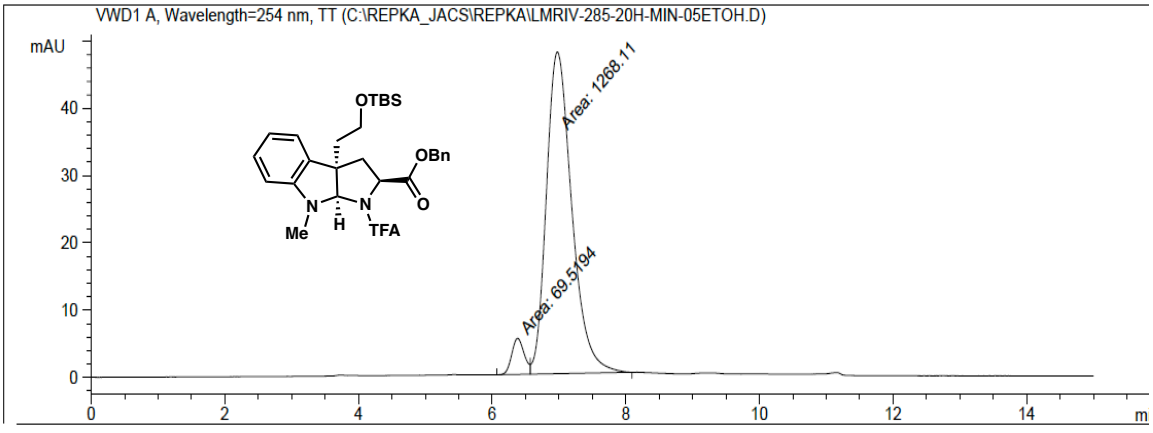
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.785	MF	0.2240	6143.67139	457.11594	18.0567
2	8.294	FM	0.2911	320.56265	18.35141	0.9422
3	12.912	MM	0.2706	830.77399	51.16518	2.4417
4	14.496	MM	0.7807	2.67294e4	570.62366	78.5595

***endo*-106f** (Scheme 2.2.1): racemic



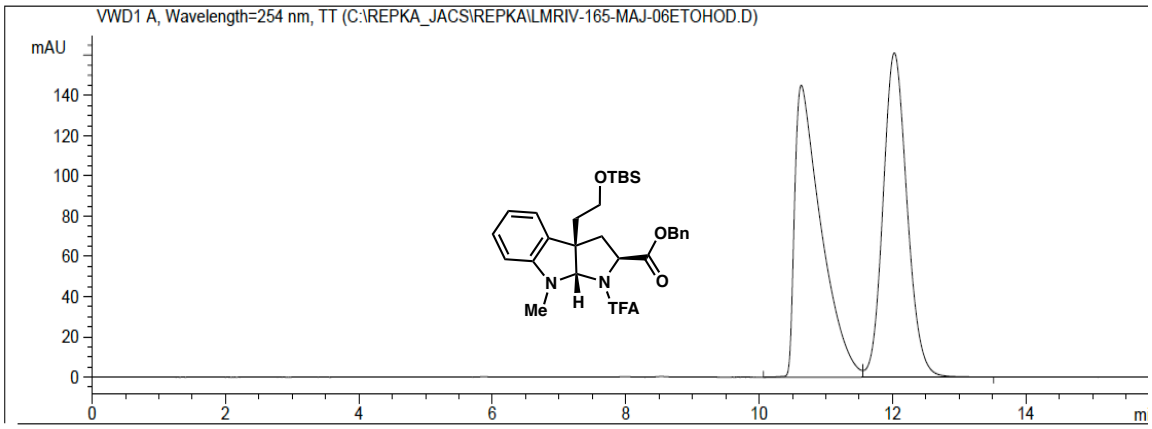
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	5.815	BV	0.2467	2234.77563	139.96280	48.1102
2	6.546	VB	0.4858	2410.33862	72.97266	51.8898

***endo*-106f** (Scheme 2.2.1): 90% ee



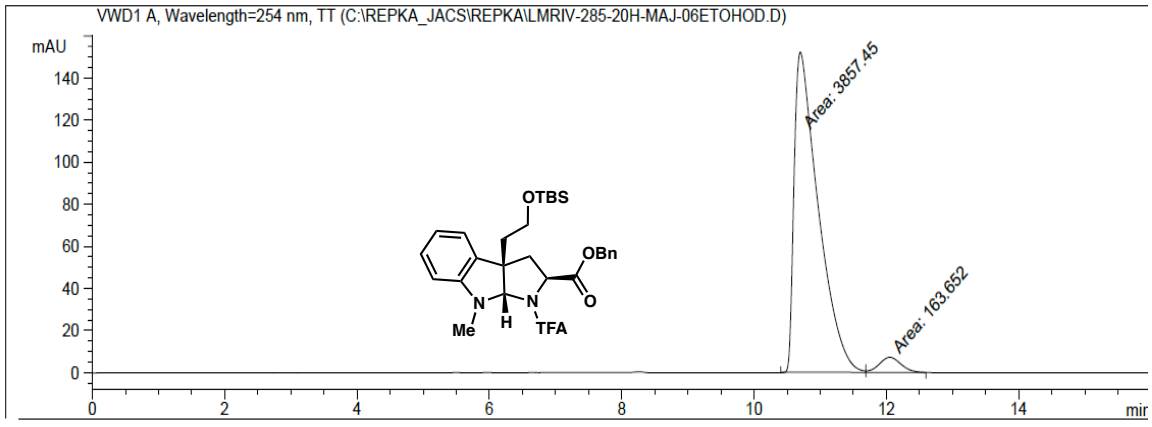
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.380	MF	0.2166	69.51939	5.34894	5.1972
2	6.976	FM	0.4419	1268.11157	47.82830	94.8028

***exo*-106f** (Scheme 2.2.1): racemic



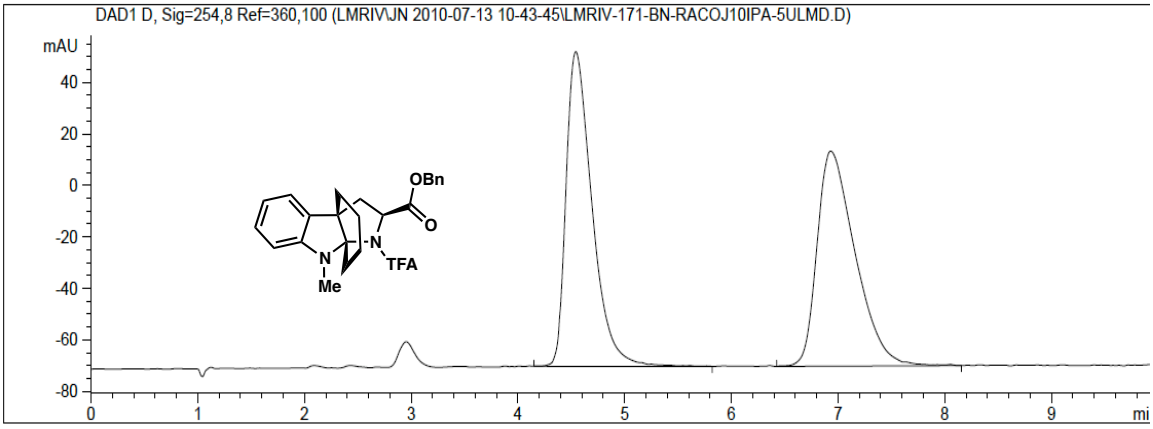
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.632	BV	0.3905	3995.52930	145.07512	49.7976
2	12.028	VB	0.3841	4028.00830	161.10678	50.2024

***exo*-106f** (Scheme 2.2.1): 92% ee



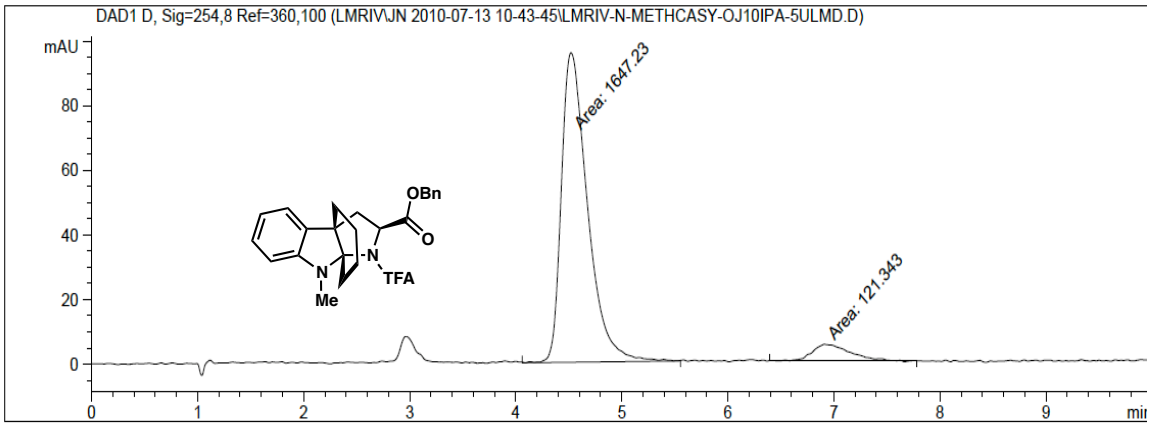
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	10.700	MF	0.4226	3857.44580	152.13763	95.9302
2	12.052	FM	0.3805	163.65164	7.16747	4.0698

106g (Scheme 2.2.1): racemic



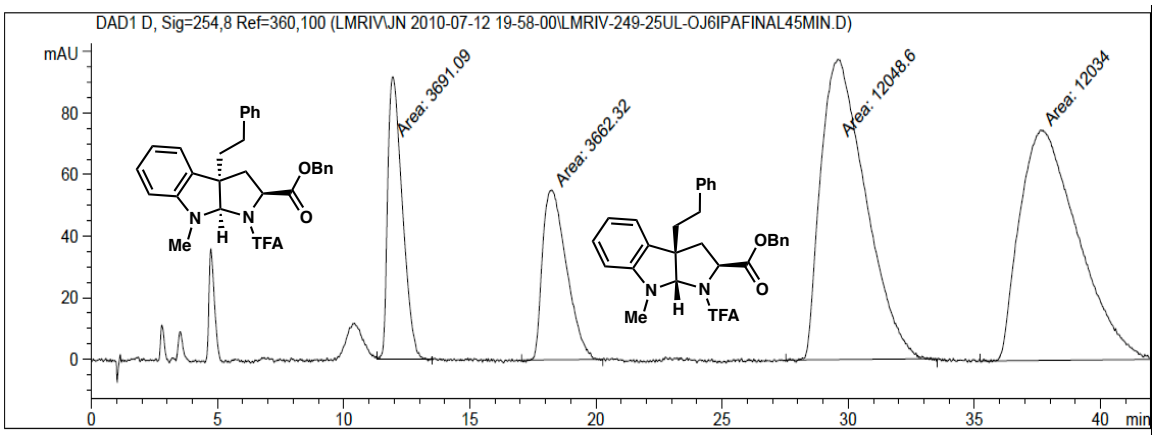
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.543	BB	0.2584	2077.59912	122.17298	50.0580
2	6.933	BB	0.3736	2072.78516	83.50713	49.9420

106g (Scheme 2.2.1): *exo:* 86% ee



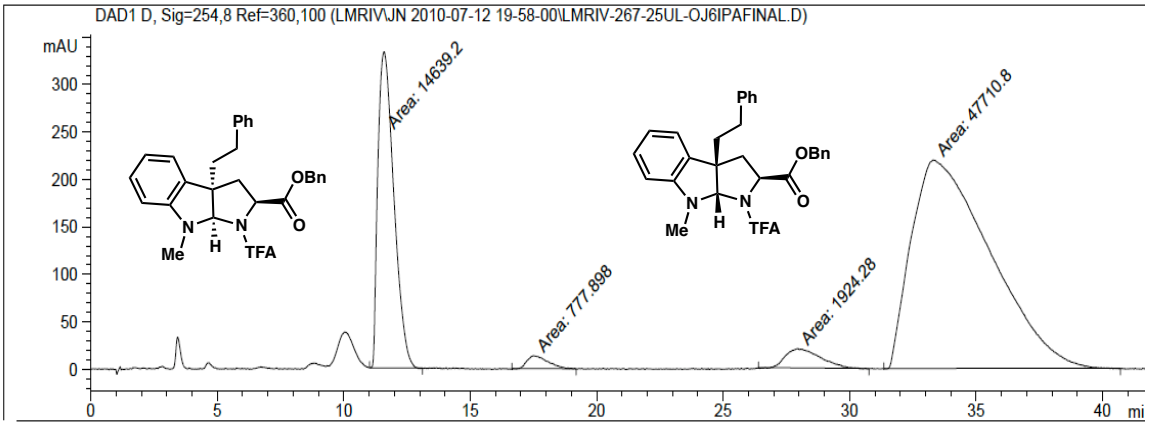
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.522	MM	0.2861	1647.22534	95.95735	93.1389
2	6.911	MM	0.3977	121.34311	5.08583	6.8611

106h (Scheme 2.2.1): racemic



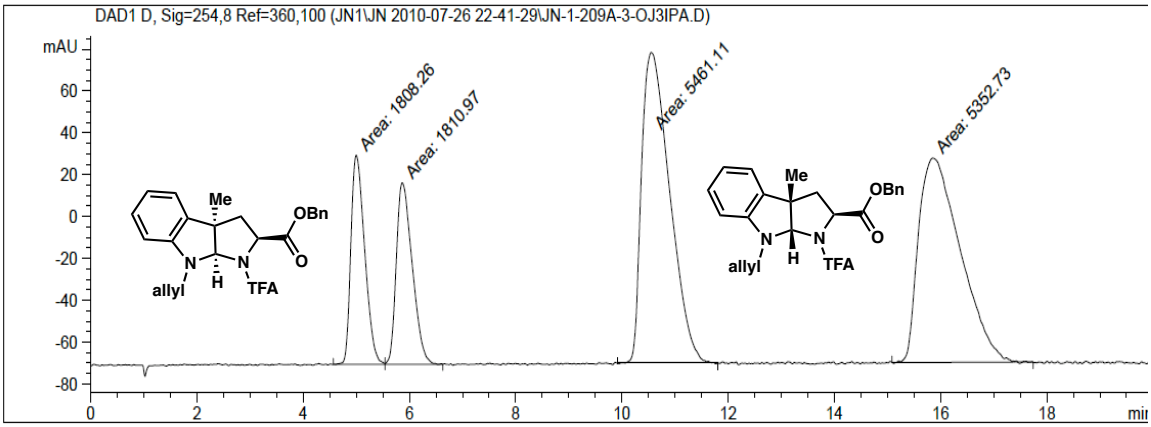
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.947	MM	0.6720	3691.09326	91.53949	11.7416
2	18.252	MM	1.1062	3662.32007	55.18063	11.6501
3	29.587	MM	2.0594	1.20486e4	97.51013	38.3273
4	37.639	MM	2.6782	1.20340e4	74.88902	38.2810

106h (Scheme 2.2.1): *exo:* 92% ee, *endo*: 90% ee



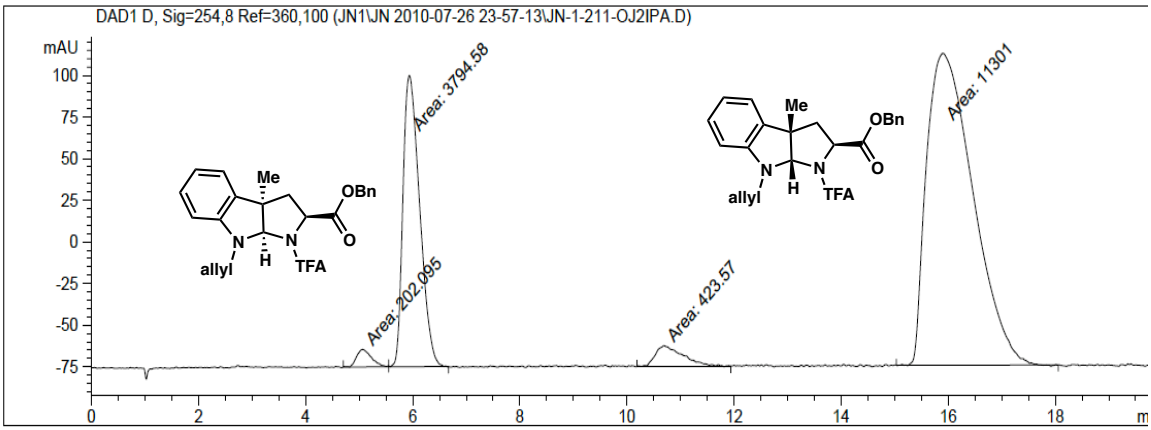
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.596	MM	0.7322	1.46392e4	333.24432	22.5038
2	17.511	MM	0.9481	777.89801	13.67496	1.1958
3	27.957	MM	1.5821	1924.28345	20.27142	2.9581
4	33.312	MM	3.6201	4.77108e4	219.65750	73.3423

106i (Scheme 2.2.1): racemic



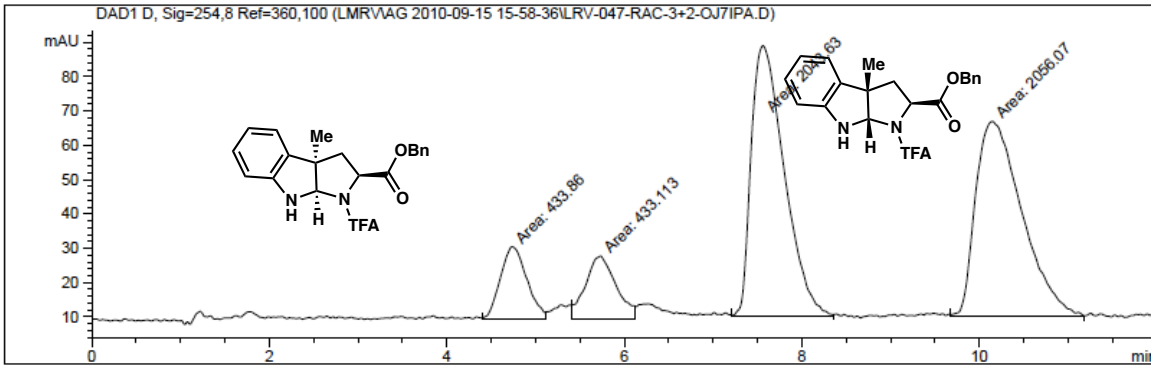
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.000	MF	0.3012	1808.26282	100.06958	12.5286
2	5.866	FM	0.3472	1810.96948	86.92387	12.5474
3	10.557	MM	0.6132	5461.11230	148.42072	37.8375
4	15.854	MM	0.9124	5352.73047	97.77415	37.0866

106i (Scheme 2.2.1): *exo*: 93% ee, *endo*: 90% ee



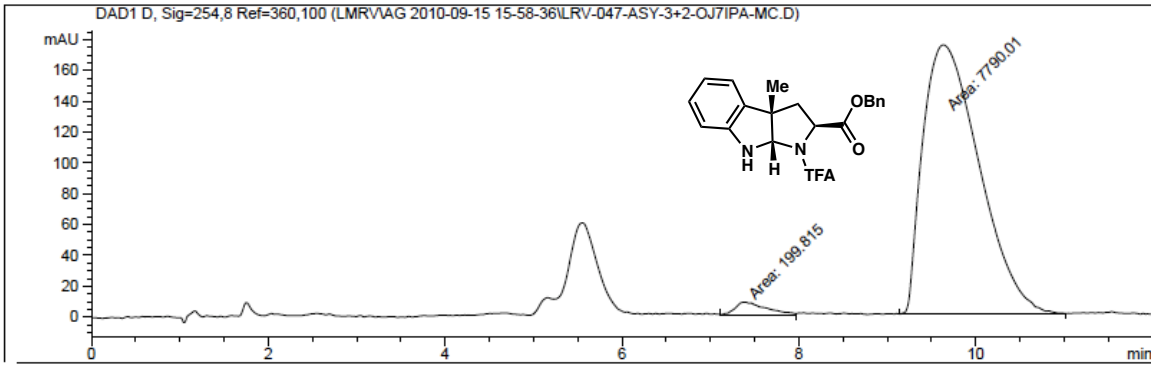
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.064	MF	0.3200	202.09525	10.52417	1.2855
2	5.937	FM	0.3612	3794.57617	175.06740	24.1367
3	10.690	MM	0.5781	423.56973	12.21119	2.6943
4	15.903	MM	1.0047	1.13010e4	187.47484	71.8835

106j (Scheme 2.2.1): racemic



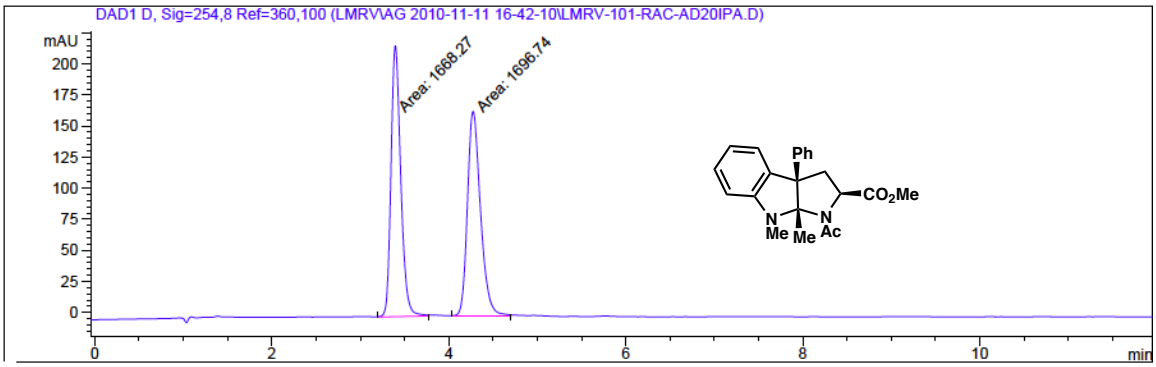
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.737	MM	0.3442	433.85974	21.00586	8.7354
2	5.733	MM	0.3971	433.11276	18.17621	8.7204
3	7.564	MM	0.4321	2043.62988	78.82232	41.1469
4	10.149	MM	0.6038	2056.07129	56.75510	41.3974

106j (Scheme 2.2.1): enantioenriched, *exo*: 95% ee



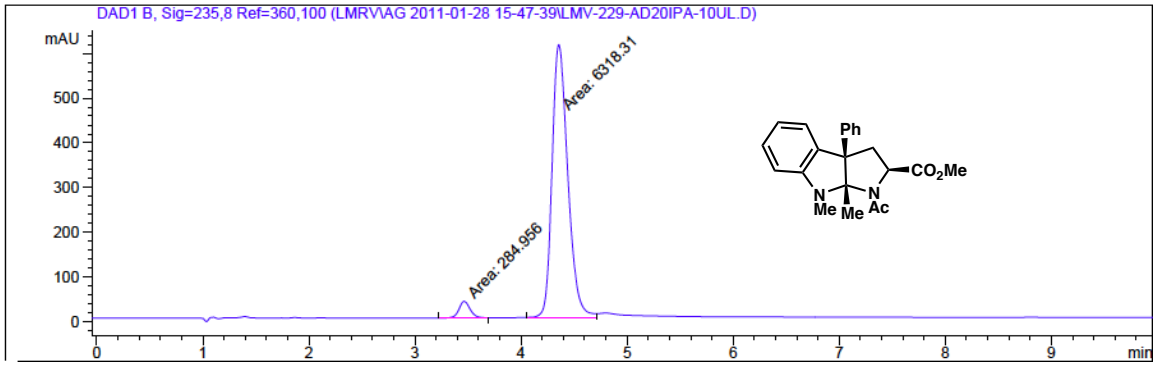
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.393	MM	0.4059	199.81528	8.20531	2.5009
2	9.640	MM	0.7421	7790.00586	174.96088	97.4991

3a-phenylpyrroloindoline 118: racemic



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.395	MM	0.1273	1668.26721	218.38173	49.5770
2	4.274	MM	0.1714	1696.73730	164.97374	50.4230

3a-phenylpyrroloindoline 118: 91% ee

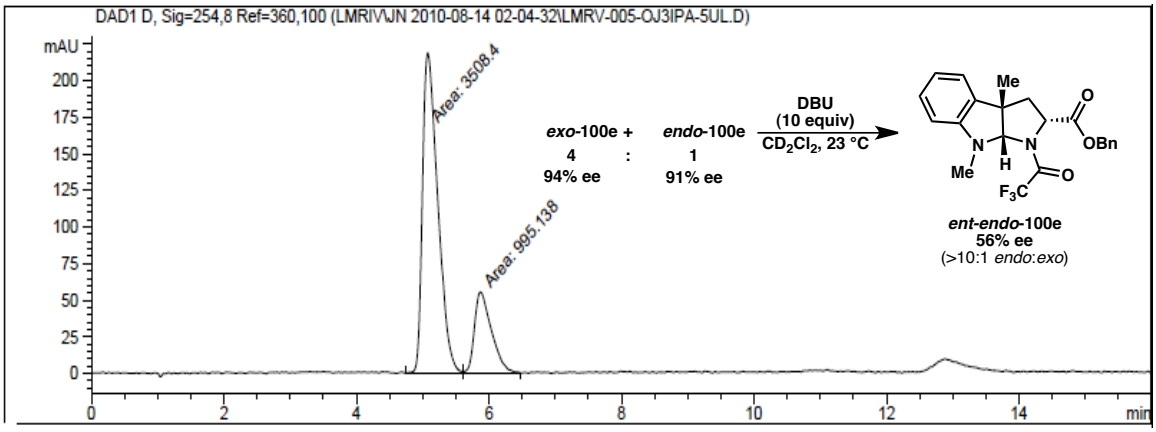


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.465	MM	0.1252	284.95630	37.91944	4.3154
2	4.357	MM	0.1722	6318.30908	611.51556	95.6846

2.5.9 General Procedure D. Epimerization Studies

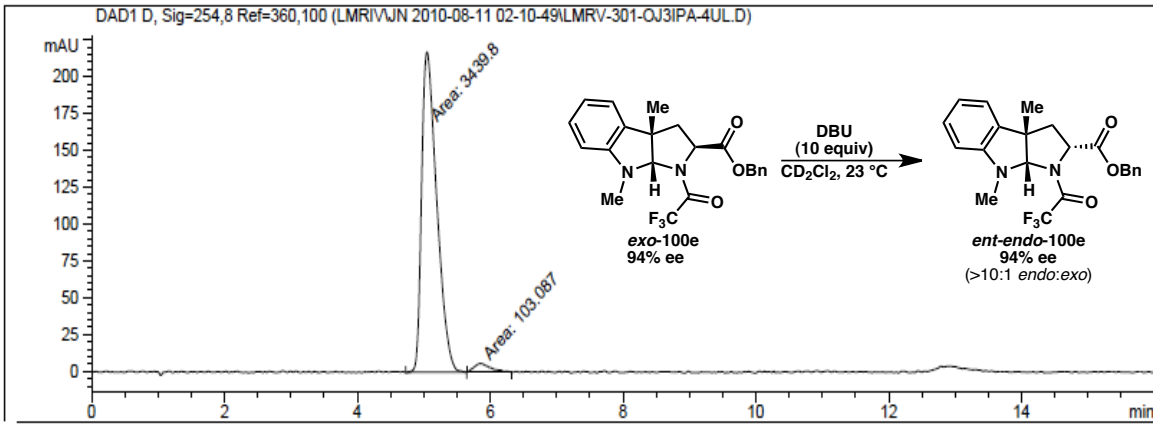
To an NMR tube was added a solution of pyrroloindoline **100e** (0.063 mmol, 1.00 equiv) in CD_2Cl_2 (0.46 mL), followed by DBU (0.63 mmol, 10.00 equiv). The reaction was monitored by ^1H NMR until the ratio of diastereomers reached an equilibrium. At this point the reaction was diluted with 3 mL $CHCl_3$ 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*-100e** (94% ee) **+** ***endo*-100e** (91% ee) with DBU (10 equiv) for 65 h to give >10:1 ***ent-endo*-100e** (56% ee).



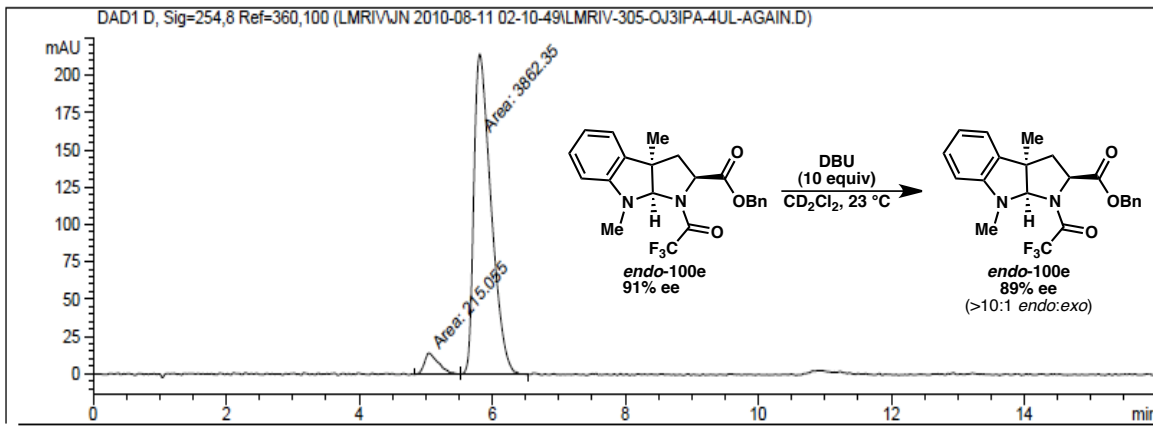
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.078	MM	0.2670	3508.40381	218.96385	77.9032
2	5.872	MM	0.2984	995.13763	55.57482	22.0968

Experiment 2: Treatment of diastereomerically pure ***exo*-100e** (94% ee) with DBU (10 equiv) for 96 h to give >10:1 ***ent-endo*-100e** (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*-100e** (91% ee) with DBU (10 equiv) for 30 h to return ***endo*-100e** (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

2.5.10 Resubjection of Pure Exo and Endo Pyrroloindolines to Reaction Conditions

To an NMR tube was added a solution of pure pyrroloindoline *exo*-**100e** (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*-**100e** (91% ee), except at a concentration of 0.065 M. In both cases, no epimerization or erosion of ee was observed.

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