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Direct, enantioselective synthesis of pyrroloindolines and indolines from simple indole derivatives

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ABSTRACT

The (*R*)-BINOL·$SnCl_4$-catalyzed formal (3+2) cycloaddition between 3-substituted indoles and benzyl 2-trifluoroacetamidoacrylate is a direct, enantioselective method to prepare pyrroloindolines from simple starting materials. However, under the originally disclosed conditions, the pyrroloindolines are formed as mixtures of diastereomers, typically in the range of 3:1 to 5:1 favoring the *exo*-product. The poor diastereoselectivity detracts from the synthetic utility of the reaction. We report here that use of methyl 2-trifluoroacetamidoacrylate in conjunction with (*R*)-3,3′-dichloro-BINOL·$SnCl_4$ provides the corresponding pyrroloindolines with improved diastereoselectivity (typically ≥10:1). Guided by mechanistic studies, a one-flask synthesis of enantioenriched indolines by in situ reduction of a persistent iminium ion is also described.

1. Introduction

Nitrogen-containing heterocycles, such as indolines[1] and pyrroloindolines,[2] are prevalent in a variety of natural products that exhibit an array of promising biological activities (see Fig. 1 for representative examples).[3] Many of these compounds possess all-carbon quaternary stereocenters at C3 of the indoline or pyrroloindoline, and the synthetic challenge presented by this structural feature has driven innovative research aimed at the discovery of new methods to stereoselectively prepare such heterocycles. These methods include several stereoselective transformations starting from tryptophan,[4] as well as catalytic asymmetric reactions using both organo-[5] and transition metal catalysts.[6]

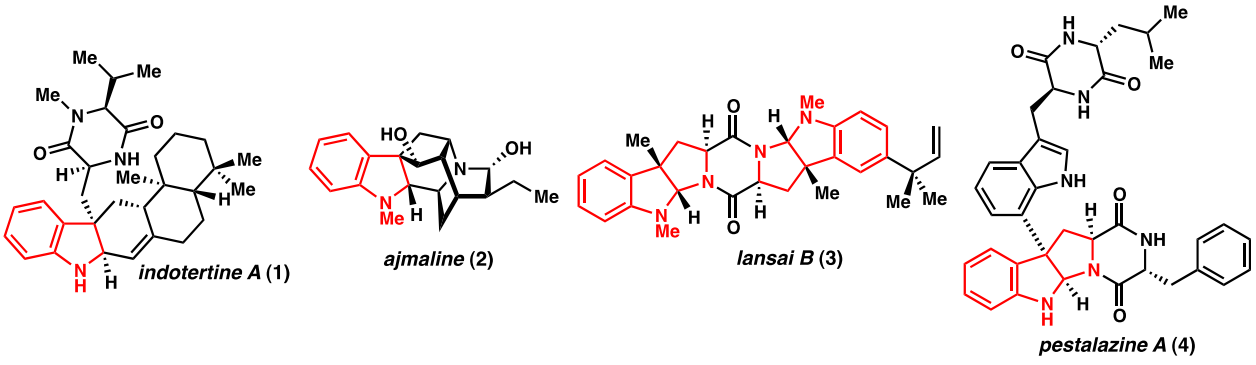

Fig. 1. Indoline and pyrroloindoline containing natural products.

In 2010, our group reported an enantioselective synthesis of pyrroloindolines (**8**) via an (*R*)-BINOL·$SnCl_4$-catalyzed formal (3+2) cycloaddition between 3-substituted indoles (**5**) and benzyl 2-trifluoroacetamidoacrylate (**6**) (Scheme 1).[7] Good yields, moderate

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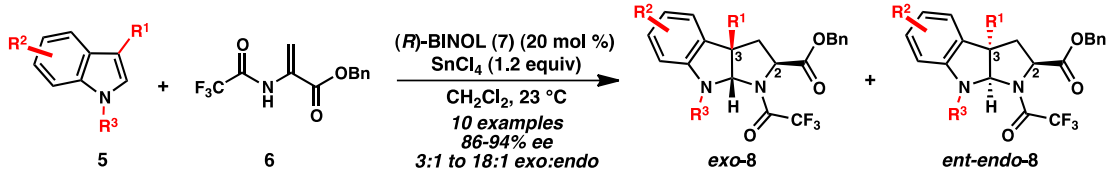
exo/*endo* diastereoselectivity, and high enantioselectivities were obtained for a variety of indole substrates. Unexpectedly, studies aimed at epimerizing C2 revealed that *exo*-**8** and *endo*-**8** possess the opposite absolute configurations at the bridgehead carbons.

The proposed mechanism is consistent with Yamamoto's prior reports that (*R*)-BINOL·$SnCl_4$ (**11**) behaves as a Lewis acid-assisted Brønsted acid (LBA), which is capable of catalyzing the enantioselective protonation of silyl enolates.[9] However, the

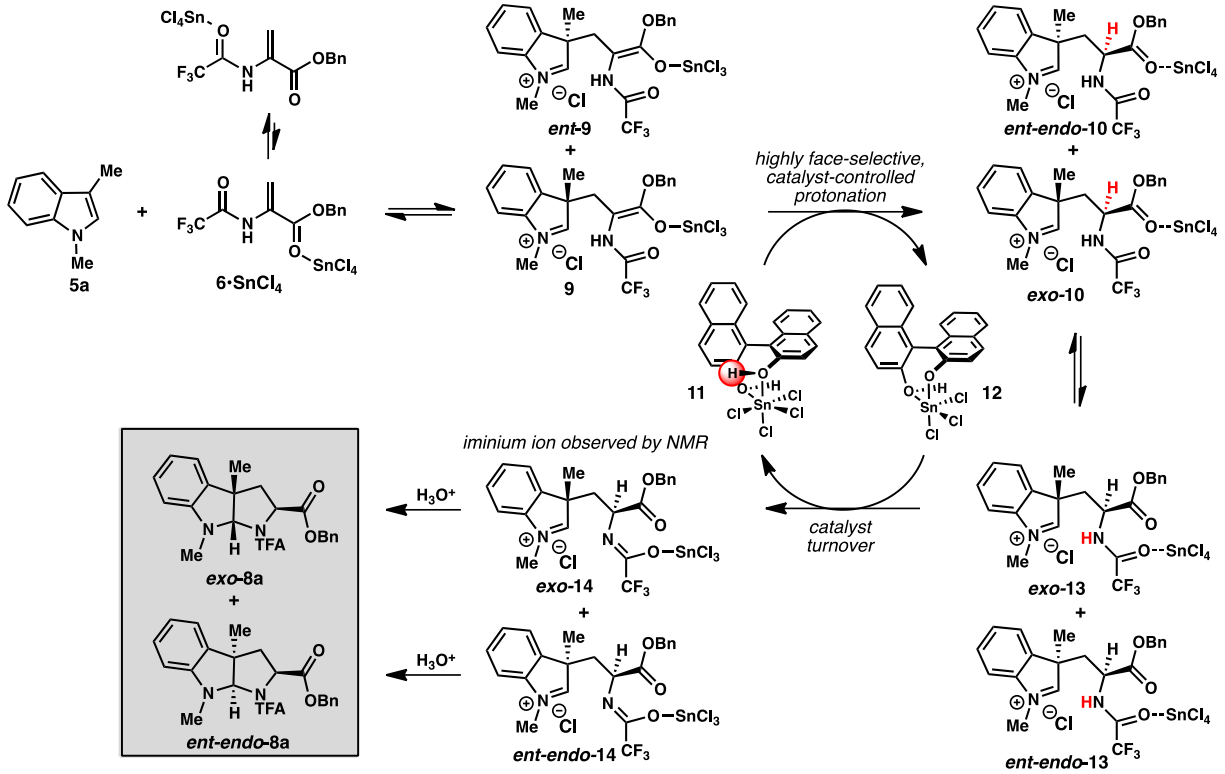


Scheme 1. (*R*)-BINOL·$SnCl_4$-catalyzed pyrroloindoline formation.

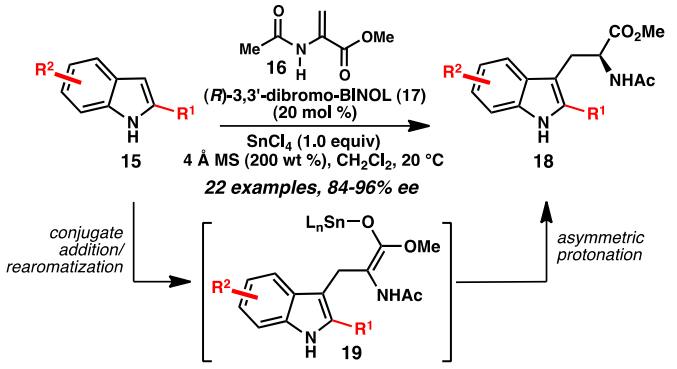
Although further mechanistic studies are required, this observation led us to propose a cooperative Lewis acid/Lewis acid-assisted Brønsted acid (LBA) mechanism, shown in Scheme 2. Activation of acrylate **6** by coordination to $SnCl_4$ would result in reversible conjugate addition by the indole to generate a racemic mixture of Sn-enolates **9** and *ent*-**9**. Highly face-selective protonation of **9**/*ent*-**9** by an (*R*)-BINOL·$SnCl_4$ complex (**11**) would serve to resolve the two enantiomers into diastereomers in a rate- and stereoselectivity-determining step. In this scenario, the ee of the two pyrroloindoline products would reflect the facial selectivity of the protonation step, while the dr would reflect the difference in protonation rates for the two chiral enolates **9** and *ent*-**9**, due to matching and mismatching effects with chiral complex **11**.[8] The stoichiometric proton source required to turn over complex **12** could potentially be the N–H of trifluoroacetamide *exo*-**13**/*ent-endo*-**13**, which upon coordination to $SnCl_4$ would be rendered sufficiently acidic.

pyrroloindoline formation described above constitutes the first example of a tandem conjugate addition/asymmetric protonation process catalyzed by **11**. Based on our mechanistic proposal for pyrroloindoline formation, we recently identified similar conditions for the synthesis of unnatural tryptophan derivatives (**18**) from 2-substituted indoles (**15**) and methyl 2-acetamidoacrylate (**16**), in which the sole stereogenic center is set during an asymmetric protonation step (Scheme 3).[10] This tandem Friedel–Crafts conjugate addition/asymmetric protonation reaction provides direct access to a variety of tryptophan derivatives (**18**) without the need for pre-functionalization of the indole substrate.

Returning to the enantioselective pyrroloindoline synthesis shown in Scheme 1, the fact that *exo*-**8** and *ent-endo*-**8** are of opposite enantiomeric series presents a practical challenge for synthetic applications. Specifically, in order to preclude erosion of ee during subsequent synthetic steps, it is imperative to separate the



Scheme 2. Proposed mechanism for pyrroloindoline formation.



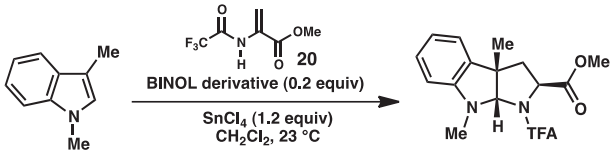
Scheme 3. **17**·$SnCl_4$-catalyzed conjugate addition/asymmetric protonation.

two diastereomers. Unfortunately, depending on the indole substitution pattern, separation of the diastereomers can be tedious using standard silica gel chromatography. In addition, the modest diastereoselectivity results in lower isolated yields of the pure *exo*-diastereomer. In an effort to identify conditions more amenable to application in total synthesis endeavors, we sought to re-optimize the reaction parameters for the formal (3+2) cycloaddition with the objective of improving the *diastereoselectivity* while maintaining synthetically useful enantioselectivity. Herein, we report the successful realization of this objective, as well as mechanism-guided studies that resulted in the development of a one-flask reduction process for the direct synthesis of related indoline derivatives.

2. Results and discussion

The optimization studies disclosed in our original report determined that the enantio- and diastereoselectivity of pyrroloindoline formation was highly dependent on the substitution of the 2-amidoacrylate: the highest *enantioselectivity* was obtained using benzyl 2-trifluoroacetamidoacrylate (**6**), while the highest *diastereoselectivity* was attained using methyl 2-trifluoroacetamidoacrylate (**20**) (Scheme 4). In the latter case, the ee's of the two diastereomers were only modestly reduced. Thus, we returned to the use of acrylate **20** in the cycloaddition, and sought to improve the ee and dr by optimizing the catalyst structure.

Table 1
Catalyst screen

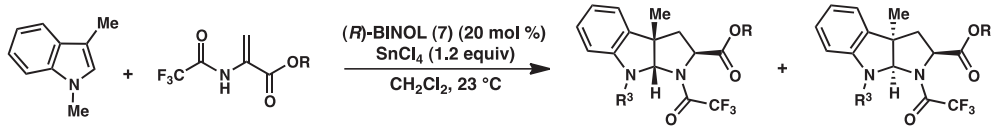


Entry	BINOL derivative	Yield (%)[a]	dr[b]	ee (%)[c]
1	H (**7**)	88	10:1	90
2	6,6′-$(OMe)_2$ (**22**)	63	6:1	82
3	6,6′-Br_2 (**23**)	65	8:1	86
4	3,3′-Me_2 (**24**)	63	8:1	90
5	3,3′-Br_2 (**17**)	63	16:1	90
6	3,3′-Cl_2 (**25**)	73	14:1	91

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

With these newly optimized conditions in hand, a survey of indole substrates was conducted (Table 2). As previously observed, indoles bearing electron-donating substituents on the aryl backbone provide the highest yields; however, both electron-rich and electron-poor substrates provide high ee's. More sterically-hindered indoles are less reactive and require 1.6 equiv of $SnCl_4$, but nevertheless furnish the desired pyrroloindolines in good yield with high selectivity.

Having identified conditions that provide the pyrroloindoline products with improved diastereoselectivity, we sought to obtain further mechanistic insight by monitoring the reaction using in situ ^1H NMR spectroscopy. For this purpose, we returned to the reaction between 1,3-dimethylindole (**5a**) and benzyl 2-trifluoroacetamidoacrylate (**6**) because it is homogeneous over the course of the reaction. Fig. 2 shows a sample of ^1H NMR spectra taken over the first 9 h of the reaction, and reveals several interesting aspects of this transformation. Notably, upon addition of $SnCl_4$ and (*R*)-BINOL (**7**) to a mixture of **5a** and **6**, the indole proton resonances broaden significantly (Fig. 2, t=0). This broadening is also observed in the absence of acrylate **6**; however, $SnCl_4$ alone does not alter the ^1H NMR spectrum of **5a**. It is possible that this broadening is due to a rapid, dynamic proton exchange process promoted by **7**·$SnCl_4$,



R	*exo*:*endo*	% ee_{exo}
Bn (6)	4:1	94
Me (20)	10:1	90

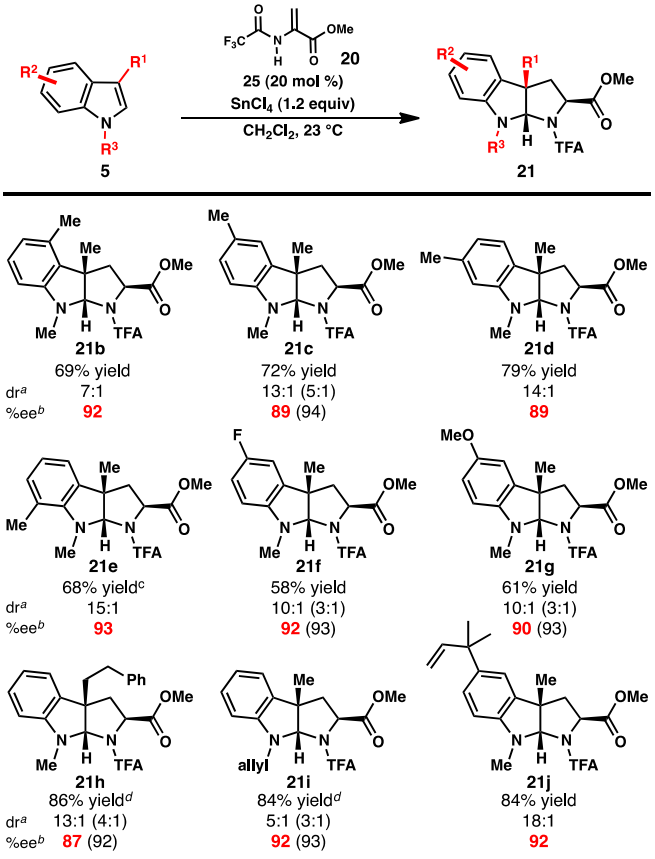
Scheme 4. Dependence of diastereoselectivity on acrylate substitution.

A screen of (*R*)-BINOL derivatives revealed that several catalysts containing substitution at the 3- and 3′-positions provided an improvement in both dr and ee. Hypothesizing that catalyst selectivity might correlate to the pK_a of the BINOL O–H protons, several 6,6′-derivatives were also prepared in order to isolate the electronic and steric effects; however, no linear correlation was observed. Ultimately, (*R*)-3,3′-Cl_2-BINOL (**25**) was identified as the catalyst that provided the optimal combination of ee, dr, and overall yield (Table 1).

which is consistent with the finding that deuterated **5a** undergoes rapid D–H exchange under the reaction conditions. Interestingly, the chemical shifts of the acrylate remain unchanged, indicating that there is no significant accumulation of an acrylate–$SnCl_4$ complex. Over the course of the reaction, resonances corresponding to an indole–acrylate adduct grow in; however, these peaks do not correspond to the pyrroloindoline product.

We hypothesized that in the presence of a strong Lewis acid, such as $SnCl_4$, coordination of the amide might favor the ring-

Table 2
Substrate scope of pyrroloindoline formation



[a] Determined by ^{1}H NMR analysis of crude reaction mixture. Values in parentheses are dr obtained using acrylate **6** and catalyst **7**. [b] Determined by SFC using chiral stationary phase. Values in parentheses are ee obtained using acrylate **6** and catalyst **7**. [c] Isolated yield of *exo*-diastereomer. [d] 1.6 equiv $SnCl_4$ was employed.

opened iminium ions *exo*-**14**/*ent-endo*-**14**. To test this hypothesis, we resubjected diastereomerically pure *exo*-**8a** to $SnCl_4$ (1.2 equiv) and varying equivalents of (*R*)-BINOL (**7**) (Fig. 3). The NMR spectra of the mixtures were dependent on the concentration of **7**. In the presence of 20 mol % **7**, the ^{1}H NMR spectrum closely resembles that of the indole–acrylate adduct observed in the ^{1}H NMR experiment. Notably, this species exhibits a resonance between 9 and 10 ppm (depending on concentration of **7**, Fig. 3a and b), which we assign to the indolinium proton (H_b). In addition, the *N*-methyl group (H_a) in this species is shifted downfield relative to the pyrroloindoline (4.0 ppm vs 3.1 and 2.9 ppm for the two rotamers of the *exo*-diastereomer), and is consistent with literature data for other iminium ions.[11] This structural assignment is further supported by 2D ^{1}H–^{13}C NMR correlation data. In the presence of $SnCl_4$ alone, the pyrroloindoline peaks broaden, likely due to dynamic interconversion between the ring-opened and -closed forms (Fig. 3c). The fact that addition of 1.2 equiv of **7** resolves this mixture into one species suggests that **7**·$SnCl_4$, an LBA,[9a] might preferentially stabilize the open structure. Importantly, following aqueous work-up, pyrroloindoline *exo*-**8a** is cleanly reisolated with no indication of epimerization or racemization.

The progress of the reaction can be quantified by integrating the vinyl protons of the acrylate relative to 1,4-diethylbenzene as an internal standard. However, further kinetic analysis of the (*R*)-BINOL-catalyzed reaction has been complicated by several factors, including the racemic background reaction (particularly at higher $SnCl_4$: (*R*)-BINOL ratios) and product inhibition.

Given that iminium ions *exo*-**14**/*ent-endo*-**14** are observed under the reaction conditions, we wondered if it would be possible to trap these intermediates with an external hydride source. The resulting product would be an indoline-containing amino acid derivative bearing an all-carbon quaternary stereocenter at the C3-position (Scheme 5). Commonly employed strategies for the enantioselective generation of indolines include asymmetric hydrogenation of prochiral indoles,[12] reduction of oxindoles,[13] C–H activation of substituted anilines,[14] and kinetic resolution of racemic mixtures of indolines.[15] However, these methods are often limited in scope or require multiple steps.

To assess the feasibility of our proposed transformation, the formal (3+2) cycloaddition was performed under the previously optimized conditions, but in the presence of a reductant (Table 3). Whereas weaker reductants such as triethylsilane and sodium triacetoxyborohydride proved ineffective, we were pleased to find that use of Hantzsch ester **29** did provide the indoline product, albeit in low yield (entry 3). Alternatively, use of sodium borohydride furnishes **28a** in good yield, 15:1 dr, and 92% ee (entry 5). The more soluble reducing agent lithium borohydride provided a lower yield of the desired product along with a greater amount of byproducts. The limited solubility of $NaBH_4$ and $LiBH_4$ in methylene chloride likely contributes to the compatibility of all the reagents, allowing the reaction to be carried out in one pot.

Having identified an optimal reducing agent, a survey of indole substrates was conducted (Table 4). Indoles with either electron-donating or -withdrawing substituents are good substrates for the reaction. At the 3-position, *n*-butyl and phenylethyl groups are tolerated, but reactivity decreases with increasing steric bulk, and 1.6 equiv of $SnCl_4$ are required to achieve good reactivity. Whereas cleavage of the protecting group was observed when TBS-protected tryptophol was employed, use of the TIPS-protected trpytophol furnished **28k** in good yield. The indole nitrogen can also be protected with an allyl group, making this method more useful when an *N*-Me functionality is not desired in the product.

The reduced products **28** are formed with the same diastereomeric and enantiomeric ratios as the corresponding pyrroloindolines, suggesting that the reduction does not affect the selectivities of the other steps. If a methylene chloride solution of pyrroloindoline *exo*-**8a** and $SnCl_4$ is re-exposed to sodium borohydride, the pyrroloindoline is reduced to indoline **28a** in quantitative yield (Scheme 6).

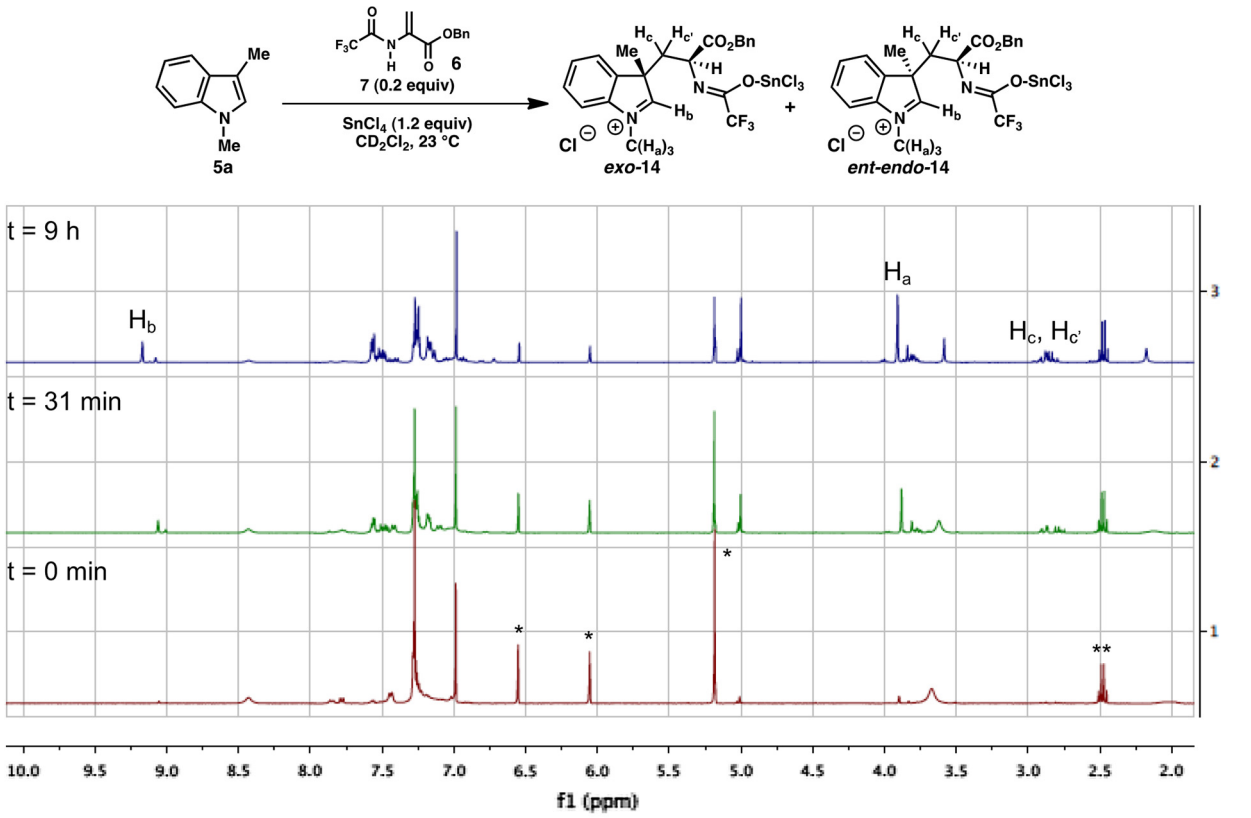
3. Conclusion

Building on our initial report of a formal (3+2) cycloaddition between 3-substituted indoles and 2-amidoacrylates to yield enantioenriched pyrroloindolines, we have further optimized the catalyst structure to significantly improve the diastereoselectivity of this reaction while maintaining comparable yields and ee's. Subsequent NMR studies have provided a more thorough understanding of this reaction, revealing that the initial product of the reaction is an indolinium ion. Based on these findings, a method has been developed to trap this intermediate with sodium borohydride to yield enantioenriched indoline products with a quaternary stereocenter at C3. The study and development of additional transformations that proceed by cooperative Lewis acid–LBA mechanisms are the subject of ongoing research in our laboratory.

4. Experimental section

4.1. General

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran



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

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

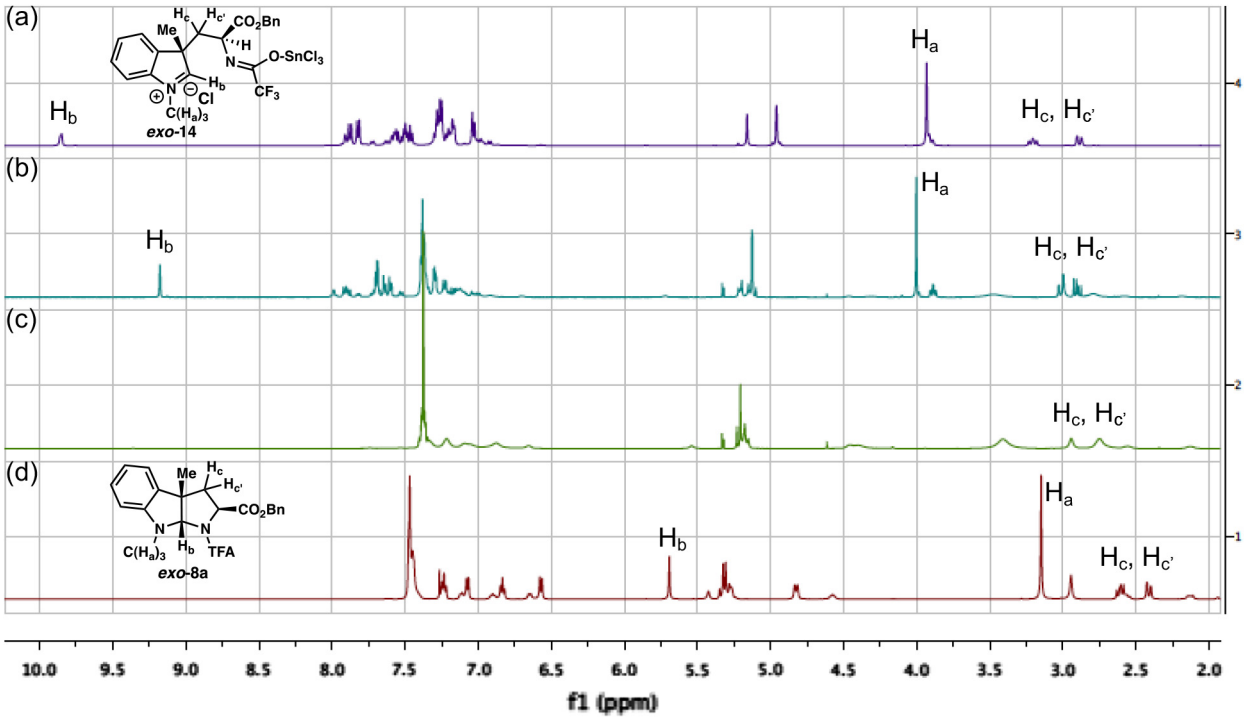
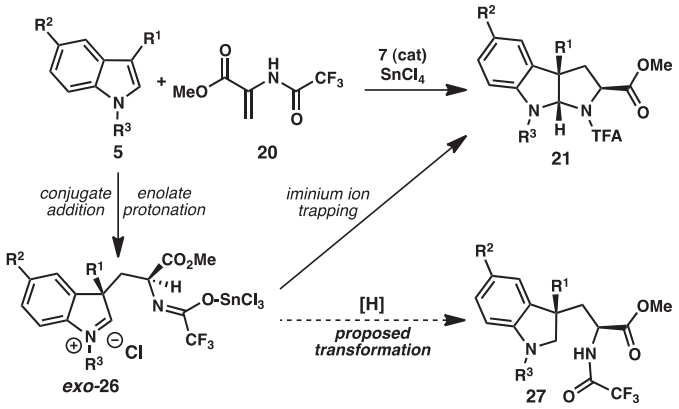
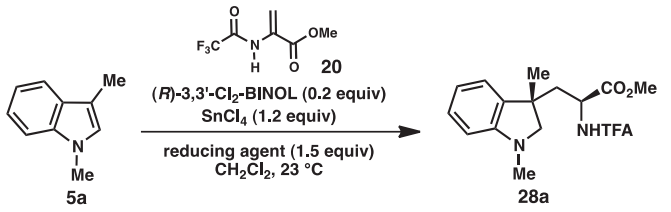


Fig. 3. NMR spectra of (a) pyrroloindoline *exo*-**8a**, $SnCl_4$ (1.2 equiv), (*R*)-BINOL (**7**) (1.2 equiv) (b) pyrroloindoline *exo*-**8a**, $SnCl_4$ (1.2 equiv), (*R*)-BINOL (**7**) (0.2 equiv) (c) pyrroloindoine *exo*-**8a**, $SnCl_4$ (1.2 equiv) (d) pyrroloindoline *exo*-**8a**.



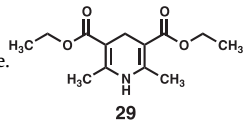
Scheme 5. Intercepting an iminium ion intermediate to yield indolines.

Table 3
Screen of reducing agents



Entry	Reductant	Yield (%)
1	Et_3SiH	0
2	$NaBH(OAc)_3$	0
3	Hantzsch ester **29**	3
4	$LiBH_4$	85
5	$NaBH_4$	93[a]

[a] Product isolated in 15:1 dr and 92% ee.



(THF), methylene chloride (CH_2Cl_2), and toluene were dried by passing through activated alumina columns. Deuterated methylene chloride (CD_2Cl_2) was dried by passing through a plug of activated alumina in a glovebox. Dimethylformamide (DMF) was dried over activated molecular sieves, dichloroethane (DCE) was distilled over calcium hydride. All other commercially obtained reagents were used as received unless specifically indicated. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F_{254} pre-coated plates (0.25 mm). Flash column chromatography was performed either as described by Still et al. (Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.) using silica gel (particle size 0.032–0.063) purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Diastereomeric ratios were determined by integration of crude NMR spectra. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz, respectively), a Varian 400 (at 400 MHz and 100 MHz, respectively) or a Varian Inova 500 (at 500 MHz and 125 MHz, respectively), and are reported relative to internal chloroform (^1H, δ=7.26, ^{13}C, δ=77.0). Data for ^1H NMR spectra are reported as follows: chemical shift (δ parts per million) (multiplicity, coupling constant (Hertz), 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}). Preparatory HPLC was performed with either an Agilent 1100 or 1200 Series HPLC utilizing an Agilent Zorbax RX-SIL 5 μm column (9.4×250 mm). Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system with Chiralcel AD-H, OJ-H columns (4.6 mm×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.

Abbreviations used: BINOL: 1,1′-Bi(2-naphthol); IPA: isopropanol; dba: dibenzylidineacetone.

4.2. Preparation of indole substrates

4.2.1. 1,3,4-Trimethyl-1H-indole. Procedure for Vilsmeier–Haack reaction followed by $LiAlH_4$ reduction was adapted from Petit et al.[16] In a flame-dried flask under nitrogen, $POCl_3$ (0.42 mL, 4.6 mmol) was added at 0 °C to 4-methyl-1*H*-indole (0.5 g, 3.8 mmol) in DMF (7.6 mL). The reaction was stirred at room temperature overnight. 2 N $NaOH_{(aq)}$ was then added, the solution was stirred for 2 h, then poured into EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude aldehyde was carried forward without further purification.

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

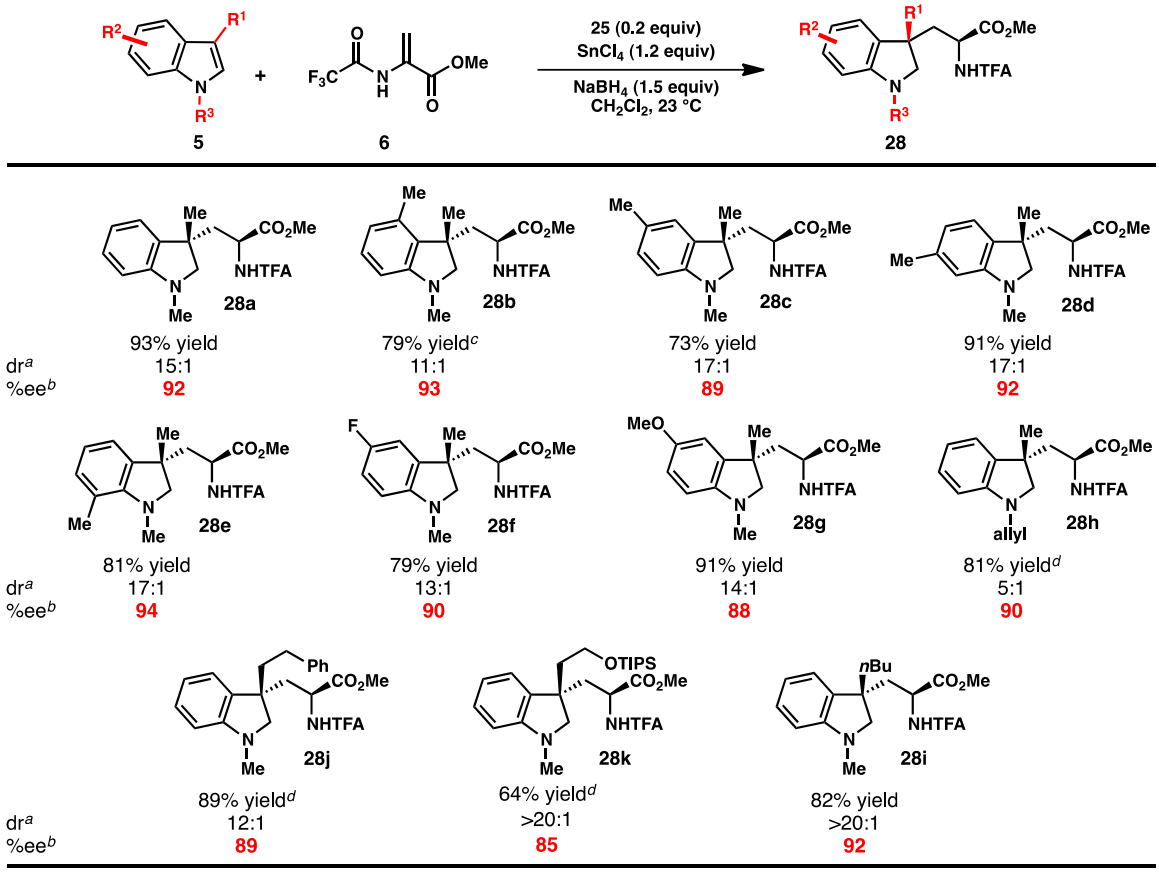
In a flame-dried flask, the indole (0.3 g, 2.1 mmol) was dissolved in THF (13 mL). Sodium hydride (60% w/w, 124 mg, 3.1 mmol) was added in one portion, then methyl iodide (0.26 mL, 4.1 mmol) was added dropwise. The reaction was stirred at room temperature until consumption of starting material was observed by TLC. The reaction was diluted with ethyl acetate and the excess NaH was quenched with water. The organic layer was separated, and the aqueous layer was extracted 3× with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography. 44% yield over three steps.

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

4.2.2. 1,3,7-Trimethyl-1H-indole. Prepared according to the procedure for 1,3,4-trimethyl-1*H*-indole. Spectral data matches that reported in the literature.[17]

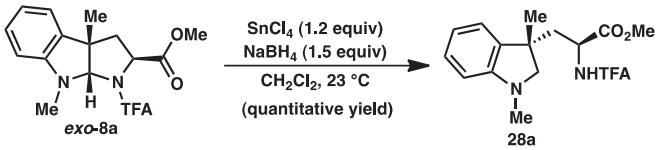
4.2.3. 1,3-Dimethyl-5-reverse prenyl-1H-indole. In a glovebox, $Pd_2(dba)_3$ (51 mg, 6 mmol) and SPhos (91 mg, 22 mmol) in THF (3 mL) were stirred at room temperature for 1 h until a dark yellow homogeneous solution was formed. The solution was then transferred to a Schlenk tube, and 5-iodo-1,3-dimethyl-1*H*-indole

Table 4
In situ reduction for the synthesis of indolines



[a] Determined by ^{1}H NMR analysis of crude reaction mixture.
[b] Determined by SFC using chiral stationary phase.
[c] Isolated yield of *exo*-diastereomer. [d] 1.6 equiv $SnCl_4$ was employed.

(300 mg, 1.11 mmol), trifluorosilane[18] (256 mg in 2.1 mL THF, 1.66 mmol), TBAF (1 M solution in THF, 1.66 mL), and THF (7 mL) were added. The reaction mixture was heated to 60 °C for 36 h. Additional portions of TBAF (1 M solution in THF, 0.55 mL) were added at 12-h intervals. 5% EtOAc in hexanes was then added to the reaction, and the mixture was filtered through a silica gel plug. The solution was concentrated, and the crude orange oil was purified by flash chromatography (5%–9% EtOAc in hexanes) to give the reverse prenylated indole as a light yellow oil (177 mg, 0.84 mmol, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$) 7.51 (t, J=0.9 Hz, 1H), 7.24 (dd, J=8.7, 1.83 Hz, 1H), 7.21 (d, J=8.5 Hz, 1H), 6.80 (d, J=1.0 Hz, 1H), 6.13 (dd, J=17.5, 10.6 Hz, 1H), 5.09 (dd, J=17.6, 1.5 Hz, 1H), 5.04 (dd, J=10.5, 1.5 Hz, 1H), 3.71 (s, 3H), 2.32 (d, J=1.0 Hz, 3H), 1.49 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) 149.1, 138.8, 135.4, 128.3, 126.7, 120.6, 115.5, 110.1, 109.9, 108.5, 41.1, 32.5, 28.8, 9.5; IR (NaCl/thin film): 3080, 2964, 2920, 1634, 1489, 1455, 1425, 1387, 1376, 1365, 1292, 1256, 1201, 1152, 1053, 1004, 909, 874, 788; HRMS (MM) calcd for $C_{15}H_{19}N$ $[M+H]^+$ 214.1590, found 214.1592.



Scheme 6. Re-exposure of pyrroloindoline *exo*-**8a** to $SnCl_4$ and $NaBH_4$.

4.3. General procedure for the 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*)-3,3′-dichloro-BINOL (0.04 mmol, 0.20 equiv). The flask was charged with CH_2Cl_2 (1.5 mL), followed by addition of $SnCl_4$ (0.24 mmol, 1.20 equiv unless specifically indicated, 1 M in CH_2Cl_2), 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 diethyl ether (3×15 mL) and the combined organic layers were washed with 3 N $NaOH_{(aq)}$ (10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by flash chromatography.

4.3.1. Pyrroloindoline ***21a****.* The dr was determined to be 14:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→10% ethyl acetate/hexanes) to yield 49.4 mg (73% yield) of **21a**. The enantiomeric excess was determined to be 91% by chiral SFC analysis (AD-H, 2.5 mL/min, 7% IPA in CO_2, λ=254 nm): t_R (major)=2.9 min t_R (minor)=2.4 min. Spectral data matches that reported in the literature.[7]

4.3.2. Pyrroloindoline ***21b****.* The dr was determined to be 7:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield 49.1 mg (69% yield) of **21b**. The enantiomeric excess was

determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 7% IPA in CO_2, λ=254 nm): t_R (major)=3.1 min t_R (minor)=2.3 min. The major diastereomer was separated by flash chromatography (0→10% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 3.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.08 (t, J=7.8 Hz, 1H*, 1H§), 6.65–6.57 (m, 1H§), 6.55 (d, J=7.6 Hz, 1H*), 6.45–6.40 (m, 1H§), 6.38 (d, J=7.8 Hz, 1H*), 5.49 (s, 1H*), 5.29 (s, 1H§), 4.74 (d, J=9.3 Hz, 1H*), 4.45 (m, 1H§), 3.83 (s, 3H*), 3.78 (s, 3H§), 3.12 (s, 3H*), 2.85 (s, 3H§), 2.68 (dd, J=13.3, 9.7 Hz, 1H*), 2.64–2.59 (m, 1H§), 2.53 (dd, J=13.3, 1.6 Hz, 1H*), 2.33 (s, 3H§), 2.31 (s, 3H*), 2.20–2.10 (m, 1H§), 1.60 (s, 3H§), 1.47 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 3.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.7*, 170.5§, 159.0§ (q, J_{C-F}=37.2 Hz), 150.6*, 149.7§, 133.1§, 132.7*, 131.6*, 130.9§, 128.8*§, 122.6§, 121.5*, 116.1* (q, J_{C-F}=288.3 Hz), 107.3§, 106.2*, 94.0*, 92.0§, 61.3§, 60.0*, 53.1*, 52.6§, 50.0*, 42.7*, 39.4§, 37.4*, 34.6§, 24.1*, 23.3§, 18.5*§; IR (NaCl/thin film): 3047, 2957, 2930, 2880, 2825, 1752, 1701, 1596, 1477, 1434, 1385, 1356, 1338, 1293, 1263, 1254, 1216, 1204, 1155, 1097, 1064, 1020, 989, 854, 772, 744, 727 cm^{-1}; $[\alpha]_D^{25}$ −158.8 (*c* 1.01, $CHCl_3$). HRMS (APCI) calcd for $C_{17}H_{19}F_3N_2O_3$ $[M+H]^+$ 357.1421, found 357.1426.

4.3.3. Pyrroloindoline ***21c****.* The dr was determined to be 13:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield 51.3 mg (72% yield) of **21c**. The enantiomeric excess was determined to be 89% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ=254 nm): t_R (major)=4.4 min t_R (minor)=2.7 min. The major diastereomer was separated by flash chromatography (0→10% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1.9:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 6.98 (d, J=7.4 Hz, 1H*, 1H§), 6.87 (s, 1H§), 6.84 (s, 1H*), 6.50 (d, J=7.8 Hz, 1H§), 6.43 (d, J=8.0 Hz, 1H*), 5.57 (s, 1H*), 5.27 (s, 1H§), 4.73 (d, J=9.3 Hz, 1H*), 4.41 (t, J=7.6 Hz, 1H§), 3.82 (s, 3H*), 3.76 (s, 3H§), 3.05 (s, 3H*), 2.86 (s, 3H§), 2.59 (dd, J=13.3, 9.7 Hz, 1H*), 2.55–2.48 (m, 1H§), 2.35 (dd, J=13.5, 2.2 Hz, 1H*), 2.28 (br s, 3H§), 2.20–2.10 (m, 1H§), 1.49 (s, 3H§), 1.38 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 1.9:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.6*, 170.7§, 159.1§ (q, J_{C-F}=37.0 Hz), 147.3*, 147.2§, 134.4*§, 129.7§, 129.2§, 129.1*, 128.2*, 122.3*§, 116.1* (q, J_{C-F}=288.2 Hz), 109.9§, 108.2*, 93.8*, 92.1§, 61.2§, 60.3*, 53.2§, 53.0*, 52.5§, 49.2*, 44.0*, 40.3§, 37.4*, 35.5§, 23.5*, 23.2§, 20.8*§; IR (NaCl/thin film): 2958, 2924, 2873, 2822, 1750, 1699, 1618, 1500, 1435, 1384, 1356, 1339, 1288, 1257, 1201, 1152, 1117, 1094, 1057, 1035, 986, 874, 844, 807, 761, 728 cm^{-1}; $[\alpha]_D^{25}$ −128.4 (*c* 1.08, $CHCl_3$). HRMS (APCI) calcd for $C_{17}H_{19}F_3N_2O_3$ $[M+H]^+$ 357.1421, found 357.1407.

4.3.4. Pyrroloindoline ***21d****.* The dr was determined to be 14:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield 56.3 mg (79% yield) of **21d**. The enantiomeric excess was determined to be 89% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ=254 nm): t_R (major)=3.4 min t_R (minor)=2.8 min. The major diastereomer was separated by flash chromatography (0→10% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 2.4:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 6.99–6.93 (m, 1H§), 6.91 (d, J=7.4 Hz, 1H*), 6.65 (d, J=6.7 Hz, 1H§), 6.58 (d, J=7.3 Hz, 1H*), 6.41 (s, 1H§), 6.34 (s, 1H*), 5.60 (s, 1H*), 5.31 (s, 1H§), 4.72 (d, J=9.0 Hz, 1H*), 4.48–4.39 (m, 1H§), 3.82 (s, 3H*), 3.77 (s, 3H§), 3.06 (s, 3H*), 2.86 (s, 3H§), 2.58 (dd, J=13.2, 9.2 Hz, 1H*), 2.52–2.45 (m, 1H§), 2.39–2.33 (m, 1H*), 2.32 (br s, 3H*, 3H§), 2.10–2.00 (m, 1H§), 1.49 (s, 3H§), 1.38 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 2.4:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.6*, 170.6§, 159.1§ (q, J_{C-F}=37.9 Hz), 149.6*, 149.4§, 139.0§, 138.9*, 131.5*, 131.4§, 121.2*§, 120.6§, 119.3*, 116.1* (q, J_{C-F}=288.4 Hz), 110.4§, 108.9*, 93.5*, 91.9§, 61.3§, 60.3*, 53.0*, 52.9§, 52.5§, 49.0*, 44.0*, 40.5§, 36.7*, 34.6§, 23.6*, 23.0§, 21.7*; IR (NaCl/thin film): 2958, 2929, 2875, 2813, 1750, 1697, 1617, 1594, 1499, 1435, 1382, 1356, 1341, 1294, 1257, 1203, 1190, 1148, 1111, 1094, 1059, 1034, 1006, 985, 877, 852, 803, 763, 729 cm^{-1}; $[\alpha]_D^{25}$ −115.4 (*c* 1.54, $CHCl_3$). HRMS (MM) calcd for $C_{17}H_{19}F_3N_2O_3$ $[M+H]^+$ 357.1421, found 357.1434.

4.3.5. Pyrroloindoline ***21e****.* The dr was determined to be 15:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→25% ethyl acetate/hexanes) to yield 48.1 mg (68% yield) of **21e** (major diastereomer only). The enantiomeric excess was determined to be 93% by chiral SFC analysis (AD-H, 2.5 mL/min, 7% IPA in CO_2, λ=254 nm): t_R (major)= 3.6 min t_R (minor)=2.5 min. ^{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 7.05–7.00 (m, 1H*), 7.00–6.93 (m, 2H*, 1H§), 6.91 (d, J=7.2 Hz, 1H§), 6.82 (t, J=7.4 Hz, 1H§), 5.27 (s, 1H§), 5.14 (d, J=1.6 Hz, 1H*), 4.59 (dd, J=9.1, 2.3 Hz, 1H§), 4.06 (dd, J=11.2, 6.6 Hz, 1H*), 3.80 (s, 3H§), 3.72 (s, 3H*), 3.26 (s, 3H§), 2.99 (s, 3H*), 2.67 (dd, J=12.6, 6.6 Hz, 1H*), 2.57 (dd, J=13.4, 9.2 Hz, 1H§), 2.30 (s, 3H§), 2.22 (s, 3H*), 2.13–2.03 (m, 1H*, 1H§), 1.47 (s, 3H*), 1.42 (s, 3H§); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 6.1:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.6§, 171.1*, 158.7*, 149.9*, 148.8§, 136.6*§, 131.4§, 131.0*, 126.6*, 124.01*, 122.6§, 121.2§, 119.6*, 119.4§, 116.0* (q, J_{C-F}=285.8 Hz), 95.6§, 92.5*, 60.3*, 59.2§, 55.1*, 52.9§, 52.4*, 49.7§, 44.0§, 41.9§, 41.0*, 38.6*, 26.3*, 26.0§, 18.9§, 17.5*; IR (NaCl/thin film): 2963, 1753, 1684, 1437, 1359, 1269, 1162, 1120, 1103, 1086, 1067, 977 cm^{-1}; $[\alpha]_D^{25}$ −27.0 (*c* 0.91, CH_2Cl_2). HRMS (MM) calcd for $C_{17}H_{19}F_3N_2O_3$ $[M+H]^+$ 357.1421, found 357.1434.

4.3.6. Pyrroloindoline ***21f****.* The dr was determined to be 10:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→25% ethyl acetate/hexanes) to yield 41.4 mg (58% yield) of **21f**. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ=254 nm): t_R (major)=3.7 min t_R (minor)=2.3 min. The major diastereomer was separated by flash chromatography (0→10% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 2.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 6.92–6.82 (m, 1H*, 1H§), 6.81–6.76 (m, 1H§), 6.74 (dd, J=8.0, 2.7 Hz, 1H*), 6.50 (dd, J=8.6, 4.1 Hz, 1H§), 6.40 (dd, J=8.6, 4.1 Hz, 1H*), 5.60 (s, 1H*), 5.31 (s, 1H§), 4.74 (d, J=9.3 Hz, 1H*), 4.43 (t, J=7.8 Hz, 1H§), 3.82 (s, 3H*), 3.77 (s, 3H§), 3.04 (s, 3H*), 2.85 (s, 3H§), 2.58 (dd, J=13.5, 9.6 Hz, 1H*), 2.53–2.45 (m, 1H§), 2.40–2.32 (m, 1H*), 2.06 (dd, J=13.3, 6.6 Hz, 1H§), 1.49 (s, 3H§), 1.38 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 2.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.4*, 170.5§, 159.0§ (q, J_{C-F}=35.8 Hz), 157.9*, 156.7§, 156.0*, 145.6*, 145.4§, 135.8§ (d, J_{C-F}=8.7 Hz), 135.6* (d, J_{C-F}=7.5 Hz), 116.0* (q, J_{C-F}=289.2 Hz), 115.1§, 114.8* (d, J_{C-F}=23.2 Hz), 110.5§ (d, J_{C-F}=7.3 Hz), 110.2§ (d, J_{C-F}=24.3 Hz), 109.4§ (d, J_{C-F}=24.1 Hz), 109.3* (d, J_{C-F}=24.4 Hz), 108.6* (d, J_{C-F}=8.1 Hz), 105.9§ (d, J_{C-FC-F}=8.0 Hz), 93.8*, 92.1§, 61.1§, 60.2*, 53.2§, 53.1*, 52.6§, 49.2§, 43.8*, 40.1§, 37.6*, 35.5§, 23.4*, 22.9§; IR (NaCl/thin film): 2959, 2880, 2825, 1750, 1699, 1611, 1495, 1436, 1386, 1356, 1339, 1270, 1229, 1202, 1178, 1152, 1118, 1091, 1052, 1034, 986, 872, 845, 808, 756, 728 cm^{-1}; $[\alpha]_D^{25}$ −108.5 (*c* 1.08, $CHCl_3$). HRMS (APCI) calcd for $C_{16}H_{16}F_4N_2O_3$ $[M+H]^+$ 361.1170, found 361.1187.

4.3.7. Pyrroloindoline ***21g****.* The dr was determined to be 10:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes)

to yield 44.8 mg (61% yield) of **21g**. The enantiomeric excess was determined to be 90% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ=254 nm): t_R (major)=3.8 min t_R (minor)=2.5 min. The major diastereomer was separated by flash chromatography (0→10% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1.8:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 6.75–6.70 (m, 1H*, 1H§), 6.67–6.65 (m, 1H§), 6.64 (d, J=2.4 Hz, 1H*), 6.55 (d, J=8.5 Hz, 1H§), 6.45 (d, J=8.5 Hz, 1H*), 5.55 (s, 1H*), 5.24 (s, 1H§), 4.74 (d, J=9.4 Hz, 1H*), 4.38 (t, J=8.0 Hz, 1H§), 3.81 (s, 3H*), 3.77 (s, 3H§), 3.76 (s, 3H*, 3H§), 3.04 (s, 3H*), 2.86 (s, 3H§), 2.59 (dd, J=13.5, 9.6 Hz, 1H*), 2.52 (dd, J=13.0, 8.7 Hz, 1H§), 2.35 (dd, J=13.5, 2.5 Hz, 1H*), 2.09–2.00 (m, 1H§), 1.48 (s, 3H§), 1.38 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 1.8:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.5*, 170.7§, 159.0§ (q, J_{C-F}=37.1, 36.6 Hz), 154.6§, 153.6*, 143.7*, 143.6§, 135.9§, 135.7*, 116.1* (q, J_{C-F}=288.3 Hz), 113.3§, 113.0*, 111.4§, 109.02*, 108.98*, 108.8§, 94.1*, 92.3§, 61.0§, 60.3*, 56.0*, 55.9§, 53.6§, 53.1*, 52.6§, 49.3*, 43.9*, 39.9§, 38.1*, 36.8§, 23.5*§; IR (NaCl/thin film): 2958, 2833, 1750, 1691, 1598, 1497, 1434, 1384, 1356, 1341, 1281, 1259, 1231, 1203, 1154, 1093, 1062, 1031, 986, 870, 844, 808, 756, 728 cm^{-1}; $[\alpha]_D^{25}$ −103.2 (c 0.82, $CHCl_3$). HRMS (APCI) calcd for $C_{17}H_{19}F_3N_2O_4$ $[M+H]^+$ 373.1370, found 373.1383.

*4.3.8. Pyrroloindoline **21h**.* The dr was determined to be 13:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→20% ethyl acetate/hexanes) to yield 74.1 mg (86% yield) of **21h**. The enantiomeric excess was determined to be 87% by chiral SFC analysis (AD-H, 2.5 mL/min, 8% IPA in CO_2, λ=254 nm): t_R (major)=5.3 min t_R (minor)=8.1 min. The major diastereomer was separated by flash chromatography (5% ethyl acetate/hexanes). ^{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 7.32–7.15 (m, 4H*, 4H§), 7.08 (br t, J=7.7 Hz, 3H*, 3H§), 6.95–6.75 (m, 1H*, 1H§), 6.65–6.50 (m, 1H*, 1H§), 5.72 (br s, 1H*), 5.46 (br s, 1H§), 4.65 (br d, J=6.3 Hz, 1H*), 4.33 (br s, 1H§), 3.78 (br s, 3H*, 3H§), 3.13 (br s, 3H*), 2.90 (br s, 3H§), 2.76–1.87 (m, 6H*, 6H§); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 2.6:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.6*, 170.6§, 159.0* (q, J_{C-F}=37.5 Hz), 150.3*§, 141.1*§, 131.9*, 131.7§, 129.0*§, 128.5*§, 128.2*§, 126.1*§, 122.0*, 121.2* (q, J_{C-F}=278.2 Hz), 119.0*, 117.2§, 114.9§, 109.8§, 108.3*, 90.5*, 89.2§; IR (NaCl/thin film): 3026, 2952, 1751, 1701, 1607, 1491, 1437, 1355, 1204, 1151, 985, 749 cm^{-1}; $[\alpha]_D^{25}$ −128.3 (c 1.22, CH_2Cl_2). HRMS (MM) calcd for $C_{23}H_{23}F_3N_2O_3$ $[M+H]^+$ 433.1734, found 433.1750.

*4.3.9. Pyrroloindoline **21i**.* The dr was determined to be 5:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→15% ethyl acetate/hexanes) to yield 61.1 mg of white needles **21i** (84% yield). The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ=254 nm): t_R (major)=7.8 min t_R (minor)=3.5 min. The major and minor diastereomers were separated by reverse phase preparatory HPLC (50→95% acetonitrile/water, 0.05% trifluoroacetic acid). ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 4.9:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.14 (td, J=7.7, 1.3 Hz, 1H*, 1H§), 7.03 (br d, J=7.3 Hz, 1H*, 1H§), 6.90–6.80 (br s, 1H§), 6.76 (t, J=7.4 Hz, 1H*), 6.67–6.58 (br s, 1H§), 6.54 (d, J=7.9 Hz, 1H*), 5.81 (dtd, J=16.5, 11.6, 11.1, 6.2 Hz, 1H*, 1H§), 5.74 (s, 1H*), 5.51 (br s, 1H§), 5.27 (br d, J=17.1 Hz, 1H*, 1H§), 5.14 (br d, J=10.2 Hz, 1H*, 1H§), 4.72 (d, J=9.1 Hz, 1H*), 4.34 (br s, 1H§), 4.25 (dd, J=16.5, 3.6 Hz, 1H*), 4.04 (dd, J=16.5, 6.2 Hz, 1H*), 4.00–3.94 (m, 1H§), 3.82 (s, 3H*), 3.76 (s, 3H§), 2.62 (dd, J=13.3, 9.7 Hz, 1H*), 2.58–2.49 (m, 1H§), 2.40 (dd, J=13.5, 2.6 Hz, 1H*), 2.11 (br s, 1H§), 1.48 (s, 3H§), 1.39 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 4.9:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.6*, 170.6§, 158.9§ (q, J_{C-F}=36.9 Hz), 148.4*, 134.7*, 133.8*, 133.3§, 128.7*, 121.7§, 121.5*, 120.3§, 118.8*, 117.8§, 116.8*, 116.0* (q, J_{C-F}=288.4 Hz), 110.8§, 108.5*, 91.3*, 89.6§, 60.9§, 59.9*, 53.0*, 52.5§, 51.8*, 50.4§, 49.4*, 44.3*, 40.8§, 23.7*, 23.4§; IR (NaCl/thin film): 3053, 2958, 2877, 1751, 1700, 1691, 1685, 1642, 1608, 1487, 1437, 1384, 1356, 1340, 1309, 1257, 1205, 1151, 1106, 1093, 1027, 991, 925, 841, 817, 792, 744 cm^{-1}; $[\alpha]_D^{25}$ −146.2 (c 1.60, $CHCl_3$). HRMS (APCI) calcd for $C_{18}H_{19}F_3N_2O_3$ $[M+H]^+$ 369.1421, found 369.1416.

*4.3.10. Pyrroloindoline ent-endo-**21i**.* ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 15.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.11–7.07 (m, 1H§), 7.06 (td, J=7.6, 1.3 Hz, 1H*), 7.06–7.03 (m, 1H§), 6.98 (dd, J=7.3, 0.7 Hz, 1H*), 6.73 (td, J=7.4, 1.0 Hz, 1H§), 6.66 (td, J=7.4, 1.0 Hz, 1H*), 6.46–6.44 (m, 1H§), 6.44 (d, J=7.9 Hz, 1H*), 5.87 (dddd, J=17.1, 10.3, 5.9, 5.1 Hz, 1H*), 5.82–5.75 (m, 1H§), 5.57 (s, 1H*), 5.53 (d, J=1.4 Hz, 1H§), 5.30 (dq, J=17.2, 1.7 Hz, 1H*), 5.22–5.19 (m, 1H§), 5.16 (dq, J=10.2, 1.5 Hz, 1H*), 5.10 (dd, J=9.5, 4.5 Hz, 1H§), 4.75 (dt, J=8.4, 1.3 Hz, 1H*), 4.24–4.13 (m, 2H*), 3.85 (ddd, J=49.3, 17.2, 5.1 Hz, 2H§), 3.53 (s, 3H§), 3.17 (s, 3H*), 2.85 (d, J=13.0 Hz, 1H*), 2.50 (dd, J=13.2, 4.5 Hz, 1H§), 2.39 (dd, J=13.0, 8.4 Hz, 1H*), 2.25 (dd, J=13.3, 9.6 Hz, 1H§), 1.44 (s, 3H§), 1.42 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 15.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 170.0*, 156.8§ (q, J_{C-F}=36.8 Hz), 149.3*, 147.8§, 134.2*, 133.2§, 132.6§, 132.0*, 128.9*, 128.6§, 122.5*, 121.7§, 118.7§, 118.0*, 117.1§, 116.3*, 116.1* (q, J_{C-F}=288.6 Hz), 108.0§, 106.8*, 88.7§, 88.1*, 60.3§, 60.1* (q, J_{C-F}=3.1 Hz), 52.6§, 52.5§, 52.4*, 50.6*, 49.0*, 46.6§, 42.5*, 41.4§, 25.7*, 22.9§; IR (NaCl/thin film): 3055, 2954, 2869, 1760, 1742, 1699, 1607, 1490, 1447, 1436, 1338, 1317, 1274, 1254, 1208, 1183, 1144, 1105, 1093, 1032, 999, 942, 922, 887, 842, 859, 742 cm^{-1}; $[\alpha]_D^{25}$ +188.1 (c 0.275, $CHCl_3$). HRMS (APCI) calcd for $C_{18}H_{19}F_3N_2O_3$ $[M+H]^+$ 369.1421, found 369.1429.

*4.3.11. Pyrroloindoline **21j**.* The dr was determined to be 18:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield 68.6 mg (84% yield) of **21j**. The enantiomeric excess was determined to be 92% by chiral SFC analysis (OD, 2.5 mL/min, 3% IPA in CO_2, λ=254 nm): t_R (major)=6.5 min t_R (minor)=5.6 min. The major diastereomer was separated by flash chromatography (0→10% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 2.1:1 mixture of rotamers the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.16 (d, J=8.1 Hz, 1H*, 1H§), 7.02 (s, 1H§), 6.99 (s, 1H*), 6.52 (d, J=7.7 Hz, 1H§), 6.45 (d, J=8.2 Hz, 1H*), 6.00 (dd, J=17.3, 10.5 Hz, 1H*, 1H§), 5.60 (s, 1H*), 5.31 (s, 1H§), 5.07–4.96 (m, 2H*, 2H§), 4.73 (d, J=9.3 Hz, 1H*), 4.47–4.41 (m, 1H§), 3.82 (s, 1H*), 3.77 (s, 1H§), 3.06 (s, 1H*), 2.86 (s, 1H§), 2.60 (dd, J=13.1, 9.9 Hz, 1H*), 2.52 (t, J=10.7 Hz, 1H§), 2.38 (d, J=12.5 Hz, 1H*), 2.14–1.98 (m, 1H§), 1.57–1.31 (m, 9H*, 9H§); ^{13}C NMR (126 MHz, $CDCl_3$); IR (NaCl/thin film): 3081, 2965, 2874, 2822, 1753, 1698, 1618, 1496, 1434, 1359, 1283, 1257, 1204, 1156, 1117, 1054, 995, 912, 844, 813; $[\alpha]_D^{25}$ −115 (c 0.450, $CHCl_3$). HRMS (ESI) calcd for $C_{21}H_{25}F_3N_2O_3$ $[M+H]^+$ 411.1890, found 411.1901.

4.4. General procedure for the formal (3+2) cycloaddition/in situ reduction

To a flame-dried flask was added indole (0.20 mmol, 1.00 equiv), acrylate (0.20 mmol, 1.00 equiv), and (*R*)-3,3′-dichloro-BINOL (0.04 mmol, 0.20 equiv). The flask was charged with CH_2Cl_2 (1.5 mL), followed by addition of $SnCl_4$ (0.24 mmol, 1.20 equiv

unless specifically indicated, 1 M in CH_2Cl_2). $NaBH_4$ (0.30 mmol, 1.50 equiv) was then added, and the reaction was stirred at room temperature for 24 h (unless specifically indicated). 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 (3×15 mL) and the combined organic layers were washed with saturated $NaHCO_{3(aq)}$ (10 mL). The aqueous layer was extracted with ethyl acetate (10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified by flash chromatography.

4.4.1. Indoline ***28a****.* Prepared from 1,3-dimethyl-1*H*-indole[19] and methyl 2-trifluoroacetamidoacrylate using the general procedure. The dr was determined to be 15:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→25% ethyl acetate/hexanes) to yield 64.1 mg (93% yield) of **28a**, a pale yellow oil. The enantiomeric excess of the major diastereomer was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ=254 nm): t_R (major)=9.9 min t_R (minor)=5.9 min. The major diastereomer was separated by flash chromatography (5% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (br d, J=5.9 Hz, 1H), 7.14 (td, J=7.7, 1.2 Hz, 1H), 6.99 (dd, J=7.3, 0.8 Hz, 1H), 6.76 (td, J=7.4, 0.8 Hz, 1H), 6.54 (d, J=7.9 Hz, 1H), 4.27 (br td, J=7.7, 4.7 Hz, 1H), 3.65 (s, 3H), 3.31 (d, J=9.1 Hz, 1H), 2.98 (d, J=9.1 Hz, 1H), 2.74 (s, 3H), 2.21 (dd, J=14.7, 4.7 Hz, 1H), 2.15 (dd, J=14.7, 8.2 Hz, 1H), 1.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 156.6 (q, J_{C-F}=37.5 Hz), 152.1, 153.3, 128.5, 122.4, 119.0, 115.6 (q, J_{C-F}=287.9 Hz), 108.4, 68.3, 52.7, 51.2, 42.8, 42.1, 35.8, 26.1; IR (NaCl/thin film): 3319, 2956, 2858, 2811, 1751, 1718, 1607, 1559, 1491, 1452, 1209, 1179, 744 cm^{-1}; $[\alpha]_D^{25}$ +79.6 (*c* 1.32, CH_2Cl_2). HRMS (MM) calcd for $[M+H]^+$ $C_{16}H_{19}F_3N_2O_3$ 345.1421, found 345.1423.

4.4.2. Indoline ***28b****.* Prepared from 1,3,4-trimethyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using the general procedure. The dr was determined to be 11:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→25% ethyl acetate/hexanes) to yield 56.8 mg (79% yield, yellow oil) of **28b** as a single diastereomer. The enantiomeric excess of the major diastereomer was determined to be 93% by chiral SFC analysis (AD-H, 2.5 mL/min, 6% IPA in CO_2, λ=254 nm): t_R (major)=3.9 min t_R (minor)=3.5 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (br d, J=4.9 Hz, 1H), 7.06 (t, J=7.7 Hz, 1H), 6.54 (d, J=7.6 Hz, 1H), 6.42 (d, J=7.9 Hz), 4.10 (ddd, J=9.0, 6.5, 4.2 Hz, 1H), 3.65 (s, 3H), 3.32 (d, J=9.3 Hz, 1H), 2.95 (d, J=9.2 Hz, 1H), 2.71 (s, 3H), 2.45 (dd, J=15.0, 4.0 Hz, 1H), 2.30 (s, 3H), 2.13 (dd, J=14.8, 8.9 Hz, 1H), 1.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 156.7 (q, J_{C-F}=37.5 Hz), 152.8, 134.5, 131.5, 128.8, 122.4, 115.6 (q, J_{C-F}=287.9 Hz), 106.7, 68.6, 52.7, 51.7, 43.7, 40.9, 35.9, 26.6, 18.7; IR (NaCl/thin film): 3315, 2956, 2812, 1750, 1710, 1593, 1559, 1484, 1457, 1209, 1179, 774 cm^{-1}; $[\alpha]_D^{25}$ +66.0 (*c* 1.04, CH_2Cl_2). HRMS (MM) calcd for $C_{17}H_{21}F_3N_2O_3$ $[M+H]^+$ 359.1577, found 359.1591.

4.4.3. Indoline ***28c****.* Prepared from 1,3,5-trimethyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using the general procedure. The dr was determined to be 17:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (10→25% ethyl acetate/hexanes) to yield 52.6 mg (73% yield) of **28c**, a yellow oil. The enantiomeric excess of the major diastereomer was determined to be 89% by chiral SFC analysis (AD-H, 2.5 mL/min, 6% IPA in CO_2, λ=254 nm): t_R (major)=4.8 min t_R (minor)=3.4 min. The major diastereomer was separated by flash chromatography (7% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (br d, J=4.8 Hz, 1H), 6.95 (d, J=7.9 Hz, 1H), 6.81 (s, 1H), 6.47 (d, J=7.9 Hz, 1H), 4.16 (q, J=6.5 Hz, 1H), 3.67 (s, 3H), 3.27 (d, J=9.1 Hz, 1H), 2.91 (d, J=9.1 Hz, 1H), 2.70 (s, 3H), 2.25 (s, 3H), 2.17 (d, J=6.5 Hz, 2H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 156.7 (q, J_{C-F}=37.5 Hz), 150.0, 135.5, 128.9, 128.8, 123.3, 115.6 (q, J_{C-F}=287.9 Hz), 108.7, 69.0, 52.7, 51.5, 42.7, 42.1, 36.4, 26.07, 20.7; IR (NaCl/thin film): 3326, 2955, 2922, 2863, 2806, 1752, 1719, 1555, 1499, 1452, 1209, 1163, 806 cm^{-1}; $[\alpha]_D^{25}$ +42.3 (*c* 0.87, CH_2Cl_2). HRMS (MM) calcd for $C_{17}H_{21}F_3N_2O_3$ $[M+H]^+$ 359.1577, found 359.1565.

4.4.4. Indoline ***28d****.* Prepared from 1,3,6-trimethyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using the general procedure. The dr was determined to be 17:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→30% ethyl acetate/hexanes) to yield 65.0 mg (91% yield) of **28d**, a yellow oil. The enantiomeric excess of the major diastereomer was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ=254 nm): t_R (major)=11.1 min t_R (minor)=5.0 min. The major diastereomer was separated by flash chromatography (5% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J=5.7 Hz, 1H), 6.88 (d, J=7.5 Hz, 1H), 6.58 (d, J=7.5 Hz, 1H), 6.37 (s, 1H), 4.22 (td, J=7.5, 4.9 Hz), 3.66 (s, 3H), 3.29 (d, J=9.1 Hz, 1H), 2.96 (d, J=9.1 Hz, 1H), 2.72 (s, 3H), 2.30 (s, 3H), 2.20–2.11 (m, 2H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 156.6 (q, J_{C-F}=37.5 Hz), 152.3, 138.6, 132.5, 122.2, 119.8, 115.6 (q, J_{C-F}=287.8 Hz), 109.3, 68.6, 52.7, 51.4, 42.5, 42.2, 35.8, 26.2, 21.6; IR (NaCl/thin film): 3321, 2956, 2923, 2870, 2804, 1750, 1716, 1615, 1557, 1497, 1455, 1208, 1179, 802 cm^{-1}; $[\alpha]_D^{25}$ +76.0 (*c* 1.56, CH_2Cl_2). HRMS (MM) calcd for $C_{17}H_{21}F_3N_2O_3$ $[M+H]^+$ 359.1577, found 359.1577.

4.4.5. Indoline ***28e****.* Prepared from 1,3,7-trimethyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using the general procedure. The dr was determined to be 17:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→30% ethyl acetate/hexanes) to yield 58 mg (81% yield) of **28e**, a pale yellow oil. The enantiomeric excess of the major diastereomer was determined to be 94% by chiral SFC analysis (AD-H, 2.5 mL/min, 6% IPA in CO_2, λ=254 nm): t_R (major)=4.3 min t_R (minor)=3.3 min. The major diastereomer was separated by flash chromatography (5% ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J=4.7 Hz, 1H), 6.90 (d, J=7.5 Hz, 1H), 6.86 (d, J=7.4 Hz, 1H), 6.73 (t, J=7.4 Hz, 1H), 4.14–4.08 (m, 1H), 3.66 (s, 3H), 3.29 (d, J=9.6 Hz, 1H), 2.97 (d, J=9.6 Hz, 1H), 2.93 (s, 3H), 2.37 (s, 3H), 2.17–2.06 (m, 2H), 1.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 156.7 (q, J_{C-F}=37.5 Hz), 149.9, 136.1, 131.8, 121.2, 120.4, 120.3, 115.6 (q, J_{C-F}=287.8 Hz), 69.7, 52.7, 51.3, 42.8, 42.3, 39.5, 26.6, 19.5; IR (NaCl/thin film): 3322, 2959, 2924, 1750, 1713, 1557, 1480, 1456, 1412, 1208, 1180, 1071, 750 cm^{-1}; $[\alpha]_D^{25}$ +84.9 (*c* 1.20, CH_2Cl_2). HRMS (APCI) calcd for $C_{17}H_{21}F_3N_2O_3$ $[M+H]^+$ 359.1577, found 359.1595.

4.4.6. Indoline ***28f****.* Prepared from 5-fluoro-1,3-dimethyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using the general procedure. The dr was determined to be 13:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (10→30% ethyl acetate/hexanes) to yield 57.0 mg (79% yield) of **28f**, a pale yellow oil. The enantiomeric excess of the major diastereomer was determined to be 90% by chiral SFC analysis (AD-H, 2.5 mL/min, 6% IPA in CO_2, λ=254 nm): t_R (major)=3.9 min t_R (minor)=2.9 min. The major diastereomer was separated by preparatory TLC (40% CH_2Cl_2/hexanes then 50% CH_2Cl_2/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (br d, J_{C-H}=5.8 Hz, 1H), 6.83 (td, J_{C-H}=8.8, 2.6 Hz, 1H), 6.72 (dd, J_{C-H}=8.2, 2.6 Hz, 1H), 6.44 (dd, J_{C-H}=8.5, 4.1 Hz, 1H), 4.25 (td, J_{C-H}=7.7, 4.8 Hz, 1H), 3.68 (s, 3H), 3.31 (d, J_{C-H}=9.2 Hz, 1H), 2.97 (d, J_{C-H}=9.2 Hz, 1H), 2.70 (s, 3H), 2.21 (dd, J_{C-H}=14.7, 4.8 Hz, 1H), 2.12 (dd, J_{C-H}=14.7, 8.1 Hz, 1H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 157.2 (d, J_{C-F}=237.2 Hz),

156.6 (q, J_{C-F}=37.8 Hz), 148.4, 137.1 (d, J_{C-F}=7.1 Hz), 116.7, 114.5 (d, J_{C-F}=23.3 Hz), 110.1 (d, J_{C-F}=24.0 Hz), 108.8 (d, J_{C-F}=8.1 Hz), 68.6, 52.8, 51.1, 42.8, 42.0, 36.4, 26.1; IR (NaCl/thin film): 3319, 2958, 2866, 2811, 1745, 1711, 1552, 1494, 1468, 1267, 1210, 1179, 808 cm^{-1}; $[\alpha]_D^{25}$ +63.7 (*c* 0.62, CH_2Cl_2). HRMS (ESI) calcd for $C_{16}H_{18}F_4N_2O_3$ $[M+H]^+$ 363.1326, found 363.1334.

4.4.7. Indoline ***28g***. Prepared from 5-methoxy-1,3-dimethyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using the general procedure. The reaction was allowed to run for 18.5 h. The dr was determined to be 14:1 by ^1H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (10→30% ethyl acetate/hexanes) to yield 68.5 mg (91% yield) of **28g**, a yellow oil. The enantiomeric excess of the major diastereomer was determined to be 88% by chiral SFC analysis (AD-H, 2.5 mL/min, 7% IPA in CO_2, λ=254 nm): t_R (major)=7.1 min t_R (minor)=3.6 min. ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (br d, J_{C-H}=5.0 Hz, 1H), 6.70 (dd, J_{C-H}=8.4, 1.9 Hz, 1H), 6.62 (d, J_{C-H}=1.8 Hz, 1H), 6.50 (d, J_{C-H}=8.3 Hz, 1H), 4.01 (dd, J_{C-H}=13.1, 6.3 Hz, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 3.28 (d, J_{C-H}=8.6 Hz, 1H), 2.89 (d, J_{C-H}=9.1 Hz, 1H), 2.68 (s, 3H), 2.23–2.08 (m, 2H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 156.8 (q, J_{C-F}=37.5 Hz), 154.1, 146.1, 137.0, 115.6 (q, J_{C-F}=287.8 Hz), 113.1, 110.8, 109.6, 69.0, 55.8, 52.7, 51.5, 43.0, 42.0, 36.9, 26.2; IR (NaCl/thin film): 3319, 2955, 2804, 1751, 1718, 1555, 1496, 1468, 1214, 1179, 1031 cm^{-1}; $[\alpha]_D^{25}$ +26.3 (*c* 1.24, CH_2Cl_2). HRMS (APCI) calcd for $C_{17}H_{21}F_3N_2O_4$ $[M+H]^+$ 375.1526, found 375.1542.

4.4.8. Indoline ***28h***. Prepared from 1-allyl-3-methyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using the general procedure, except the formal (3+2) cycloaddition was allowed to run for 24 h before adding $NaBH_4$. After adding $NaBH_4$, the reaction was allowed to run for another 24 h. The dr was determined to be 5:1 by ^1H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→20% ethyl acetate/hexanes) to yield 60.0 mg (81% yield) of **28h**, a yellow oil. The enantiomeric excess of the major diastereomer was determined to be 90% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ=254 nm): t_R (major)=7.2 min t_R (minor)=6.2 min. Isolated as a 5:1 mixture of diastereomers; the major diastereomer is denoted by *, minor diastereomer denoted by §. ^1H NMR (500 MHz, $CDCl_3$) δ 8.26 (br d, *J*=8.5 Hz, 1H§), 7.16–7.05 (m, 2H*, 1H§), 6.98 (ddd, *J*=7.4, 1.2, 0.5 Hz, 1H*, 1H§), 6.78 (td, *J*=7.4, 1.0 Hz, 1H§), 6.72 (td, *J*=7.4, 1.0 Hz, 1H*), 6.64 (d, *J*=7.9 Hz, 1H§), 6.56 (d, *J*=7.9 Hz, 1H*), 5.93–5.83 (m, 1H*, 1H§), 5.32–5.20 (m, 1H*, 1H§), 4.81–4.75 (m, 1H§), 4.40 (td, *J*=7.6, 5.0, 1H*), 3.79 (ddt, *J*=15.0, 5.9, 1.4 Hz, 1H*, 1H§), 3.73–3.70 (m, 1H§), 3.65–3.59 (m, 1H*), 3.63 (s, 3H*), 3.42 (s, 3H§), 3.31 (d, *J*=9.3 Hz, 1H*), 3.28 (d, *J*=9.6 Hz, 1H§), 3.07 (d, *J*=9.6 Hz, 1H§), 3.05 (d, *J*=9.3 Hz, 1H*), 2.35 (ddd, *J*=14.8, 5.9, 0.6 Hz, 1H§), 2.23 (dd, *J*=14.6, 4.9 Hz, 1H*), 2.18 (dd, *J*=14.9, 4.6 Hz, 1H§), 2.13 (dd, *J*=14.7, 7.8 Hz, 1H*), 1.41 (s, 3H§), 1.38 (s, 3H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2*, 170.1§, 156.6* (q, J_{C-F}=37.6 Hz), 150.8*, 135.4*, 133.3*, 132.4§, 128.6§, 128.4*, 123.3§, 122.5*, 119.4§, 118.9§, 118.7*, 118.1*, 115.5* (q, J_{C-F}=287.9 Hz), 109.9§, 108.4*, 65.2§, 65.1*, 52.7*, 52.5§, 52.1§, 51.8*, 50.9*, 50.5§, 42.7§, 42.6*, 42.5§, 42.1*, 27.8§, 26.1*; IR (NaCl/thin film): 3316, 2957, 2923, 1750, 1718, 1605, 1554, 1487, 1460, 1437, 1209, 1165, 744 cm^{-1}; $[\alpha]_D^{25}$ +33.412 (*c* 1.62, CH_2Cl_2). HRMS (MM) calcd for $C_{18}H_{21}F_3N_2O_3$ $[M+H]^+$ 371.1577, found 371.1582.

4.4.9. Indoline ***28i***. Prepared from 3-butyl-1-methyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using the general procedure. The dr was determined to be >20:1 by ^1H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→20% ethyl acetate/hexanes) to yield 63.4 mg (82% yield) of **28i**, a pale yellow oil. The enantiomeric excess of the major diastereomer was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ=254 nm): t_R (major)=7.2 min t_R (minor)=5.3 min. The major diastereomer was separated by flash chromatography (5% ethyl acetate/hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (br d, J_{C-H}=5.5 Hz, 1H), 7.13 (td, J_{C-H}=7.7, 1.2 Hz, 1H), 6.96 (dd, J_{C-H}=7.3, 0.7 Hz, 1H), 6.75 (t, J_{C-H}=7.3 Hz, 1H), 6.53 (d, J_{C-H}=7.8 Hz, 1H), 4.22–4.15 (m, 1H), 3.64 (s, 3H), 3.24 (d, J_{C-H}=9.3 Hz, 1H), 3.08 (d, J_{C-H}=9.3 Hz, 1H), 2.74 (s, 3H), 2.23 (dd, J_{C-H}=14.7, 8.4 Hz, 1H), 2.17 (dd, J_{C-H}=14.7, 4.7 Hz, 1H), 1.86–1.77 (m, 1H), 1.69–1.57 (m, 1H), 1.40–1.24 (m, 3H), 1.19–1.08 (m, 1H), 0.89 (t, J_{C-H}=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 156.6 (q, J_{C-F}=37.5 Hz), 152.3, 134.3, 128.6, 123.0, 119.0, 115.5 (q, J_{C-F}=287.8 Hz), 108.4, 66.4, 52.7, 51.2, 46.2, 40.6, 39.3, 35.9, 26.5, 23.2, 14.0; IR (NaCl/thin film): 3319, 2956, 2932, 2860, 2809, 1751, 1718, 1606, 1559, 1491, 1465, 1207, 1178, 743 cm^{-1}; $[\alpha]_D^{25}$ +62.0 (*c* 1.15, CH_2Cl_2). HRMS (ESI) calcd for $C_{19}H_{25}F_3N_2O_3$ $[M+H]^+$ 387.1890, found 387.1902.

4.4.10. Indoline ***28j***. Prepared from 1-methyl-3-phenethyl-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using the general procedure, except the formal (3+2) cycloaddition was allowed to run for 24 h before adding $NaBH_4$. After adding $NaBH_4$, the reaction was allowed to run for another 24 h. The dr was determined to be 12:1 by ^1H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→20% ethyl acetate/hexanes) to yield 77.6 mg (89% yield) of **28j**. The enantiomeric excess of the major diastereomer was determined to be 89% by chiral SFC analysis (AD-H, 2.5 mL/min, 7% IPA in CO_2, λ=254 nm): t_R (major)=9.5 min t_R (minor)=8.1 min. The major diastereomer was separated by flash chromatography (10% ethyl acetate/hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.22 (m, 3H), 7.21–7.11 (m, 4H), 6.99 (dd, J_{C-H}=7.4, 1.0 Hz, 1H), 6.75 (td, J_{C-H}=7.4, 0.7 Hz, 1H), 6.55 (d, J_{C-H}=7.9 Hz, 1H), 4.27 (dt, J_{C-H}=12.6, 6.4 Hz, 1H), 3.63 (s, 3H), 3.30 (d, J_{C-H}=9.3 Hz, 1H), 3.17 (d, J_{C-H}=9.3 Hz, 1H), 2.76 (s, 3H), 2.68 (td, J_{C-H}=13.0, 5.0 Hz, 1H), 2.47 (td, J_{C-H}=12.9, 4.7 Hz, 1H), 2.34–2.22 (m, 2H), 2.13 (ddd, J_{C-H}=13.7, 12.3, 5.1 Hz, 1H), 1.97 (ddd, J_{C-H}=13.8, 12.6, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 156.6 (q, J_{C-F}=37.5 Hz), 152.4, 141.7, 133.5, 128.7, 128.5, 128.2, 126.0, 122.9, 119.0, 115.5 (q, J_{C-F}=287.8 Hz), 108.4, 66.0, 52.7, 51.1, 46.3, 41.5, 40.7, 35.8, 30.8; IR (NaCl/thin film): 3317, 2951, 2858, 2812, 1749, 1716, 1606, 1555, 1494, 1453, 1208, 1178, 745 cm^{-1}; $[\alpha]_D^{26}$ +23.1 (*c* 0.87, CH_2Cl_2). HRMS (MM) calcd for $C_{23}H_{25}F_3N_2O_3$ $[M+H]^+$ 435.1890, found 435.1882.

4.4.11. Indoline ***28k***. Prepared from 1-methyl-3-(2-((triisopropylsilyl)oxy)ethyl)-1*H*-indole and methyl 2-trifluoroacetamidoacrylate using the general procedure, except the formal (3+2) cycloaddition was allowed to run for 20.5 h before adding $NaBH_4$. After adding $NaBH_4$, the reaction was allowed to run for another 24 h. The dr was determined to be >20:1 by ^1H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (5→30% ethyl acetate/hexanes) to yield 68.3 mg (64% yield) of **28k**, a yellow oil. The enantiomeric excess of the major diastereomer was determined to be 85% by chiral SFC analysis (AD-H, 2.5 mL/min, 5% IPA in CO_2, λ=254 nm): t_R (major)=8.7 min t_R (minor)=7.5 min. ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (br s, 1H), 7.15 (t, J_{C-H}=7.6 Hz, 1H), 7.00 (d, J_{C-H}=7.2 Hz, 1H), 6.75 (t, J_{C-H}=7.1 Hz, 1H), 6.54 (d, J_{C-H}=7.3 Hz, 1H), 4.22–4.15 (m, 1H), 3.81 (dd, J_{C-H}=6.96, 5.35 Hz, 2H), 3.64 (s, 3H), 3.34–3.26 (m, 1H), 3.26–3.18 (m, 1H), 2.74 (s, 3H), 2.46–2.36 (m, 1H), 2.24 (dd, J_{C-H}=14.7, 3.7 Hz, 1H), 2.11–1.94 (m, 2H), 1.08–1.03 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 156.7 (q, J_{C-F}=37.6 Hz), 152.1, 134.3, 128.7, 123.0, 118.9, 115.6 (q, J_{C-F}=287.8 Hz), 108.5, 67.6, 60.0, 52.6, 51.2, 45.3, 41.2, 39.5, 18.0, 18.0, 11.9; IR (NaCl/thin film): 3323, 2943, 2866, 1719, 1606, 1552, 1491, 1463, 1207, 1175, 1104, 882,

742 cm^{-1}; $[\alpha]_D^{25}$ +27.4 (*c* 0.85, CH_2Cl_2). HRMS (APCI) calcd for $C_{26}H_{41}F_3N_2O_4Si$ $[M+H]^+$ 531.2860, found 531.2883.

4.5. General procedure for in situ monitoring of the formal (3+2) cycloaddition by ^1H NMR

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

The concentration of acrylate over the course of the reaction was determined by integrating its resonance at 6.3 ppm, then normalizing by the internal standard's resonance at 2.74 ppm.

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