Chapter 2

Enantioselective Synthesis of Tryptophan Derivatives by a Tandem Friedel–Crafts Conjugate Addition/Asymmetric Protonation Reaction[†]

2.1 INTRODUCTION

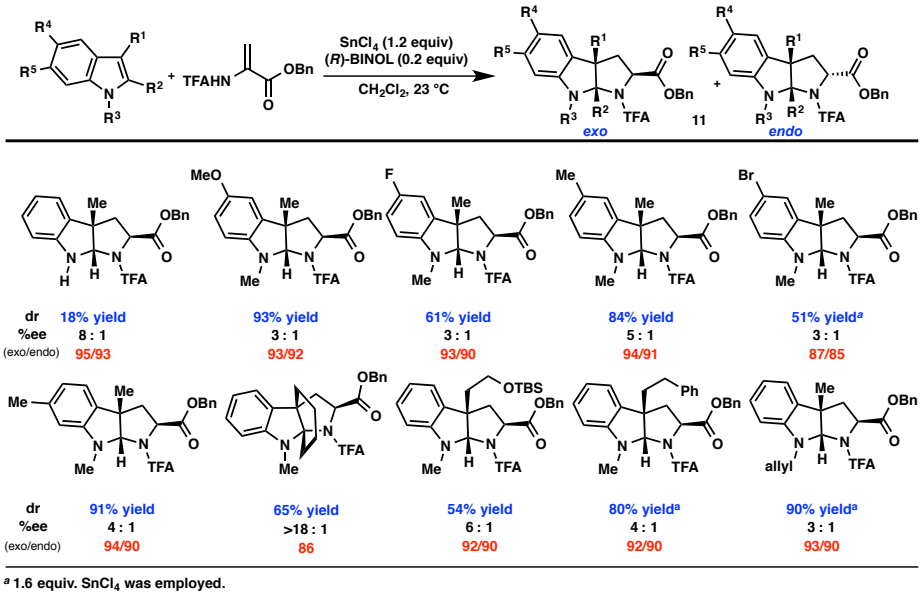
The biological importance of tryptophan as discussed in **Chapter 1** has inspired a variety of racemic, enzymatic, auxiliary-controlled, and enantiospecific methodologies.[1] There are, however, very few reported catalytic asymmetric methods for the preparation of tryptophan derivatives containing no β-stereocenter.[2,3,4]

In 2010, our laboratory reported a highly enantioselective formal (3 + 2) cycloaddition reaction utilizing catalytic (*R*)-BINOL and superstoichiometric $SnCl_4$ (**Table 2.1**).[5,6,7] By exploiting the intrinsic nucleophilicity of 3-substituted indoles and the electrophilicity of 2-amidoacrylates, functionalized pyrroloindoline scaffolds can be convergently synthesized in a single step. Both the enantio- and diastereoselectivity of

[†] Portions of this chapter have been reproduced from published studies (Kieffer, M. E.; Repka, L. M.; Reisman, S. E. *J. Am. Chem. Soc.* **2012**, *134*, 5131) and the supporting information found therein. Work was conducted in collaboration with Dr. Lindsay M. Repka.

this transformation were found to be highly dependent on the protecting groups of the acrylate, with benzyl 2-trifluoroacetamidoacrylate providing the best results for a variety of indole nucleophiles (**Table 2.1**).

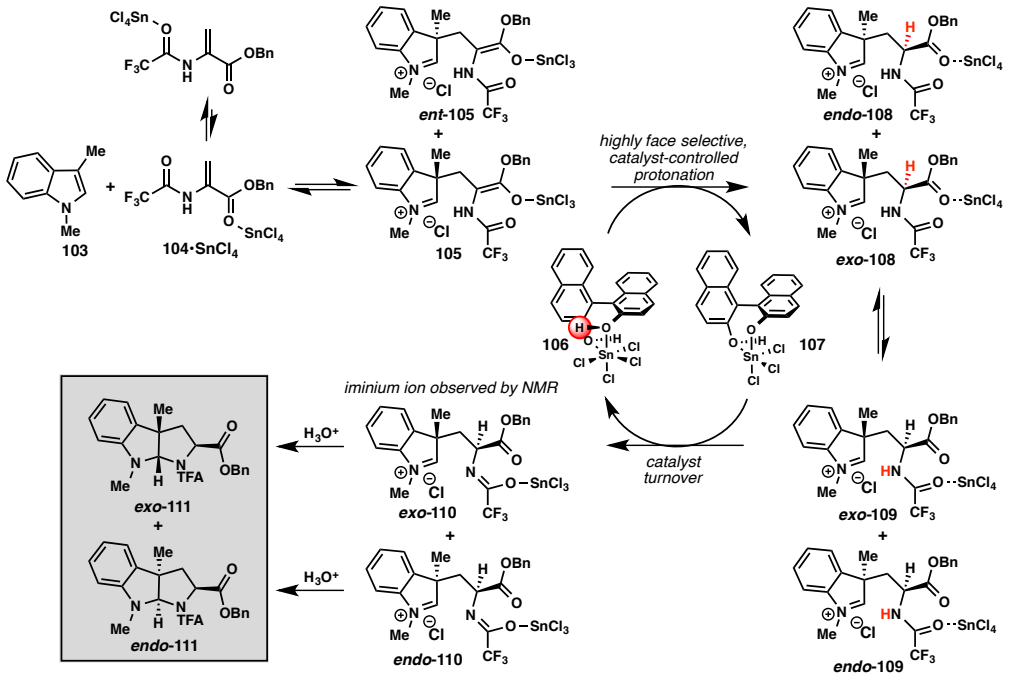
Table 2.1. *Substrate scope of formal (3+2) cycloaddition reaction*



Interestingly, a series of epimerization studies revealed that the reaction produced *endo/exo*-diastereomers of opposite enantiomeric series. In accord with preliminary mechanistic data, one limiting scenario that could explain this finding is if the initial conjugate addition proceeds reversibly to provide an enantiomeric mixture of enolate intermediates **105** and ***ent*-105**. A face-selective, catalyst controlled protonation would serve to irreversibly resolve the enantiomers, providing diastereomers **endo-** and **exo-108**. Subsequent cyclization of the amide onto the iminium ion provides the product in moderate diastereoselectivity and high enantioselectivity. Importantly, under this mechanistic scenario, the diastereomeric ratio is dependent upon the relative rates of protonation of **105** and ***ent*-105**. Following the precedence of Yamamoto and co-workers,

it is anticipated that (*R*)-BINOL•$SnCl_4$ serves as the asymmetric proton source in this reaction *via* a Lewis acid-assisted Brønsted acid (LBA).

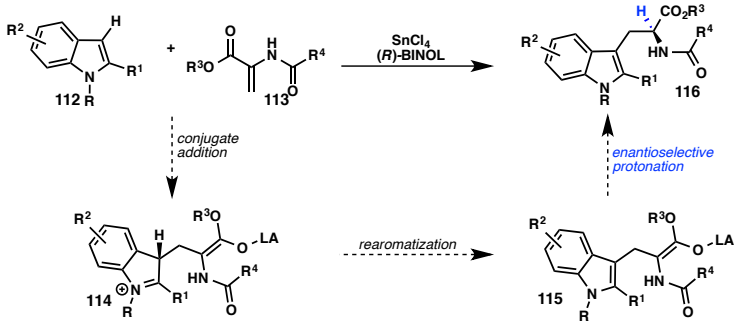
Scheme 2.1. *Proposed mechanism of formal (3+2) cycloaddition reaction*



Given this mechanistic insight, we reasoned that the related Friedel–Crafts alkylation of 3-*un*substituted indoles would further probe the role of such an enantioselective protonation, instead providing functionalized tryptophan products rather than pyrroloindolines. Mechanistically, this reaction would occur through initial conjugate addition of an indole into a Lewis-acid activated acrylate (**Scheme 2.2**). Rearomatization, followed by catalyst-controlled protonation of the resultant enolate was expected to provide alkylation product **116**. Successful implementation of this strategy would not only be mechanistically useful, but would also allow direct access to enantioenriched tryptophan derivatives from simple indole starting materials. This chapter describes our efforts towards the synthesis of enantioenriched tryptophan

derivatives through a tandem Friedel–Crafts conjugate addition/asymmetric protonation reaction.

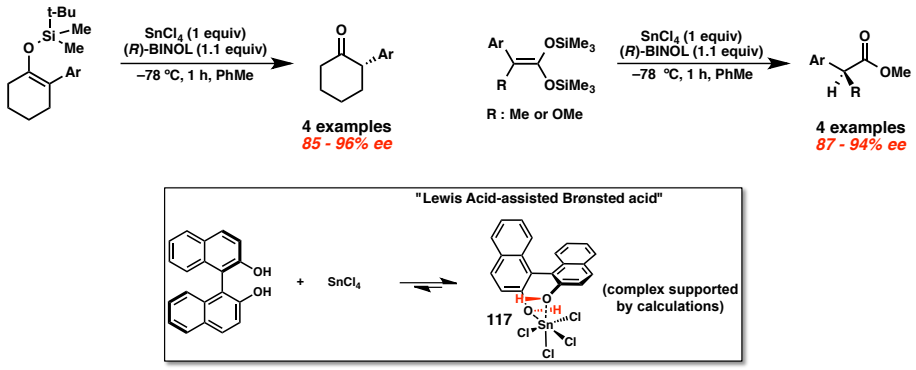
Scheme 2.2. *Proposed mechanism for the formation of enantioenriched tryptophan*



2.1.1 Precedence for Asymmetric Protonation

Our hypothesis that the Friedel–Crafts conjugate addition might undergo a selective protonation is consistent with work published by Yamamoto and co-workers, in which they report that $SnCl_4$•(*R*)-BINOL acts as an asymmetric proton source.[8] Upon subjection to stoichiometric $SnCl_4$ and (*R*)-BINOL, silyl enol ethers were cleanly converted to α-arylated ketones and esters in good yields and in excellent enantioselectivities (**Scheme 2.3**). Yamamoto proposes complex **117** acts as a Lewis acid-assisted Brønsted acid (LBA), in which complexation of (*R*)-BINOL to $SnCl_4$ greatly acidifies the alcohols, providing a selective proton source. Although subsequent reports were able to render this reaction catalytic through the addition of stoichiometric phenol derivatives, these complexes have never previously been applied to tandem conjugate addition/asymmetric protonation reactions.

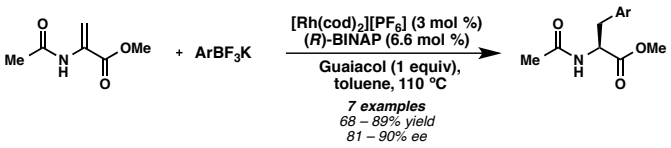
Scheme 2.3. *Yamamoto's enantioselective protonation*



2.1.2 Previous Conjugate Addition/Asymmetric Protonation Reactions

The synthesis of enantioenriched compounds employing conjugate addition/asymmetric protonation reactions has gained considerable momentum within the last decade, and a variety of nucleophiles and electrophiles have been found to be competent coupling partners.[9] One particularly relevant example comes from the labs of Genet and Darses, where they were able to construct enantioenriched phenylalanine derivatives using this approach (**Scheme 2.4**).[10]

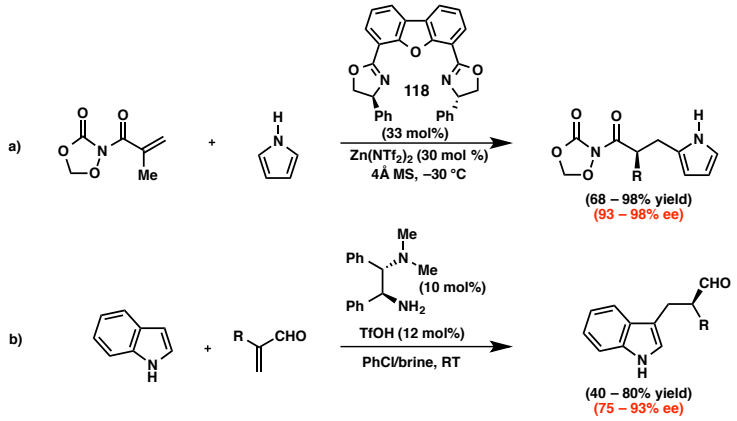
Scheme 2.4. *Tandem conjugate addition/asymmetric protonation*



Despite the prevalence of conjugate addition/asymmetric protonation reactions in the literature, the first report of a *Friedel–Crafts* conjugate addition/asymmetric protonation reaction was not disclosed until 2008. In their publication, Sibi and co-workers reveal the use of a novel isoxazolidinone auxiliary, which provides high levels of rotamer control of the enolate (**Scheme 2.5**).[11] When used in conjunction with $Zn(NTf_2)_2$

and chiral ligand **118**, they observe enantioenriched pyrrole products (**Scheme 2.5**, **a**). Concomitant to our work in this field, the Luo lab developed a chiral diamine catalyzed Friedel–Crafts conjugate addition/asymmetric protonation reaction that proceeds through an enamine intermediate.[12] They found this reaction was general for a range of α-substituted acroleins and indoles, providing products in good yield and moderate to high enantioselectivity (**Scheme 2.5**, **b**). Notably, there are no examples of Friedel–Crafts conjugate addition/asymmetric protonation reactions using indole-based nucleophiles to give tryptophan derivatives.

Scheme 2.5. *Tandem Friedel–Crafts conjugate addition/asymmetric protonation*



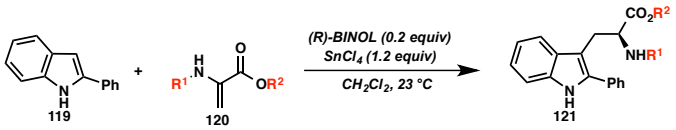
2.2 SCREENING AND OPTIMIZATION

2.2.1 Initial Screening of Acrylate and Additives

Our efforts to effect a tandem Friedel–Crafts conjugate addition/asymmetric protonation reaction began with model substrate 2-phenyl indole (**119**), which we subjected to the conditions optimized for pyrroloindoline formation. After two hours, we were disappointed to see only 12% yield of the desired product in low enantiomeric excess (**Table 2.2**, **entry 1**). As tuning of the acrylate was found to greatly affect the enantioselectivity in the pyrroloindoline methodology, a screen of 2-amido acrylates was

conducted. Gratifyingly, the use of commercially available methyl-2-acetamido acrylate provided the product in 73% yield and 78% ee (**entry 3**). Control experiments confirmed that while $SnCl_4$ alone catalyzes a background reaction, a substantial rate increase is observed upon addition of (*R*)-BINOL. No reaction was observed in the absence of $SnCl_4$ (**entry 7**).

Table 2.2. *Optimization of acrylate*



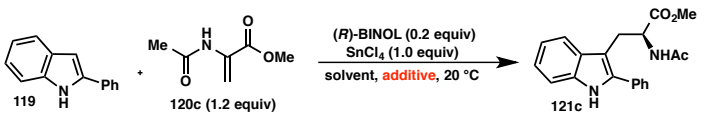
entry	R^1	R^2	time (h)	yield (%)[b]	ee (%)[c]	pdt
1	TFA	Bn	2	12	35	121a
2	TFA	Me	2	12	42	121b
3	Ac	Me	5	73	78	121c
4	CO_2Me	Me	13	nd	39	121d
5	Ts	Me	13	0	–	121e
6[d]	Ac	Me	2	13	–	121c
7[e]	Ac	Me	2	0	–	121c

[a] Reaction conducted under inert atmosphere on 0.2 mmol scale. [b] Isolated yield. [c] Determined by chiral stationary phase SFC. [d] No (*R*)-BINOL was employed. [e] No $SnCl_4$ was employed.

As the screening process progressed, we began to observe inconsistencies in the selectivity of the reaction. For example, a freshly opened bottle of $SnCl_4$ provided acetamido ester **121c** in 80% ee (**Table 2.3**, **entry 1**). However, switching to older sources of $SnCl_4$ decreased enantioenrichment to 76% (**entry 2**). Similarly, we noted a marked decrease in ee as the reaction progressed (**entries 3–7**) and suspected that HCl formed by the reaction of adventitious water with $SnCl_4$ was serving as a non-selective proton source. To this end, we investigated additives known to scavenge water or neutralize HCl. While insoluble bases such as K_2CO_3 appeared to have no effect on the reaction (**entry 9**), coordinating bases such as 2,6-lutidine completely shut down reactivity (**entry 10**). Instead, the use of activated 4Å molecular sieves increased both the yield and selectivity of the reaction, furnishing tryptophan **121c** in 86% yield and 81% ee

(**entry 11**). A small solvent screen confirmed that dichloromethane was indeed the optimal solvent for this transformation (**entries 11–13**).

Table 2.3. *Tandem Friedel–Crafts conjugate addition/asymmetric protonation*



entry	solvent	time (h)	additive	yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	2	–	nd	80[d]
2	CH_2Cl_2	2	–	nd	76[e]
3	CH_2Cl_2	0.25	–	nd	84
4	CH_2Cl_2	0.5	–	nd	84
5	CH_2Cl_2	1	–	nd	82
6	CH_2Cl_2	2	–	nd	80
7	CH_2Cl_2	7	–	nd	80
8	CH_2Cl_2	2	–	73	78
9	CH_2Cl_2	2	K_2CO_3	73	78
10	CH_2Cl_2	2	2,6-lutidine	0	–
11	CH_2Cl_2	2	4Å MS	86	81
12	DCE	2	4Å MS	87	79
13	$CHCl_3$	2	4Å MS	80	72

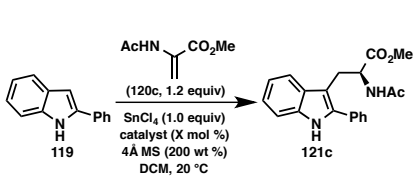
[a] Reactions conducted under inert atmosphere on 0.2 mmol scale. [b] Isolated yield. [c] Determined by chiral stationary phase SFC. [d] Reaction conducted using freshly opened $SnCl_4$. [e] Reaction conducted using previously opened $SnCl_4$.

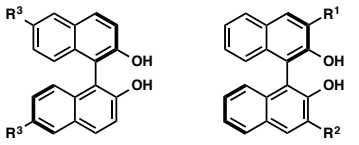
2.2.2 Screening of Chiral Ligands

With an optimal acrylate, solvent, and additive in hand, we next turned to the optimization of the catalyst structure (**Table 2.4**). Although there appeared to be no profound effect on selectivity when altering the electronics of the BINOL backbone (**entries 1–3**), we were pleased to find that modifications to the steric profile of the ligand exhibited a clearer trend. Dimethyl catalyst **122e** provided tryptophan **121c** in improved selectivities and comparable yields. Further augmentation of the steric bulk of the catalyst by substitution with phenyl groups lowered reactivity and selectivity (**entry 6**). Interestingly, dimethoxy catalyst **122g** delivered acetamido ester **121c** in low yield and as a racemate. This is likely due to its ability to participate in alternate binding modes,

resulting in a less reactive and selective catalyst. Gratifyingly, 3,3'-disubstitution with halides furnished the highest selectivities, with (*R*)-3,3'-dibromo-BINOL providing the best results (**entries 8–10**).[13] Although we found that catalyst loading could be decreased to 5 mol % while still observing 88% ee, we chose to employ 20 mol % loading as it gave reliably higher enantioselectivites for more functionalized substrates.

Table 2.4. *Optimization of a chiral ligand*





122a: R^3 = OMe 122b: R^3 = Me 122c: R^3 = Br 122d: R^1 = R^2 = H 122e: R^1 = R^2 = Me 122f: R^1 = R^2 = Ph 122g: R^1 = R^2 = OMe 122h: R^1 = R^2 = Cl 122i: R^1 = R^2 = Br 122j: R^1 = H, R^2 = Cl

entry	catalyst	loading (mol %)	yield (%)	ee (%)	entry	catalyst	loading (mol %)	yield (%)	ee (%)
1	122a	20	86	54	8	122h	20	85	90
2	122b	20	88	78	9	122i	20	76	93
3	122c	20	82	78	10	122j	20	76	84
4	122d	20	86	81	11	122i	5	72	88
5	122e	20	83	87	12	122i	10	75	92
6	122f	20	17	37	13	122i	15	77	93
7	122g	20	7	1	14	122i	40	76	93

[a] Reactions conducted under inert atmosphere on 0.2 mmol scale for 2 h. [b] Isolated yield. [c] Determined by chiral stationary phase SFC.

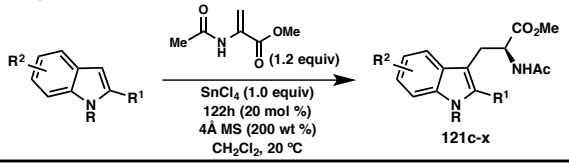
2.3 SUBSTRATE SCOPE

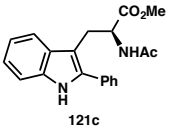
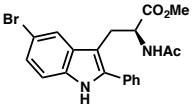
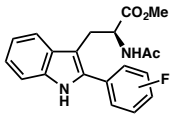
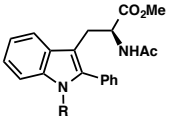
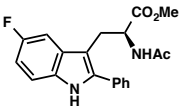
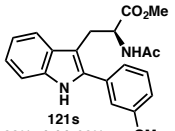
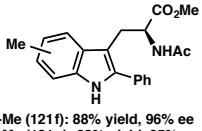
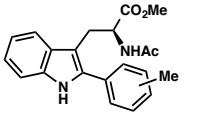
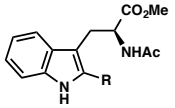
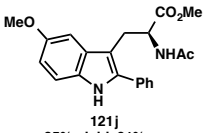
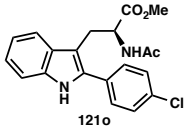
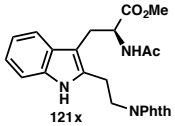
2.3.1 Friedel–Crafts/asymmetric protonation of substituted indoles

With optimal conditions in hand, an exploration of substrate scope was conducted (**Table 2.5**). In contrast to the findings from the formal (3+2) cycloaddition, we observed optimal results using *N*-protio indoles; however, methylated and allylated substrates were accommodated in slightly reduced selectivities. Substitution of the 4–7 positions of the indole backbone provided acetamido ester **121f–121i** in uniformly high yield and ee. Although both electron-rich and electron-poor indoles furnished tryptophans in high ee,

electron-deficient substrates display markedly decreased reaction rates, a finding consistent with a Friedel–Crafts type mechanism.

Table 2.5. *Substrate Scope*



entry	entry	entry
 121c 1) 76% yield, 93% ee	 121k 9)[b] 60% yield, 93% ee	 14) 4-F (121p): 78% yield, 93% ee 15) 3-F (121q): 76% yield, 92% ee 16) 2-F (121r): 35% yield, 92% ee
 2) R = Me (121d) 63% yield, 85% ee 3) R = allyl (121e) 68% yield, 85% ee	 121l 10)[b] 63% yield, 92% ee	 121s 17) 88% yield, 92% ee
 4) 4-Me (121f): 88% yield, 96% ee 5) 5-Me (121g): 83% yield, 95% ee 6) 6-Me (121h): 80% yield, 89% ee 7) 7-Me (121i): 94% yield, 94% ee	 11) 4-Me (121m): 86% yield, 94% ee 12) 2-Me (121n): 26% yield, 87% ee	 18) R = Me (121t): 61% yield, 85% ee 19) R = *n*-Bu (121u): 72% yield, 91% ee 20) R = *i*-Pr (121v): 66% yield, 92% ee 21) R = *t*-Bu (121w): 29% yield, 84% ee
 121j 8) 85% yield, 91% ee	 121o 13) 75% yield, 93% ee	 121x 22) 80% yield, 90% ee

[a] Reactions conducted under inert atmosphere on 0.1 or 0.2 mmol scale for 2 h. Isolated yields are reported. Enantiomeric excess was determined by chiral stationary phase SFC. [b] 1.6 equiv $SnCl_4$ were employed.

We found that the reaction was amenable to substrates with both alkyl and aryl substitution at the 2-position of the indole. 2-Aryl indoles bearing both electron donating and electron withdrawing substituents at the *para* and *meta* positions were tolerated (**121o**–**121s**). Unfortunately, even small functionality at the *ortho* position, such as fluoro, resulted in diminished reactivity (**121r**); a slightly larger methyl group further attenuated both yield and ee (**121n**). For 2-alkyl indoles, the ee improved when moving from a methyl group to bulkier *n*-butyl and *i*-propyl; however, a drastic decrease in yield

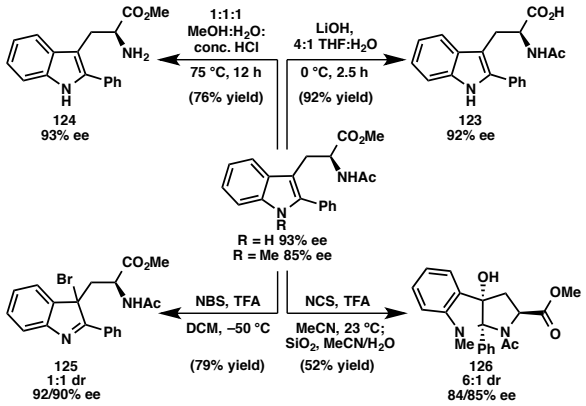
and ee is observed with the introduction of a *t*-butyl substituent (**121t**–**121w**). Remarkably, a phthalimide-containing indole proceeds in 80% yield and 90% ee (**121x**).

2.3.2 Scale-up and derivatization

Although optimization and substrate exploration were run in the glove box to streamline the screening protocol, this reaction has been reproduced on the bench top using standard Schlenk technique. Using 2-phenyl indole on 5 mmol scale, acetamido ester **121c** was isolated in 77% yield and 93% ee. Furthermore, we have shown that the methyl ester of **121c** can be selectively hydrolyzed upon subjection to aqueous LiOH in THF at 0°C (**Scheme 2.6**). Alternatively, orthogonal acetamide deprotection proceeds in methanolic HCl at 75 °C to afford free amine **124** in 76% yield with no erosion of ee.

Further functionalization of tryptophan **121c** was explored by subjection to NBS and TFA, common conditions for the oxidative cyclization of tryptophan derivatives to pyrroloindolines. Surprisingly, uncyclized imine **125** is remarkably stable, and was isolated in 79% yield as a 1:1 mixture of diasteromers. Instead, successful cyclization was achieved through exposure to NCS and TFA to initially form the 2-phenyl-3-chloro pyrroloindoline (detected by HRMS). Subsequent silica gel promoted hydrolysis delivers 2-phenyl-3-hydroxy pyrroloindoline **126** in 52% yield as a 6:1 mixture of diastereomers, constituting a new class of pyrroloindolines.

Scheme 2.6. *Derivatization of tryptophan products*



2.4 MECHANISTIC STUDIES

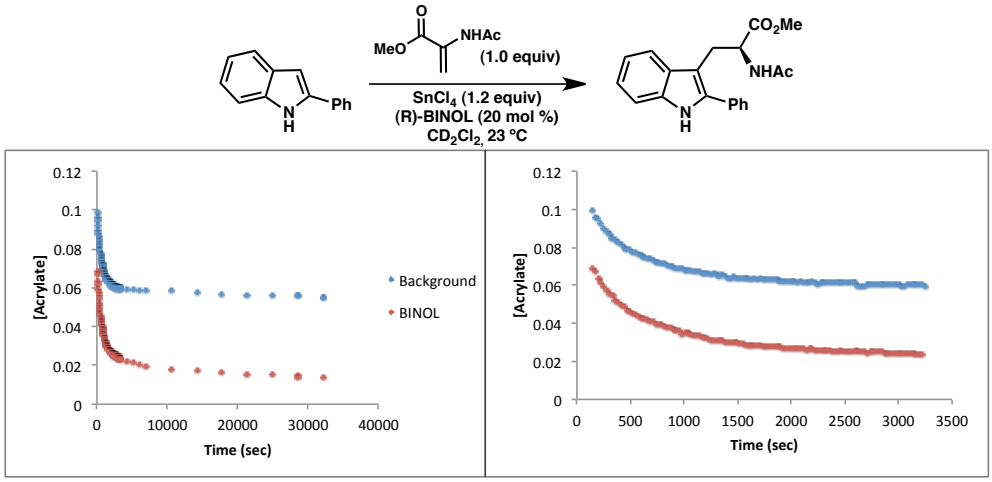
2.4.1 ^{1}H NMR Studies

As was seen in the pyrroloindoline methodology, the Friedel–Crafts conjugate addition/asymmetric protonation reaction exhibits excellent enantioselectivity, even in the presence of stoichiometric $SnCl_4$. Therefore, to better understand the mechanism of this reaction, a variety of ^{1}H NMR and deuterium labeling experiments were carried out.

We first set out to understand the relative rate of the background reaction compared to that of the $SnCl_4$•(*R*)-BINOL catalyzed reaction. A ^{1}H NMR experiment was designed in which the consumption of acrylate was monitored over time. As can be seen in **Figure 2.1**, the background reaction employing only $SnCl_4$ proceeded quickly (blue line); within thirty minutes (2000 seconds), the reaction reached 50% conversion. However, addition of catalytic (*R*)-BINOL (red line) pushed the reaction to greater than 80% conversion in the same time period. Closer examination of the first 3000 seconds of the reaction revealed that the rate of acrylate consumption is actually quite comparable for both the background and $SnCl_4$•(*R*)-BINOL catalyzed reactions. This suggests that the (*R*)-BINOL promoted rate acceleration might occur in the first two minutes of the

reaction, before ^{1}H NMR data is available. Attempts to slow the reaction through dilution and decreased catalyst loading in order to facilitate enhanced monitoring by ^{1}H NMR proved unfruitful.

Figure 2.1. *^{1}H NMR studies*

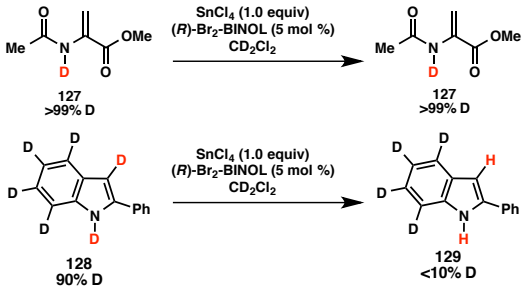


2.4.2 Deuterium labeling studies

To better understand the asymmetric protonation, we sought to find the stoichiometric proton source, which likely serves to turn over the chiral diol. Excluding adventitious water, there are three exchangeable protons: (i) the N-H of the acrylate, (ii) the N-H of the indole, or (iii) the C3 proton of the indole (which is lost in rearomatization). Therefore, *N*-deutero acrylate **127** and perdeutero indole **128** were prepared. Control reactions were carried out on each to determine if exchange occurred under the reaction conditions. Molecular sieves were omitted to prevent undesired deuterium/proton exchange between the substrates and sieves. Additionally, solutions of each substrate in dry CD_2Cl_2 were prepared in the glovebox in order to minimize exposure to moisture. Upon addition of $SnCl_4$ and (*R*)-Br_2-BINOL, each substrate was

monitored by ^{1}H NMR analysis. Although deutero acrylate **127** exhibited no deuterium-proton scrambling, perdeutero indole **128** underwent rapid exchange. In only a few minutes the substrate exhibited less than 10% deuterium incorporation. Unfortunately, the facile exchange of deuterium under the reaction conditions renders these labeling studies inconclusive. Furthermore, despite efforts to rigorously exclude moisture from these experiments, adventitious water cannot be ruled out as the stoichiometric proton source.

Scheme 2.7. *Deuterium labeling studies*

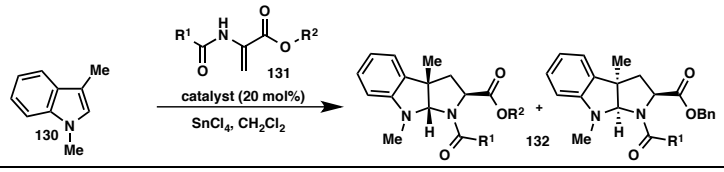


2.4.3 Comparison studies

Due to the apparent mechanistic similarities of the formal (3+2) cycloaddition and the Friedel–Crafts, we wondered if our newly optimized conditions for the Friedel–Crafts could be applied to the synthesis of pyrroloindolines to enhance selectivity. Using methyl-2-acetamido acrylate, indole **130** was subjected to optimal Friedel–Crafts conditions (**entry 2**). While there was a discernible increase in the selectivity of the product mixture compared to the originally reported conditions for acrylate **131** (**entry 1**), better results were still achieved using benzyl-2-trifluoroacetamido acrylate (**entry 3**). Interestingly, use of acrylate **131**, with optimal Friedel–Crafts conditions delivered the product in good dr and excellent enantioselectivity (**entry 4**). Unfortunately, use of (*R*)-3,3'-Br_2-BINOL and 4Å molecular sieves also mitigates the reactivity of the transformation, returning an inadmissibly low yield of product. Thus, appropriate

matching of catalyst and acrylate is necessary to synthesize either tryptophan derivatives (**121**) or pyrroloindolines (**132**) in both high yield and ee.

Table 2.6. *Comparison studies*



entry	conditions	R^1, R^2	yield (%)[a]	dr[b]	ee (%)[c]
1	(*R*)-BINOL	Me, Me	70	5:1	65/80
2	(*R*)-Br_2-BINOL, 4Å MS	Me, Me	58	8:1	87/85
3	(*R*)-BINOL	CF_3, Bn	86	4:1	94/91
4	(*R*)-Br_2-BINOL, 4Å MS	CF_3, Bn	39	7:1	98/95

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis of crude reaction mixture. [c] Determined by chiral stationary phase SFC. [d] Reaction run with 1.0 equiv acrylate, 1.2 equiv $SnCl_4$. [e] Reaction run with 1.2 equiv acrylate, 1.0 equiv $SnCl_4$.

2.5 CONCLUSION

In summary, this report describes the development of a $SnCl_4$•(*R*)-Br_2-BINOL catalyzed tandem Friedel–Crafts conjugate addition/asymmetric protonation reaction. Utilizing a wide range of 2-substituted indoles and methyl-2-acetamido acrylate, we are able to access non-canonical tryptophan derivatives in a convergent manner. We have demonstrated that the acetamide and methylester functionality can be orthogonally deprotected and that acetamido ester **121c** can be advanced to more functionalized compounds. Moreover, experiments directed towards elucidation of the mechanism have been carried out. While the rapid rate of this reaction as well as deuterium scrambling under the reaction conditions has complicated analysis, data suggest that catalytically generated **122i**•$SnCl_4$ is serving as a chiral Lewis-acid assisted Brønsted acid to protonate an intermediate Sn-enolate. Future work is directed towards further expansion of substrate scope to include C2 unsubstituted indoles.

2.6 EXPERIMENTAL SECTION

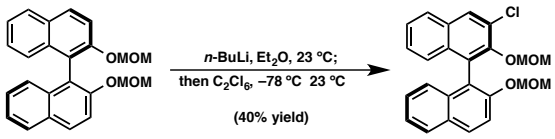
2.6.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Methylene chloride, deuterated methylene chloride, dioxane, ether, tetrahydrofuran, and toluene were dried by passing through activated alumina. Dichloroethane and chloroform were distilled over calcium hydride. Powdered 4Å molecular sieves were flame-dried under vacuum immediately prior to use. Potassium carbonate was dried for 12 h at 130 °C under vacuum and 2,6-lutidine was distilled over $AlCl_3$. All other commercially obtained reagents were used as received unless specifically indicated. (*R*)–BINOL, 2-phenylindole and 2-methylindole were purchased from Alfa Aesar, *N*-methyl-2-phenylindole was obtained from Sigma-Aldrich, and 1 M $SnCl_4$ in CH_2Cl_2 was purchased from Acros Organics. (*R*)- 3,3'-diphenyl-BINOL, (*R*)-3,3'-dimethyl-BINOL, (*R*)-3,3'-dichloro- BINOL, (*R*)-3,3'-dibromo-BINOL, (*R*)-3,3'-dimethoxy-BINOL, (*R*)-6,6'-dimethyl-BINOL, (*R*)-6,6'-dibromo-BINOL, (*R*)-2'-methoxy-[1,1'-binaphthalen]-2-ol, (*R*)-2'-isopropoxy-[1,1'-binaphthalen]-2-ol, (*R*)-3,3'-difluoro-BINOL, (*R*)-3-phenyl-BINOL, (*R*)- 5,5',6,6',7,7',8,8'-octahydro-BINOL, (*R*)-2'-benzoyl-[1,1'-binaphthalen]-2-ol, (*R*)-3-bromo-BINOL and (*R*)-3-iodo-BINOL, TADDOL, Napthyl-TADDOL, and 2-(trimethylsilyl)indole, were prepared according to literature procedures. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm). Silica gel column chromatography was performed either as described by Still et al. (W.C. Still, M. Kahn, A. Mitra, *J. Org. Chem*. **1978**, *43*, 2923.) using silica gel (particle size 0.032-0.063)

purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiSilica gel Rf system (Teledyne ISCO Inc.). ^{1}H and ^{13}C NMR were recorded on a Varian Inova 500 (at 500 MHz and 125 MHz respectively) or a Varian Inova 600 (at 600 MHz and 150 MHz respectively, and are reported relative to internal chloroform (^{1}H, δ = 7.26, ^{13}C, δ = 77.0) or internal acetonitrile (^{1}H, δ = 1.94, ^{13}C, δ = 1.32). 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. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system with Chiralcel AD-H, OD-H, AS-H, and OB-H columns (4.6 mm x 25 cm). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. 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.

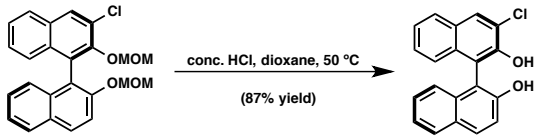
2.6.2 Catalyst and substrate preparation

Preparation of (*R*)-3-chloro-BINOL (122h)



To a flame-dried 100 mL flask containing MOM–protected (*R*)-BINOL **S1** (748 mg, 2.00 mmol, 1.00 equiv) was added Et_2O (45 mL), followed by dropwise addition of *n*-BuLi as a solution in hexanes (2.5 M, 960 μL, 2.40 mmol, 1.20 equiv) at room

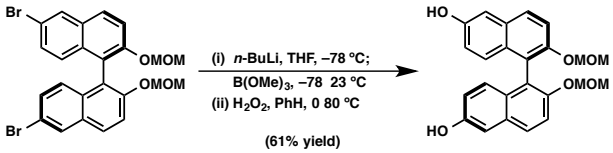
temperature. The mixture was then stirred at room temperature for 3 h and subsequently cooled to –78 ºC, followed by addition of C_2Cl_6 (569 mg, 2.40 mmol, 1.20 equiv) in one portion. The reaction mixture was allowed to warm to room temperature over 3 h, then diluted with EtOAc (15 mL) and washed with saturated aqueous NH_4Cl (50 mL). The aqueous layer was extracted with EtOAc (45 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude yellow oil was purified by silica gel chromatography (0:100 to 12:88 EtOAc:hexanes) to yield 328 mg (40% yield) of **SI-1** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.97 (d, *J* = 9.0 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.59 (d, *J* = 9.1 Hz, 1H), 7.42 (ddd, *J* = 8.1, 6.7, 1.3 Hz, 1H), 7.37 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.28 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.24 (ddd, *J* = 8.5, 6.7, 1.3 Hz, 1H), 7.18 (dddd, *J* = 8.6, 1.3, 0.7, 0.7 Hz, 1H), 7.16 (ddd, *J* = 8.5, 1.8, 0.8 Hz, 1H), 5.15 (d, *J* = 7.0 Hz, 1H), 5.04 (d, *J* = 7.0 Hz, 1H), 4.80 (d, *J* = 5.6 Hz, 1H), 4.75 (d, *J* = 5.6 Hz, 1H), 3.19 (s, 3H), 2.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 148.9, 133.8, 132.6, 131.1, 130.0, 129.5, 128.8, 128.0, 127.9, 127.8, 127.0, 126.7, 126.4, 126.1, 125.8, 125.5, 124.2, 119.9, 116.3, 98.8, 94.9, 56.5, 55.9; IR (NaCl/thin film): 2955, 2902, 1594, 1508, 1354, 1241, 1159, 1149, 1034, 1014, 961, 922 cm^{-1}; $[\alpha]_D^{25}$ = +69.1 (*c* = 0.90, $CHCl_3$). HRMS (FAB+) calc'd for M^+ 408.1128, found 408.1128.



A 10 mL flask was charged with **SI-1** (305 mg, 0.75 mmol, 1.00 equiv), dioxane (3.7 mL) and aqueous HCl (12 M, 130 μL, 1.58 mmol, 2.10 equiv), then heated to 50 ºC for 2 h. The mixture was cooled to room temperature, then diluted with H_2O (30 mL) and

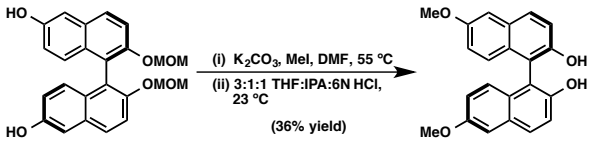
extracted with EtOAc (6 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by silica gel chromatography (0:100 to 20:80 EtOAc:hexanes) to yield 210 mg (87% yield) of (*R*)-3-chloro-BINOL (**122j**) as a white foam, which was dried over P_2O_5 under vacuum. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.97 (d, *J* = 8.9 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.45 – 7.35 (m, 3H), 7.34 – 7.28 (m, 2H), 7.16 (d, *J* = 8.5 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 5.60 (s, 1H), 4.94 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 148.3, 133.1, 132.4, 131.3, 129.7, 129.32, 129.26, 128.4, 127.7, 127.5, 127.3, 125.1, 124.6, 124.1, 123.9, 122.4, 117.7, 113.6, 111.7; IR (NaCl/thin film): 3503, 3057, 1620, 1596, 1502, 1451, 1379, 1265, 1212, 1184, 1146, 828 cm^{-1}; $[\alpha]_D^{25}$ = +55.4 (*c* = 1.01, $CHCl_3$). HRMS (MM) calc'd for $[M-H]^-$ 319.0531, found 319.0549.

Preparation of (*R*)-6,6'-dimethoxy-BINOL



(*R*)-6,6'-dimethoxy-BINOL was prepared following a procedure adapted from a reported synthesis of (*R*)-3,3'-dimethoxy-BINOL. To a 25 mL flask containing MOM–protected (*R*)-6,6'-dibromo-BINOL (1.10 g, 2.07 mmol, 1.00 equiv) was added THF (6.3 mL). The flask was cooled to –78 ºC, followed by dropwise addition of *n*-BuLi as a solution in hexanes (2.5 M, 2.50 mL, 6.20 mmol, 3.00 equiv). After stirring 1 hour at –78 ºC, $B(OMe)_3$ (645 mg, 6.20 mmol, 3.00 equiv) was added and the reaction was allowed to warm to room temperature. After 14 hours, the reaction mixture was concentrated to give the crude borate intermediate, which was suspended in benzene (7.2 mL) and cooled to 0 ºC, followed by dropwise addition of aqueous hydrogen peroxide

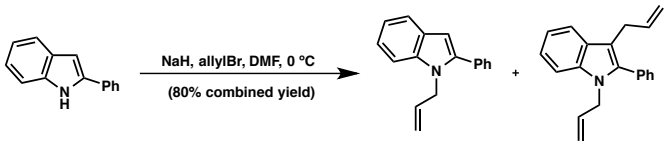
(30 wt %, 0.61 mL, 5.98 mmol, 2.89 equiv). The suspension was heated to reflux for 4 hours, then cooled to room temperature, poured into ice-cold saturated aqueous $NaSO_3$ (20 mL), and extracted with EtOAc (3 x 15 mL). The combined organics were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified by silica gel chromatography (0:100 to 50:50 EtOAc:hexanes) to yield 512 mg (61% yield) of the product as a light yellow foam. ^{1}H NMR (500 MHz, CD_3CN) δ 7.80 (ddd, *J* = 9.1, 0.8, 0.4 Hz, 2H), 7.51 (d, *J* = 9.1 Hz, 2H), 7.20 (ddd, *J* = 2.5, 0.5, 0.5 Hz, 2H), 7.09 (br s, 2H), 6.93 (ddd, *J* = 9.1, 0.7, 0.7 Hz, 2H), 6.87 (dd, *J* = 9.1, 2.5 Hz, 2H), 5.02 (d, *J* = 6.7 Hz, 2H), 4.94 (d, *J* = 6.7 Hz, 2H), 3.11 (s, 6H) ; ^{13}C NMR (125 MHz, CD_3CN) δ 154.4, 151.6, 132.1, 129.6, 128.4, 127.8, 122.1, 119.6, 118.7, 110.1, 96.0, 56.1; IR (NaCl/thin film): 3368, 2914, 1624, 1599, 1511, 1240, 1196, 1148, 1023 cm^{-1}; $[\alpha]_D^{25}$ = +87.1 (*c* = 1.00, MeCN). HRMS (MM) calc'd for $[M-H]^-$ 405.1344, found 405.1350.



A 15 mL flask was charged with (R)-MOM-hydroxy-BINOL (200 mg, 0.493 mmol, 1.00 equiv) and K_2CO_3 (177 mg, 1.28 mmol, 2.60 equiv). DMF (2 mL) was added, followed by MeI (123 μL, 1.97 mmol, 4.00 equiv) dropwise. The reaction was then heated to 55 °C for 22 hours, then cooled to room temperature and quenched with saturated aqueous NH_4Cl (2 mL) and Et_3N (3 drops). The mixture was stirred at room temperature for 6 hours, then diluted with H_2O (15 mL) and extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (15 mL), dried (Na_2SO_4), and concentrated. THF (28 mL) and IPA (9.5 mL) were added to the crude residue, followed

by dropwise addition of aqueous HCl (6.0 M, 9.4 mL). The reaction was stirred at room temperature for 3 hours, then diluted with H_2O (70 mL) and extracted with EtOAc (3 x 30 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (2 x 45 mL) and brine (45 mL), then dried (Na_2SO_4), filtered, and concentrated. The crude oil was purified by silica gel chromatography (0:100 to 30:70 EtOAc:hexanes) to yield 62 mg (36% yield) of (*R*)-6,6'-dimethoxy-BINOL as a light brown solid, which was dried over P_2O_5 under hi-vacuum. Spectral data are in agreement with the literature.

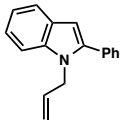
Preparation of 1-allyl-2-phenylindole



To a 50 mL flask was added NaH (620 mg, 15.5 mmol, 3.00 equiv) and DMF (8 mL) and the suspension was cooled to 0 ºC in an ice bath. A solution of 2-phenylindole (1.00 g, 5.18 mmol, 1.00 equiv) in DMF (3 mL) was added slowly to the suspension over 15 minutes and the reaction mixture was further stirred at 0 ºC for 20 minutes, followed by dropwise addition of allyl bromide (670 μL, 7.77 mmol, 1.50 equiv). The ice bath was then removed and the mixture was stirred for 15 minutes, then quenched by addition of saturated aqueous NH_4Cl (5 mL) and Et_3N (5 drops). After 2 hours, the reaction was diluted with H_2O (40 mL) and extracted with EtOAc (3 x 30 mL). The combined organics were washed with brine (120 mL), dried (Na_2SO_4), filtered, and concentrated. The crude was then purified by reverse phase preparatory HPLC (55:45 to 95:5 MeCN:H_2O) using an Agilent 1200 Series HPLC with an Agilent XDB-C18 5 μM column (9.4 x 250 mm and 21.2 x 150 mm) to yield 687 mg (57% yield) of 1-allyl-2-

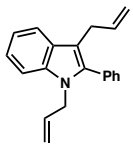
phenylindole as a yellow solid and 331 mg (23% yield) of 1,3-diallyl-2-phenylindole as a yellow oil.

1-allyl-2-phenylindole :



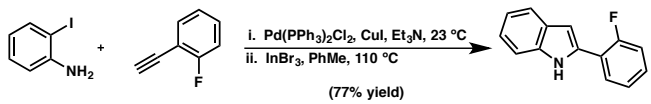
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (ddd, *J* = 7.8, 1.2, 0.8 Hz, 1H), 7.55 – 7.51 (m, 2H), 7.48 – 7.43 (m, 2H), 7.42 – 7.38 (m, 1H), 7.33 (br d, *J* = 8.2 Hz, 1H), 7.22 (ddd, *J* = 7.0, 7.0, 1.3 Hz, 1H), 7.15 (ddd, *J* = 7.0, 7.0, 1.0 Hz, 1H), 6.60 (br s, 1H), 6.02 (ddt, *J* = 17.2, 10.5, 4.4 Hz, 1H), 5.22 (dtd, *J* = 10.5, 1.8, 1.1 Hz, 1H), 5.00 (dtd, *J* = 17.1, 2.0, 1.2 Hz, 1H), 4.74 (dt, *J* = 4.2, 1.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.5, 137.8, 133.8, 132.7, 129.1, 128.5, 128.1, 128.0, 121.7, 120.5, 120.0, 116.5, 110.3, 102.0, 46.5; IR (NaCl/thin film): 3055, 2917, 1602, 1462, 1443, 1392, 1345, 1317, 1162 cm^{-1}; HRMS (APCI) calc'd for $[M+H]^+$ = 234.1277, found 234.1284.

1,3-diallyl-2-phenylindole:



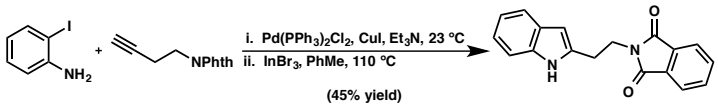
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (ddd, *J* = 7.8, 1.2, 0.7 Hz, 1H), 7.50 – 7.40 (m, 5H), 7.33 (ddd, *J* = 8.1, 0.9, 0.9 Hz, 1H), 7.24 (ddd, *J* = 7.0, 7.0, 1.2 Hz, 1H), 7.16 (ddd, *J* = 7.0, 7.0, 1.1 Hz, 1H), 6.05 (ddt, *J* = 17.0, 10.1, 5.9 Hz, 1H), 5.91 (ddt, *J* = 17.1, 10.4, 4.7 Hz, 1H), 5.14 (dtd, *J* = 10.4, 1.8, 1.2 Hz, 1H), 5.08 – 5.02 (m, 2H), 4.92 (dtd, *J* = 17.1, 1.9, 1.3 Hz, 1H), 4.62 (dt, *J* = 4.6, 1.9 Hz, 2H), 3.46 (dt, *J* = 6.0, 1.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 137.9, 136.7, 133.9, 131.8, 130.4, 128.3, 128.2, 128.1, 128.0, 121.7, 119.34, 119.30, 116.2, 114.6, 110.9, 110.1, 46.4, 29.2; IR (NaCl/thin film): 3056, 2915, 1637, 1463, 1443, 1408, 1360, 1340, 1191 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ = 274.1590, found 274.1591.

Preparation of 2-(2-fluorophenyl)indole:



2-(2-fluorophenyl)indole was prepared by an analogous procedure to that reported by Sakai et. al. A flame-dried flask was charged with 2-iodoaniline (200 mg, 0.90 mmol, 1.00 equiv), ethynyl-2-fluorobenzene (133 mg, 1.10 mmol, 1.20 equiv), $Pd(PPh_3)_2Cl_2$ (13 mg, 0.02 mmol, 0.02 equiv), copper (I) iodide (2.0 mg, 0.025 mmol, 0.01 equiv) and Et_3N (4 mL). The mixture was stirred overnight at room temperature, then filtered through a plug of silica, concentrated and redissolved in PhMe (5 mL). $InBr_3$ (16 mg, 0.05 mmol, 0.05 equiv) was added in one portion and the mixture was heated to 110 ºC for 5 h, then cooled to room temperature, filtered through celite, and concentrated. The crude residue was purified by silica gel chromatography (10:90 EtOAc:hexanes) to yield 148 mg (77% yield) of 2-(2-fluorophenyl)indole as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (br s, 1H), 7.80 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1H), 7.66 (dddd, *J* = 2.5, 1.3, 0.8, 0.8 Hz, 1H), 7.43 (ddd, *J* = 8.1, 1.5, 0.8 Hz, 1H), 7.32 – 7.26 (m, 1H), 7.26 – 7.16 (m, 3H), 7.14 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.97 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3 (d, $J_{C\text{-}F}$= 246.4 Hz), 134.6 (d, $J_{C\text{-}F}$ = 501.8 Hz), 128.8 (d, $J_{C\text{-}F}$ = 8.8 Hz), 128.1, 128.0 (d, $J_{C\text{-}F}$ = 4.1 Hz), 124.8 (d, $J_{C\text{-}F}$ = 3.2 Hz), 122.7, 120.6, 120.2, 119.9 (d, $J_{C\text{-}F}$ = 11.0 Hz), 116.6, 116.4, 111.0, 101.6 (d, $J_{C\text{-}F}$ = 3.0 Hz); IR (NaCl/thin film): 3469, 3042, 2918, 2848, 1577, 1472, 1460, 1212, 1178, 1109, 928 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 212.0870, found 212.0869.

Preparation of 2-(ethylphthalimide)indole:



2-(ethylphthalimide)indole was prepared by an analogous procedure to that reported by Sakai et. al. A flame-dried flask was charged with 2-iodoaniline (500 mg, 2.30 mmol,

1.00 equiv), 2-(but-3-yn-1-yl)isoindoline-1,3-dione (550 mg, 2.75 mmol, 1.20 equiv), $Pd(PPh_3)_2Cl_2$ (32 mg, 0.05 mmol, 0.02 equiv), copper (I) iodide (4.5 mg, 0.025 mmol, 0.01 equiv) and Et_3N (8 mL). The mixture was stirred overnight at room temperature, then filtered through a plug of silica, concentrated and redissolved in PhMe (10 mL). $InBr_3$ (40 mg, 0.1 mmol, 0.05 equiv) was added in one portion and the mixture was heated to 110 ºC for 5 h, then cooled to room temperature, filtered through celite and concentrated. The crude residue was purified by silica gel chromatography (60:40 EtOAc:hexanes) to yield 302 mg (45% yield) of 2-(ethylphthalimide)indole as a light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (br s, 1H), 7.83 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.51 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.13 (ddd, J = 8.2, 7.1, 1.2 Hz, 1H), 7.06 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H), 6.33 (d, J = 1.2 Hz, 1H), 4.06 (t, *J* = 7.5 Hz, 2H), 3.21 (t, J = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 136.1, 134.9, 134.1, 131.9, 128.6, 123.4, 121.4, 120.0, 119.7, 110.6, 101.1, 37.1, 27.4.; IR (NaCl/thin film): 3366, 1772, 1707, 1653, 1617, 1466, 1395, 1363, 1293 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 291.1128, found 291.1138.

2.6.3 Optimization of Reaction Parameters

2.6.3.1 General Procedure 1

An oven-dried vial was charged with 2-phenylindole (0.20 mmol, 1.00 equiv), the acrylate (0.24 mmol, 1.20 equiv) and an (*R*)-BINOL derivative and pumped into a glove box. The vial was charged with solvent to an indole concentration of 0.12 M, and $SnCl_4$ (1.00 equiv, as a 1.0 M solution in CH_2Cl_2) was added. The reaction was stirred at 20 °C for 2 hours, after which time it was removed from the glove box and quenched by

dilution with 1 M HCl (5 mL) and MeCN (1 mL). The aqueous layer was extracted with EtOAc (2 x 5 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL), dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified by silica gel chromatography.

Additive screens. Reactions were performed following General Procedure 1 using 0.20 equiv (*R*)-BINOL. After the vial was pumped into the glove box, one of the following additives was added:

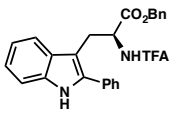
- flame-dried powdered 4Å molecular sieves (200 wt % relative to indole)
- K_2CO_3 (1.00 equiv)
- 2,6-lutidine (1.00 equiv)

Upon addition of the additive, DCM was added to an indole concentration of 0.12 M and the reaction was further conducted as described above.

Catalyst screens. Reactions were performed following General Procedure 1 using flame-dried powdered 4Å molecular sieves (200 wt % relative to indole) as an additive and DCM as a solvent.

2.6.3.2 Characterization Data

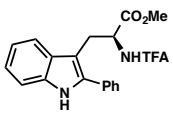
(*S*)-N_α-Trifluoroacetyl-2-phenyltryptophan benzyl ester (121a)



Prepared from benzyl 2-trifluoroacetamidoacrylate (65.5 mg, 0.24 mmol) following General Procedure 1. The crude residue was purified by silica gel chromatography (30:70 to 70:30 DCM:hexanes) to yield 11.1 mg (12% yield) of **121a** as a yellow solid. The enantiomeric excess was determined to be 35% by chiral SFC analysis (OB-H, 2.5 mL/min, 15% IPA in CO_2, λ = 254 nm): t_R(major) = 11.0 min,

t_R(minor) = 12.9 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (br s, 1H), 7.57 (ddd, *J* = 7.9, 1.8, 0.7 Hz, 1H), 7.54 – 7.50 (m, 2H), 7.50 – 7.45 (m, 2H), 7.42 – 7.36 (m, 2H), 7.34 – 7.29 (m, 3H), 7.24 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 7.16 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 7.11 – 7.07 (m, 2H), 6.67 (br d, *J* = 7.6 Hz, 1H), 4.95 (d, *J* = 12.2 Hz, 1H), 4.88 (dt, *J* = 7.8, 6.0 Hz, 1H), 4.53 (d, *J* = 12.2 Hz, 1H), 3.65 – 3.56 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 156.6 (q, J_{C-F} = 37.8 Hz), 136.3, 135.6, 134.6, 132.4, 129.2, 128.9, 128.5, 128.44, 128.38, 128.2, 128.1, 122.8, 120.3, 118.6, 115.3 (q, J_{C-F} = 287.9 Hz), 111.0, 105.6, 67.5, 53.3, 26.7; IR (NaCl/thin film): 3391, 3061, 2924, 1714, 1542, 1457, 1210, 1173 cm^{-1}; $[\alpha]_D^{25}$ = +3.5 (*c* = 0.44, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 467.1577, found 467.1580.

(*S*)-N_α-Trifluoroacetyl-2-phenyltryptophan methyl ester (121b)



Prepared from methyl 2-trifluoroacetamidoacrylate (47.3 mg, 0.24 mmol) following General Procedure 1. The crude residue was purified by silica gel chromatography (0:100 to 5:95 EtOAc:toluene, then 0:100 to 20:80 EtOAc:hexanes) to yield 9.0 mg (12% yield) of **121b** as a yellow solid. The enantiomeric excess was determined to be 42% by chiral SFC analysis (AS-H, 2.5 mL/min, 10% IPA in CO_2, λ = 254 nm): t_R(major) = 8.7 min, t_R(minor) = 7.7 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (br s, 1H), 7.58 – 7.52 (m, 3H), 7.52 – 7.47 (m, 2H), 7.43 – 7.39 (m, 1H), 7.38 (ddd, *J* = 8.1, 0.9, 0.9 Hz, 1H), 7.23 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.16 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.65 (br d, *J* = 7.3 Hz, 1H), 4.83 (dt, *J* = 7.8, 5.6 Hz, 1H), 3.66 – 3.56 (m, 2H), 3.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 156.6 (q, J_{C-F} = 37.7 Hz), 136.3, 135.6, 132.5, 129.2, 129.0, 128.4, 128.2, 122.8, 120.3, 118.5, 115.3 (q, J_{C-F}= 287.7 Hz), 111.0, 105.5, 53.2, 52.5, 26.4; IR (NaCl/thin film): 3391, 3057, 2917, 2849, 1718, 1542, 1458,

1449, 1211, 1170 cm^{-1} ; $[\alpha]_D^{25}$ = +22.3 (*c* = 0.39, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 391.1264, found 391.1267.

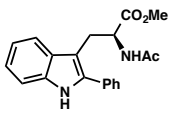
2.6.4 Optimized Conjugate Addition/Asymmetric Protonation

2.6.4.1 General Procedure 2

An oven-dried vial was charged with the indole (1.00 equiv), methyl 2-acetamidoacrylate (1.20 equiv) and (*R*)-3,3'-dibromo-BINOL (0.20 equiv) and pumped into a glove box. To the vial was added flame-dried powdered 4Å molecular sieves (200 wt % relative to indole). The vial was charged with DCM to an indole concentration of 0.12 M, and $SnCl_4$ (1.00 equiv unless specifically indicated, as a 1 M solution in DCM) was added. The reaction was stirred at 20 °C for 2 hours, after which time it was removed from the glove box and quenched by dilution with 1 M HCl (5 mL) and MeCN (1 mL). The aqueous layer was extracted with EtOAc (2 x 5 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL), dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified by silica gel chromatography.

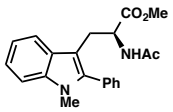
2.6.4.2 Characterization Data

(*S*)-*N*α-Acetyl-2-phenyltryptophan methyl ester (121c)



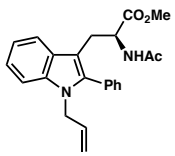
Prepared from 2-phenylindole (19.0 mg, 0.10 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 25.6 mg (76% yield) of **121c** as a white foam. The enantiomeric excess was determined to be 93% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO_2, λ = 254 nm). t_R(major) = 5.7 min, t_R(minor) = 6.9 min. $[\alpha]_D^{25}$ = +37.7 (*c* = 0.94, $CHCl_3$). Spectral data matches that reported in the literature.

(*S*)-N_α-Acetyl-1-methyl-2-phenyltryptophan methyl ester (121d)



Prepared from 1-methyl-2-phenylindole (41.4 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (0:100 to 55:45 EtOAc:hexanes) to yield 43.4 mg (63% yield) of **121d** as a yellow solid. The enantiomeric excess was determined to be 85% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO_2, λ = 254 nm): t_R(major) = 4.6 min, t_R(minor) = 3.9 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (ddd, *J* = 7.9, 1.2, 0.7 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.48 – 7.44 (m, 1H), 7.42 – 7.38 (m, 2H), 7.34 (ddd, *J* = 8.2, 0.9, 0.9 Hz, 1H), 7.26 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.17 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 5.72 (br d, *J* = 7.8 Hz, 1H), 4.74 (dt, *J* = 8.0, 5.6 Hz, 1H), 3.57 (s, 3H), 3.39 (s, 3H), 3.41 (dd, *J* = 14.7, 5.7 Hz, 1H), 3.34 (dd, *J*=14.8, 5.6 Hz, 1H), 1.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 169.5, 139.2, 136.9, 131.6, 130.7, 128.7, 128.4, 127.9, 122.0, 119.7, 118.7, 109.5, 106.7, 52.8, 52.0, 30.8, 26.6, 23.0.; IR (NaCl/thin film): 3288, 3055, 2950, 1743, 1657, 1539, 1469, 1441, 1368, 1238, 1212 cm^{-1}; $[\alpha]_D^{25}$ = +21.3 (*c* = 0.91, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 351.1703, found 351.1708.

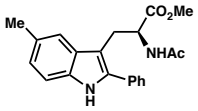
(*S*)-N_α-Acetyl-1-allyl-2-phenyltryptophan methyl ester (121e)



Prepared from 1-allyl-2-phenylindole (46.6 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (0:100 to 55:45 EtOAc:hexanes) to yield 51.3 mg (68% yield) of **121e** as a yellow foam. The enantiomeric excess was determined to be 85% by chiral SFC analysis (AS-H, 2.5 mL/min, 30% IPA in CO_2, λ = 254 nm): t_R(major) = 2.9 min, t_R(minor) = 2.4 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (ddd, *J* = 7.8, 1.0, 1.0 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.47 – 7.42 (m, 1H), 7.42 – 7.37 (m, 2H), 7.30 (ddd, *J* = 8.1,

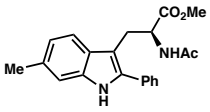
0.9, 0.9 Hz, 1H), 7.23 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.17 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 5.85 (ddt, *J* = 17.1, 10.3, 4.7 Hz, 1H), 5.76 (br d, *J* = 7.9 Hz, 1H), 5.11 (dtd, *J* = 10.4, 1.7, 1.2 Hz, 1H), 4.82 (dtd, *J* = 17.1, 1.9, 1.3 Hz, 1H), 4.76 (dt, *J* = 8.0, 5.8 Hz, 1H), 4.56 (dt, *J* = 4.7, 1.8 Hz, 2H), 3.39 (s, 3H), 3.36 (dd, *J* = 14.7, 5.7 Hz, 1H), 3.29 (dd, *J* = 14.7, 5.9 Hz, 1H), 1.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 169.5, 139.0, 136.3, 133.5, 131.5, 130.5, 128.7, 128.5, 128.1, 122.0, 119.8, 118.8, 116.3, 110.2, 107.2, 52.8, 52.0, 46.3, 26.8, 23.0; IR (NaCl/thin film): 3435, 3287, 3056, 2950, 2926, 2851, 1744, 1658, 1538, 1500, 1408, 1367, 1219, 1196, 1134; $[\alpha]_D^{25}$ = +13.8 (*c* = 2.96, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 377.1860, found 377.1865.

(*S*)-N_α-Acetyl-4-methyl-2-phenyltryptophan methyl ester (121f)



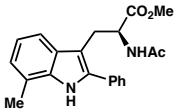
Prepared from 4-methyl-2-phenylindole (21.0 mg, 0.10 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 30.8 mg (88% yield) of **121f** as a white foam. The enantiomeric excess was determined to be 96% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO_2, λ = 254 nm): t_R(major) = 9.9 min, t_R(minor) = 8.9 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (br s, 1H), 7.55 – 7.45 (m, 4H), 7.44 – 7.37 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.08 (m, 1H), 6.91 (m, 1H), 5.44 (br d, J = 7.6 Hz, 1H), 4.63 (td, *J* = 8.2, 5.0 Hz, 1H), 3.69 – 3.45 (m, 2H), 3.44 (s, 3H), 2.78 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 169.7, 136.3, 136.1, 133.1, 130.5, 129.2, 128.9, 128.3, 126.9, 122.5, 122.3, 109.0, 107.6, 54.2, 52.1, 27.6, 22.8, 20.5; IR (NaCl/thin film): 3295, 3052, 2952, 1741, 1659, 1602, 1547, 1514, 1492, 1449, 1372, 1218; $[\alpha]_D^{25}$ = -29.0 (*c* = 0.63, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 351.1703, found 351.1698.

(*S*)-N_α-Acetyl-6-methyl-2-phenyltryptophan methyl ester (121g)



Prepared from 6-methyl-2-phenylindole (21.0 mg, 0.10 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 27.9 mg (80% yield) of **121g** as a colorless oil. The enantiomeric excesses was determined to be 89% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO_2, λ = 254 nm): t_R(major) = 9.1 min, t_R(minor) = 10.1 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (br s, 1H), 7.55 (ddd, *J* = 5.8, 4.0, 2.1 Hz, 2H), 7.48 – 7.44 (m, 3H), 7.39 – 7.33 (m, 1H), 7.14 (s, 1H), 6.97 (dd, *J* = 8.3, 1.5 Hz, 1H), 5.78 (br d, *J* = 7.8 Hz, 1H), 4.83 (dt, *J* = 8.0, 5.4 Hz, 1H), 3.55 – 3.49 (m, 2H), 3.30 (s, 3H), 2.47 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 172.1, 169.6, 136.1, 135.2, 133.3, 132.4, 129.1, 128.2, 127.9, 127.3, 121.8, 118.5, 110.9, 106.5, 52.7, 52.0, 26.6, 22.9, 21.7; IR (NaCl/thin film): 3292, 3052, 2958, 2908, 1741, 1658, 1545, 1530, 1511, 1446, 1375, 1216; $[\alpha]_D^{25}$ = +39.3 (*c* = 0.38, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 351.1703, found 351.1698.

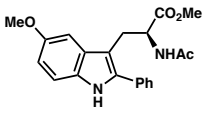
(*S*)-N_α-Acetyl-7-methyl-2-phenyltryptophan methyl ester (121h)



Prepared from 7-methyl-2-phenylindole (21.0 mg, 0.10 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (30:70 to 100:0 EtOAc:hexanes) to yield 33.0 mg (94% yield) of **121h** as a white foam. The enantiomeric excess was determined to be 94% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO_2, λ = 254 nm): t_R(major) = 5.6 min, t_R(minor) = 5.0 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (br s, 1H), 7.61 – 7.54 (m, 2H), 7.51 – 7.45 (m, 2H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.11 – 7.04 (m, 1H), 7.03 – 6.97 (m, 1H), 5.79 (br d, *J* = 8.1 Hz, 1H), 4.82 (dt, *J* = 8.1, 5.7 Hz, 1H), 2.55 (dd,

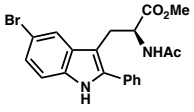
J = 12.5, 3.1 Hz, 1H), 3.51 (dd, *J* = 12.5, 3.1 Hz, 1H), 3.30 (s, 3H), 2.50 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 169.6, 135.8, 135.3, 133.3, 129.1, 128.9, 128.4, 128.0, 123.1, 120.20, 120.18, 116.5, 107.1, 52.7, 51.9, 26.6, 22.8, 16.6; IR (NaCl/thin film): 3283, 3053, 2950, 1736, 1659, 1518, 1438, 1372, 1306, 1266, 1219, 1137, 1043; $[\alpha]_D^{25}$ = +26.5 (*c* = 0.20, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 351.1703, found 351.1708.

(*S*)-*N*$_\alpha$-Acetyl-5-methoxy-2-phenyltryptophan methyl ester (121i)



Prepared from 5-methoxy-2-phenylindole (45.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 62.0 mg (85% yield) of **121i** as a colorless oil. The enantiomeric excess was determined to be 91% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO_2, λ = 254 nm): t_R(major) = 4.7 min, t_R(minor) = 6.5 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (br s, 1H), 7.58 – 7.49 (m, 2H), 7.50 – 7.41 (m, 2H), 7.36 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.24 (d, J = 8.7 Hz, 1H), 7.05 (d, J = 2.3 Hz, 1H), 6.90 – 6.80 (m, 1H), 5.82 (br d, J = 7.9 Hz, 1H), 4.82 (td, J = 7.9, 5.4 Hz, 1H), 3.87 (s, 3H), 3.49 (m, 2H), 3.29 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 169.6, 154.4, 136.7, 133.2, 130.8, 129.8, 129.1, 128.2, 128.0, 112.7, 111.7, 106.5, 100.5, 55.9, 52.7, 52.0, 26.6, 22.9; IR (NaCl/thin film): 3291, 3057, 2926, 1739, 1652, 1558, 1539, 1520, 1483, 1455, 1374, 1218, 1178; $[\alpha]_D^{25}$ = +32.6 (*c* = 0.93, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 367.1652, found 367.1658.

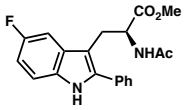
(*S*)-*N*$_\alpha$-Acetyl-5-bromo-2-phenyltryptophan methyl ester (121j)



Prepared from 5-bromo-2-phenylindole (54.0 mg, 0.20 mmol) with 1.6

equiv $SnCl_4$ following General Procedure 2. The crude residue was purified by silica gel chromatography (30:70 to 100:0 EtOAc:hexanes) to yield 49.5 mg (60% yield) of **121j** as a white foam. The enantiomeric excess was determined to be 93% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO_2, λ = 254 nm): t_R(major) = 5.3 min, t_R(minor) = 7.9 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (br s, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.49 – 7.43 (m, 2H), 7.42 – 7.34 (m, 1H), 7.28 – 7.24 (m, 1H), 7.22 – 7.18 (m, 1H), 5.75 (br d, *J* = 8.1 Hz, 1H), 4.82 (dt, *J* = 8.1, 5.7 Hz, 1H), 3.53 (dd, J = 14.9, 5.5 Hz, 1H), 3.46 (dd, J = 14.9, 4.8 Hz, 1H), 3.36 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 169.6, 137.2, 134.2, 132.6, 131.1, 129.2, 128.3, 128.2, 125.2, 121.6, 113.1, 112.4, 106.4, 52.6, 52.1, 26.5, 22.8; IR (NaCl/thin film): 3417, 3369, 3282, 1734, 1654, 1521, 1466, 1437, 1374, 1215; $[\alpha]_D^{25}$ = +47.2 (*c* = 1.04, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 415.0652, found 415.0653.

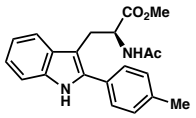
(*S*)-N_α-Acetyl-5-fluoro-2-phenyltryptophan methyl ester (121k)



Prepared from 5-fluoro-2-phenylindole (42.0 mg, 0.20 mmol) with 1.6 equiv $SnCl_4$ following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 44.7 mg (63% yield) of **121k** as a colorless oil. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO_2, λ = 254 nm): t_R(major) = 3.8 min, t_R(minor) = 5.2 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (br s, 1H), 7.60 – 7.52 (m, 2H), 7.50 – 7.43 (m, 2H), 7.42 – 7.34 (m, 1H), 7.27 – 7.24 (m, 1H), 7.21 (dd, *J* = 9.8, 2.6 Hz, 1H), 6.94 (ddd, *J* = 9.0, 9.0, 2.6 Hz, 1H), 5.77 (br d, *J* = 7.8 Hz, 1H), 4.82 (dt, *J* = 8.1, 5.4 Hz, 1H), 3.53 (dd, J = 14.9, 5.6 Hz, 1H), 3.47 (dd, J = 14.9, 5.0 Hz, 1H), 3.35 (s, 3H), 1.64 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 169.8, 168.3,

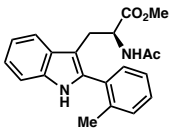
135.6, 134.2, 132.5, 131.9, 128.6, 123.5, 121.8, 119.7, 118.2, 110.8, 107.4, 52.9, 52.4, 37.0, 27.0, 25.3, 23.1; IR (NaCl/thin film): 3275, 3062, 2952, 1733, 1652, 1584, 1558, 1539, 1520, 1486, 1456, 1436, 1374, 1266, 1217, 1180; $[\alpha]_D^{25}$ = +49.9 (*c* = 1.25, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 355.1452, found 355.1455.

(*S*)-*N*α-Acetyl-2-(4-methylphenyl)tryptophan methyl ester (121l)



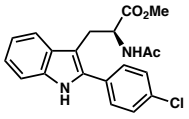
Prepared from 2-(4-methylphenyl)indole (41.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 60.1 mg (86% yield) of **121l** as a white foam. The enantiomeric excess was determined to be 94% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO_2, λ = 254 nm). t_R(major) = 6.6 min, t_R(minor) = 8.8 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (br s, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 8.1, 2H), 7.34 (d, *J* = 8.1, 1H), 7.28 (d, *J* = 8.1, 2H), 7.19 (ddd, *J* = 7.8, 7.1, 1.2 Hz, 1H), 7.15 – 7.09 (m, 1H), 5.77 (br d, *J* = 8.1, 1H), 4.82 (dt, *J* = 7.8, 5.5 Hz, 1H), 3.54 (dd, J = 13.1, 4.0 Hz, 1H), 3.50 (dd, J = 13.1, 3.7 Hz, 1H), 3.33 (s, 3H), 2.40 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 169.6, 138.0, 136.1, 135.6, 130.2, 129.8, 129.4, 128.1, 122.3, 119.9, 118.7, 110.9, 106.4, 52.8, 52.0, 26.6, 22.8, 21.2; IR (NaCl/thin film): 3365, 3271, 3052, 2951, 1737, 1657, 1519, 1460, 1439, 1375, 1305, 1217 cm^{-1}; $[\alpha]_D^{25}$ = 43.2 (*c* = 0.74, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 351.1703, found 351.1700.

(*S*)-N_α-Acetyl-2-(2-methylphenyl)tryptophan methyl ester (121m)



Prepared from 2-(2-methylphenyl)indole (21.0 mg, 0.1 mmol) following General Procedure 2. The crude residue was purified by flash chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 9.2 mg (26% yield) of **121m**. The enantiomeric excess was determined to be 87% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO_2, λ = 254 nm): t_R(major) = 4.3 min, t_R(minor) = 4.9 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (br s, 1H), 7.62 – 7.55 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.38 – 7.32 (m, 4H), 7.31 – 7.27 (m, 1H), 7.22 (ddd, J = 8.1, 5.6, 2.1 Hz, 1H), 7.16 (ddd, J = 7.1, 5.6, 1.1 Hz, 1H), 5.71 (br d, J = 7.9 Hz, 1H), 4.82 – 4.68 (dt, *J* = 7.9, 5.4 Hz, 1H), 3.38 – 3.29 (m, 4H), 3.28 – 3.16 (m, 1H), 2.28 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 169.6, 137.3, 135.8, 135.5, 132.1, 130.9, 130.8, 128.9, 128.7, 126.0, 122.3, 119.9, 118.8, 110.8, 107.6, 52.8, 52.0, 26.6, 23.0, 20.0; IR (NaCl/thin film): 3385, 3271, 3062, 2924, 2853, 1734, 1653, 1559, 1539, 1521, 1457, 1437, 1374; $[\alpha]_D^{25}$ = +21.5 (*c* = 0.29, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 351.1703, found 351.1709.

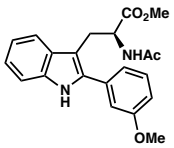
(*S*)-*N*α-Acetyl-2-(4-chlorophenyl)tryptophan methyl ester (121n)



Prepared from 2-(4-chlorophenyl)indole (45.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 55.2 mg (75% yield) of **121n** as a colorless oil. The enantiomeric excess was determined to be 93% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO_2, λ = 254 nm): t_R(major) = 6.1 min, t_R(minor) = 7.0 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (br s, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.43 – 7.37 (m, 2H), 7.33 (ddd, *J* = 8.1, 8.1, 1.0 Hz, 1H), 7.23 – 7.18 (m, 1H), 7.14 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 5.85 (br d, *J* = 8.1 Hz, 1H), 4.83 (dt,

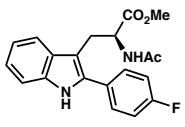
J = 8.1, 5.5 Hz, 1H), 3.55 – 3.38 (m, 2H), 3.34 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 169.6, 135.8, 134.6, 133.9, 131.5, 129.4, 129.3, 122.7, 120.1, 118.9, 111.1, 107.1, 52.8, 52.1, 29.6, 26.7, 22.9; IR (NaCl/thin film): 3280, 3058, 2948, 1737, 1657, 1519, 1487, 1458, 1439, 1373, 1310, 1216, 1093 cm^{-1}; $[\alpha]_D^{25}$ = +40.8 (*c* = 0.96, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 371.1157, found 371.1158.

(*S*)-N_α-Acetyl-2-(3-methoxyphenyl)tryptophan methyl ester (121o)



Prepared from 2-(3-methoxyphenyl)indole (45.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (30:70 to 100:0 EtOAc:hexanes) to yield 65.0 mg (88% yield) of **121o** as a colorless oil. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO_2, λ = 254 nm): t_R(major) = 5.9 min, t_R(minor) = 7.6 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (br s, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.40 – 7.31 (m, 2H), 7.19 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.16 – 7.10 (m, 2H), 7.08 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.91 (ddd, *J* = 8.3, 2.6, 0.8 Hz, 1H), 5.82 (br d, *J* = 7.8 Hz, 1H), 4.83 (dt, *J* = 7.8, 5.5 Hz, 1H), 3.85 (s, 3H), 3.57 – 3.49 (m, 2H), 3.35 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 169.6, 160.0, 135.8, 135.6, 134.4, 130.2, 129.3, 122.5, 120.6, 119.9, 118.8, 113.8, 113.5, 111.0, 106.7, 55.4, 52.8, 52.0, 26.6, 22.8; IR (NaCl/thin film): 3282, 3058, 2951, 1738, 1658, 1603, 1520, 1462, 1439, 1373, 1218, 1040; $[\alpha]_D^{25}$ = +40.3 (*c* = 1.16, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 367.1652, found 367.1656.

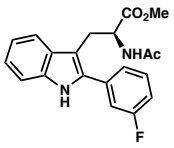
(*S*)-N_α-Acetyl-2-(4-fluorophenyl)tryptophan methyl ester (121p)



Prepared from 2-(4-fluorophenyl)indole (42.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica

gel chromatography (40:60 to 100:0 EtOAc/hexanes) to yield 55.6 mg (78% yield) of **121p** as a colorless oil. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO_2, λ = 254 nm): t_R(major) = 6.1 min, t_R(minor) = 6.9 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, J = 47.9 Hz, 1H), 7.57 (dd, *J* = 7.9, 1.1 Hz, 1 H), 7.54 – 7.51 (m, 2H), 7.36 (ddd, *J* = 8.1, 8.1, 0.9 Hz, 1H), 7.23 – 7.10 (m, 4H), 5.82 (d, J = 8.1 Hz, 1H), 4.83 (dt, J = 8.1, 5.5 Hz, 1H), 3.55 – 3.40 (m, 2H), 3.34 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 169.5, 135.6, 135.0, 130.1, 130.1, 129.4, 122.7, 120.2, 118.9, 116.2, 116.1, 110.9, 106.9, 52.8, 52.0, 26.7, 22.9.; IR (NaCl/thin film): 3364, 3271, 3061, 2925, 2853, 1738, 1661, 1553, 1505, 1460, 1440, 1373, 1221, 1158; $[\alpha]_D^{25}$ = +38.2 (*c* = 0.65, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 355.1452, found 355.1460.

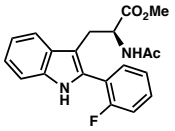
(*S*)-*N*α-Acetyl-2-(3-fluorophenyl)tryptophan methyl ester (121q)



Prepared from 2-(3-fluorophenyl)indole (42.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 ethyl acetate/hexanes) to yield 50.6 mg (76% yield) of **121q** as a white foam. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO_2, λ = 254 nm): t_R(major) = 3.8 min, t_R(minor) = 4.6 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (br s, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.41 – 7.37 (m, 1H), 7.33-7.31 (m, 2H), 7.27-7.24 (m, 1H), 7.19 (ddd, *J* = 8.2, 7.0, 1.0 Hz, 1H), 7.13 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 7.07 – 7.03 (m, 1H), 5.89 (br d, *J* = 8.1 Hz, 1H), 4.84 (dt, *J* = 8.1, 5.5 Hz, 1H), 3.53 (dd, J = 13.6, 4.7 Hz, 1H), 3.49 (dd, J = 13.6, 4.2 Hz, 1H), 3.34 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 169.7, 162.9 (d, J_{C-F} = 246.3 Hz), 135.8, 135.2 (d, J_{C-F} = 7.5 Hz), 134.5 (d, J_{C-F} = 2.5 Hz),

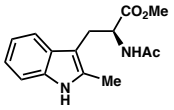
130.6 (d, $J_{C\text{-}F}$ = 8.8 Hz), 129.2, 123.9 (d, $J_{C\text{-}F}$ = 3.8 Hz), 122.8, 120.0, 118.9, 115.1 (d, $J_{C\text{-}F}$ = 21.2 Hz), 114.7 (d, $J_{C\text{-}F}$ = 21.2 Hz), 111.1, 107.3, 52.8, 52.0, 26.7, 22.8; IR (NaCl/thin film): 3370, 3275, 3060, 2952, 1735, 1655, 1614, 1585, 1522, 1438, 1374, 1266, 1200, 1155 cm^{-1}; $[\alpha]_D^{25}$ = +37.6 (*c* = 1.21, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 355.1452, found 355.1450.

(*S*)-N_α-Acetyl-2-(2-fluorophenyl)tryptophan methyl ester (121r)



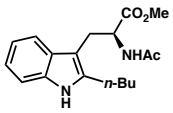
Prepared from 2-(2-fluorophenyl)indole (21.0 mg, 0.10 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 12.4 mg (35% yield) of **121r**. The enantiomeric excesses was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO_2, λ = 254 nm): t_R(major) = 9.5 min, t_R(minor) = 8.4 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.55 (ddd, J = 7.5, 7.5, 1.8 Hz, 1H), 7.45 – 7.35 (m, 2H), 7.29 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.19 – 7.10 (m, 1H), 5.83 (br d, J = 7.6 Hz, 1H), 4.85 (dt, J = 7.9, 5.5 Hz, 1H), 3.55 – 3.39 (m, 2H), 3.36 (s, 2H), 1.73 (s, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 169.5, 159.8 (d, $J_{C\text{-}F}$ = 246.3 Hz), 135.9, 131.4 (d, $J_{C\text{-}F}$ = 3.8 Hz) 130.2 (d, $J_{C\text{-}F}$ = 8.8 Hz), 129.73, 128.65, 124.8 (d, $J_{C\text{-}F}$ = 3.8 Hz), 122.84, 120.6 (d, $J_{C\text{-}F}$ = 15.0 Hz), 120.0, 119.0, 116.4 (d, $J_{C\text{-}F}$ = 21.3 Hz), 111.0, 108.8, 52.5, 52.0, 26.8, 26.8, 22.9; IR (NaCl/thin film): 3275, 3058, 2925, 2853, 1734, 1653, 1523, 1490, 1457, 1437, 1374, 1245, 1216, 1130, 1104; $[\alpha]_D^{25}$ = +39.8 (*c* = 0.41, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 355.1452, found 355.1463.

(*S*)-*N*α-Acetyl-2-methyltryptophan methyl ester (121s)



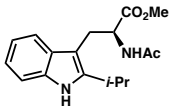
Prepared from 2-methylindole (26.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (50:50 to 100:0 EtOAc:hexanes) to yield 31.0 mg (61% yield) of **121s** as a white foam. The enantiomeric excess was determined to be 85% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO_2, λ = 254 nm): t_R(major) = 3.9 min, t_R(minor) = 2.7 min. $[\alpha]_D^{25}$ = +25.9 (*c* = 0.99, $CHCl_3$). Spectral data matches that reported in the literature.

(*S*)-N_α-Acetyl-2-butyltryptophan methyl ester (121t)



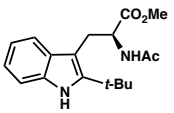
Prepared from 2-butylindole (35.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 45.8 mg (72% yield) of **121t** as a colorless oil. The enantiomeric excess was determined to be 91% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO_2, λ = 254 nm): t_R(major) = 5.1 min, t_R(minor) = 4.2 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (br s, 1H), 7.46 – 7.40 (m, 1H), 7.31 – 7.24 (m, 1H), 7.15 – 6.99 (m, 2H), 6.00 (br d, *J* = 7.8 Hz, 1H), 4.88 (dt, *J* = 8.1, 5.7 Hz, 1H), 3.65 (s, 3H), 3.26 (dd, *J* = 5.7, 0.9 Hz, 2H), 2.69 (td, *J* = 7.8 2.2 Hz, 2H), 1.93 (s, 3H), 1.66 – 1.57 (m, 2H), 1.45 – 1.31 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 169.6, 137.4, 135.2, 128.8, 121.3, 119.5, 117.9, 110.4, 105.26, 105.29, 53.0, 52.3, 31.8, 26.8, 25.7, 23.2, 22.6, 13.9; IR (NaCl/thin film): 3296, 3058, 2955, 2871, 1737, 1658, 1562, 1530, 1463, 1439, 1376, 1217, 1129; $[\alpha]_D^{25}$ = +16.3 (*c* = 0.83, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 317.1860, found 317.1855.

(*S*)-*N*α-Acetyl-2-isopropyltryptophan methyl ester (121u)



Prepared from 2-isopropylindole (32.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 39.6 mg (66% yield) of **121u** as a colorless oil. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AD-H, 2.5 mL/min, 15% IPA in CO_2, λ = 254 nm). t_R(major) = 6.4 min, t_R(minor) = 5.6 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (br s, 1H), 7.48 – 7.41 (m, 1H), 7.30 – 7.27 (m, 1H), 7.15 – 7.02 (m, 2H), 6.04 (br d, *J* = 8.0 Hz, 1H), 4.89 (dt, *J* = 8.1, 5.7 Hz, 1H), 3.66 (s, 3H), 3.29 (dd, J = 12.7, 4.0 Hz, 1H), 3.26 (dd, J = 12.7, 3.4 Hz, 1H), 3.18 (m, 1H), 1.93 (s, 3H1.31 (d, J = 3.3 Hz, 3H), 1.30 (d, J = 3.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 169.7, 142.7, 135.2, 128.7, 121.3, 119.5, 117.9, 110.6, 103.6, 53.0, 52.3, 26.7, 25.3, 23.2, 23.0; IR (NaCl/thin film): 3305, 2962, 1734, 1700, 1653, 1559, 1539, 1506, 1457, 1436, 1374, 1299, 1217 cm^{-1}; $[\alpha]_D^{25}$ = +22.2 (*c* = 0.35, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 303.1703, found 303.1709.

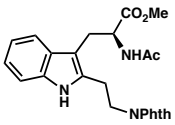
(*S*)-*N*$_\alpha$-Acetyl-2-(tert-butyl)tryptophan methyl ester (121v)



Prepared from 2-(tert-butyl)indole (35.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 18.1 mg (29% yield) of **121v** as a yellow oil. The enantiomeric excess was determined to be 84% by chiral SFC analysis (OD-H, 2.5 mL/min, 10% IPA in CO_2, λ = 254 nm): t_R(major) = 12.8 min, t_R(minor) = 14.2 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (br s, 1H), 7.47 (dd, J = 14.0, 7.1 Hz, 1H), 7.27 (dd, J = 5.8, 4.8 Hz, 1H), 7.15 – 7.03 (m, 2H), 6.06 (br d, J = 7.4 Hz,

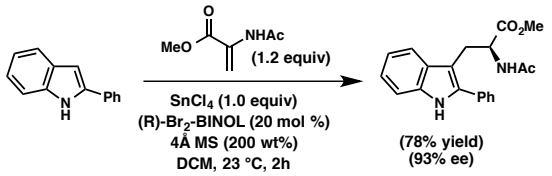
1H), 4.84 (m, 1H), 3.54 (s, 3H), 3.38 – 3.29 (m, 2H), 1.86 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 169.6, 143.4, 133.9, 129.8, 121.3, 119.4, 117.7, 110.4, 104.3, 53.7, 52.2, 33.2, 30.7, 28.6, 23.0; IR (NaCl/thin film): 3326, 3047, 2961, 2918, 2868, 1734, 1653, 1539, 1457, 1436, 1374, 1303, 1254, 1211, 1128; $[\alpha]_D^{25}$ = +12.4 (*c* = 0.36, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 317.1860, found 317.1856.

(*S*)-N_α-Acetyl-2-(ethylphthalimide)tryptophan methyl ester (121w)

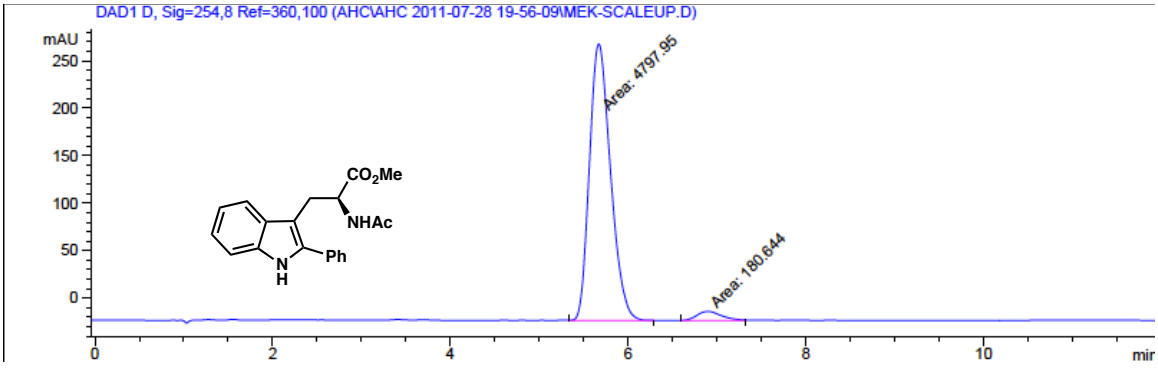


Prepared from 2-(ethylphthalimide)indole (29.0 mg, 0.10 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (70:30 to 100:0 EtOAc:hexanes) to yield 34.6 mg (80% yield) of **121w** as a yellow foam. The enantiomeric excess was determined to be 90% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO_2, λ = 254 nm): t_R(major) = 7.3 min, t_R(minor) = 6.3 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (br s, 1H), 7.83 (dd, *J* = 5.4, 2.9 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.31 (ddd, *J* = 8.1, 8.1, 1.0 Hz, 1H), 7.13 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.07 (ddd, *J* = 10.5, 5.8, 2.2 Hz, 1H), 6.13 (br d, *J* = 8.1 Hz, 1H), 4.92 (dt, *J* = 8.2, 6.0 Hz, 1H), 4.05 – 3.89 (m, 2H), 3.66 (s, 3H), 3.33 – 2.98 (m, 4H), 1.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 169.8, 168.3, 135.6, 134.2, 132.5, 131.9, 128.6, 123.5, 121.8, 119.7, 118.2, 110.8, 107.4, 52.9, 52.4, 37.0, 27.0, 25.3, 23.1; IR (NaCl/thin film): 3369, 3280, 3052, 2948, 1770, 1738, 1711, 1659, 1530, 1438, 1397, 1371; $[\alpha]_D^{25}$ = +14.8 (*c* = 0.96, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 355.1452, found 355.1455.

2.6.5 Scale-up Procedure



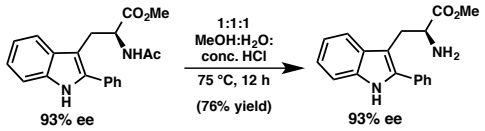
To a flame-dried flask under nitrogen containing freshly activated powdered 4Å molecular sieves (200 wt %) was added 2-phenylindole (1.00 g, 5.20 mmol, 1.00 equiv), methyl 2-acetamidoacrylate (890 mg, 6.20 mmol, 1.20 equiv), and (*R*)-3,3'-dibromo-BINOL (457 mg, 1.00 mmol, 0.20 equiv). The flask was charged with DCM (40 mL) and $SnCl_4$ (1 M in DCM, 5.20 mL, 5.20 mmol, 1.00 equiv) was added. The reaction was stirred at room temperature for 2 hours, then quenched by addition of 1 M HCl (50 mL). The aqueous layer was extracted with EtOAc (2 x 50 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 1.33 g (77% yield) of **121c** as a pale yellow foam. The enantiomeric excess was determined to be 93% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO_2, λ = 254 nm): t_R(major) = 5.7 min, t_R(minor) = 6.9 min.



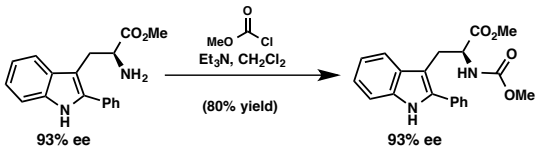
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.670	MM	0.2746	4797.95020	291.18689	96.3716
2	6.889	MM	0.3168	180.64430	9.50427	3.6284

2.6.6 Functionalization of Tryptophan 121c

2.6.6.1 Acetamide Hydrolysis of 121c

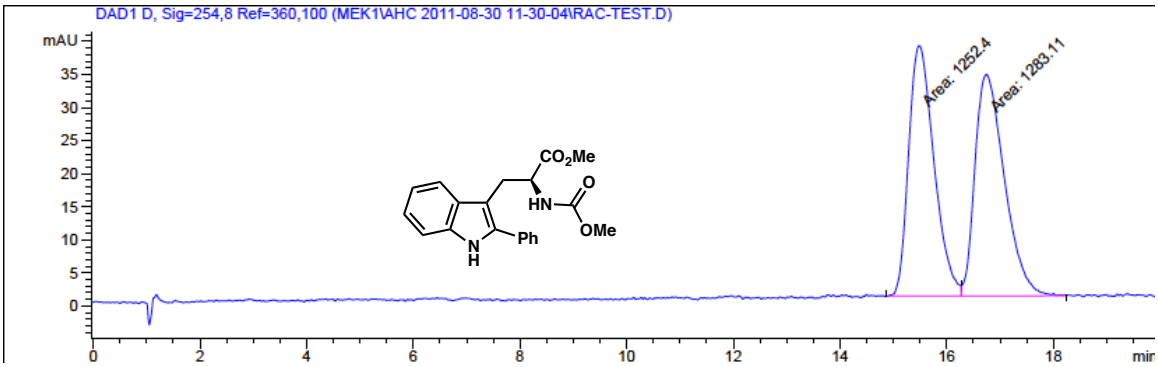


A vial was charged with (*S*)-*N*α-acetyl-2-phenyltryptophan methyl ester (**121c**, 30.0 mg, 0.09 mmol), MeOH (1 mL), H_2O (1 mL) and aqueous HCl (12 M, 1 mL). The reaction was heated to 75 °C for 12 hours, then concentrated, redissolved in DCM (10 mL) and washed with saturated aqueous $NaHCO_3$ (3 X 5 mL). The aqueous layers were combined and extracted with DCM (4 X 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by silica gel chromatography (99:1 CH_2Cl_2:MeOH) to yield 20.0 mg (76% yield) of **124** as a light yellow oil. The enantiomeric excess was determined by chiral SFC analysis of the corresponding methylcarbamate (see below). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (br s, 1H), 7.67 (dd, *J* = 7.6, 0.7 Hz, 1H), 7.62 – 7.60 (m, 2H), 7.50 – 7.43 (m, 2H), 7.41 – 7.34 (m, 2H), 7.22 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.15 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 3.89 (dd, J = 8.4, 5.0 Hz, 1H), 3.56 (s, 3H), 3.47 – 3.38 (m, 1H), 3.27 – 3.14 (m, 1H), 1.69 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 136.1, 135.8, 132.9, 129.1, 129.0, 128.3, 128.0, 122.5, 119.9, 119.2, 110.9, 108.2, 55.2, 51.9, 30.2; IR (NaCl/thin film): 3367, 3062, 2948, 1732, 1603, 1489, 1457, 1207; $[\alpha]_D^{25}$ = -12.4 (*c* = 0.85, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 295.1441, found 295.1446.



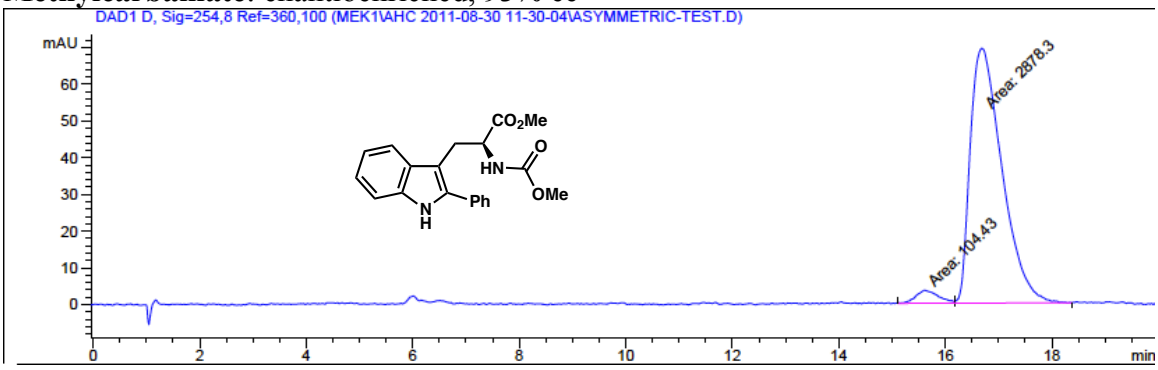
A flame-dried flask was charged with free amine **124** (19.5 mg, 0.70 mmol, 1.00 equiv), Et_3N (19 µL, 0.13 mmol, 2.0 equiv) and DCM (5 mL). Methylchloroformate (6.0 µL, 0.73 mmol, 1.10 equiv) was added and the solution was stirred at room temperature for 3 hours, then quenched with saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc (2 X 5 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by silica gel chromatography (25:75 EtOAc:hexanes) to yield 18.5 mg (80% yield) of methylcarbamate as a colorless oil. The enantiomeric excess was determined to be 93% by chiral SFC analysis (OD-H, 2.5 mL/min, 15% IPA in CO_2, λ = 254 nm): t_R(major) = 16.7 min, t_R(minor) = 15.6 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (br s, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.57 – 7.52 (m, 1H), 7.48 – 7.45 (m, 2H), 7.40 – 7.35 (m, 2H), 7.25 – 7.19 (m, 1H), 7.16 (m, 1H), 5.06 (br d, J = 7.7 Hz, 1H), 4.63 – 4.59 (m, 1H), 3.54 (s, 3H), 3.50 (m, 2H), 3.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 156.1, 136.2, 135.7, 132.9, 129.2, 129.0, 128.3, 128.0, 122.5, 120.0, 118.9, 110.9, 106.7, 54.5, 52.12, 52.07, 27.1; IR (NaCl/thin film) 3338, 2953, 2923, 2852, 1718, 1701, 1507, 1457, 1363, 1213, 1072 cm^{-1}; $[\alpha]_D^{25}$ = +22.6 (*c* = 0.10, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 353.1496, found 353.1497.

Methylcarbamate: racemic



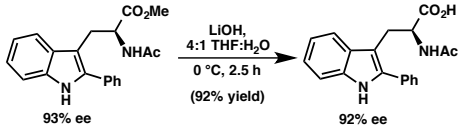
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.480	MF	0.5516	1252.40308	37.84099	49.3945
2	16.749	FM	0.6385	1283.11060	33.49063	50.6055

Methylcarbamate: enantioenriched, 93% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.610	MF	0.4860	104.43002	3.58131	3.5012
2	16.684	FM	0.6913	2878.30273	69.39832	96.4988

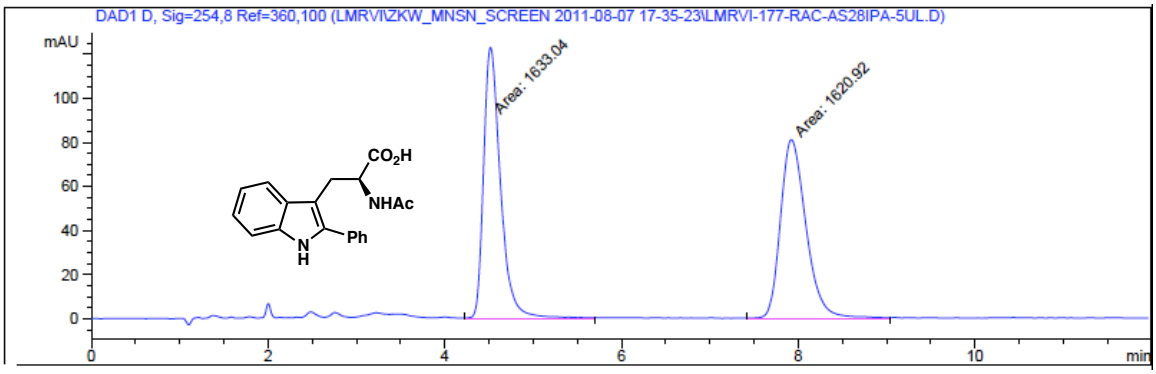
2.6.6.2 Methyl Ester Hydrolysis of 121c



A 10 mL flask was charged with (*S*)-*N*α-acetyl-2-phenyltryptophan methyl ester **121c** (67.2 mg, 0.20 mmol, 1.00 equiv) and THF (0.9 mL) then cooled to 0 ºC, followed by dropwise addition of aqueous LiOH (1.75 M, 230 μL, 0.40 mmol, 2.00 equiv). The reaction was vigorously stirred at 0 ºC for 2 hours, then diluted with H_2O (15 mL) and extracted with EtOAc (2 x 10 mL). The aqueous layer was acidified to pH = 1.5 and extracted with EtOAc (5 x 15 mL). The combined organic layers from the acidic aqueous extraction were dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified by silica gel chromatography (0:99:1 to 15:84:1 MeOH:DCM:AcOH) to yield 59.2 mg (92% yield) of carboxylic acid **123** as a pale yellow foam. The enantiomeric excess was determined to be 92% by chiral SFC analysis (AS-H, 2.5 mL/min, 28% IPA

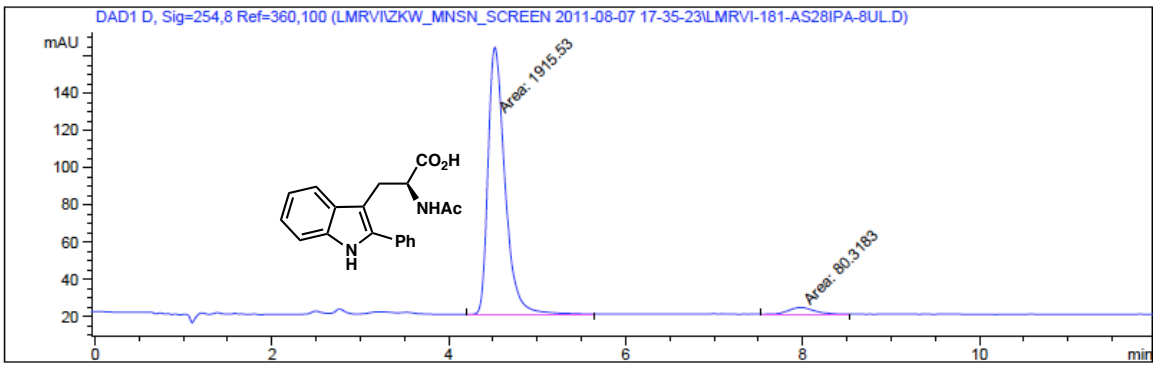
in CO_2, λ = 254 nm): t_R(major) = 4.5 min, t_R(minor) = 8.0 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (br s, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.47 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.40 (m, 1H), 7.37 (ddd, *J* = 8.0, 0.8, 0.8 Hz, 1H), 7.21 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 7.14 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 5.72 (br d, *J* = 7.4 Hz, 1H), 4.73 (td, *J* = 7.1, 5.4 Hz, 1H), 3.56 (dd, *J* = 14.9, 5.2 Hz, 1H), 3.49 (dd, *J*=15.0, 6.9 Hz, 1H), 1.62 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 170.9, 136.2, 135.7, 132.9, 129.13, 129.05, 128.3, 128.2, 122.6, 120.1, 118.8, 111.0, 106.8, 53.1, 26.2, 22.6; IR (NaCl/thin film): 3391, 3306, 3055, 3011, 2921, 2850, 1717, 1615, 1527, 1457, 1448, 1215 cm^{-1}; $[\alpha]_D^{25}$ = +9.2 (*c* = 1.05, MeCN). HRMS (MM) calc'd for $[M+H]^+$ 323.1390, found 323.1390.

Racemic



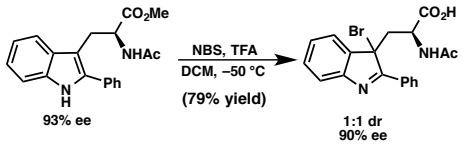
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.517	MM	0.2216	1633.03918	122.81268	50.1863
2	7.923	MM	0.3341	1620.91711	80.86505	49.8137

Enantioenriched, 92% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.521	MM	0.2225	1915.53430	143.46094	95.9757
2	7.970	MM	0.3592	80.31825	3.72675	4.0243

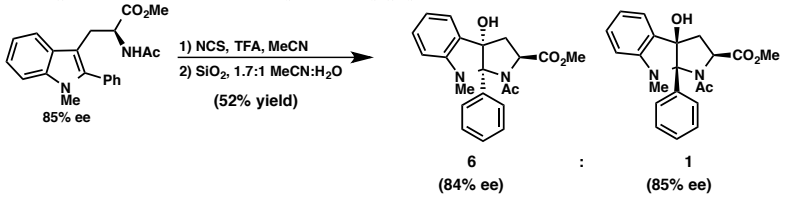
2.6.6.3 Preparation of bromo-dehydroindoline 125



A solution of (*S*)-*N*α-acetyl-2-phenyltryptophan methyl ester **121c** (101 mg, 0.30 mmol, 1.00 equiv) in DCM (8.4 mL) was cooled to –50 °C in an acetonitrile/dry ice bath. NBS (53.4 mg, 0.30 mmol, 1.00 equiv) was then added, followed by TFA (900 µL). The reaction was stirred in the dark at –50 °C for 3 hours, then poured onto ice, quenched with aqueous ammonia (1.5 mL) and extracted with DCM (3 x 25 mL). The combined organics were washed (40 mL H_2O, then 40 mL brine), dried (Na_2SO_4), filtered, and concentrated. The product **125** was formed in a 1:1 ratio of diastereomers (determined by ^{1}H NMR analysis of the crude reaction mixture) and was purified by silica gel chromatography (30:70 to 70:30 EtOAc:hexanes) to yield 98 mg (79% yield) of the combined diastereomers as a bright yellow foam. The enantiomeric excesses of the two diastereomers were determined to be 92% and 90% by chiral SFC analysis (AS-H, 2.5

mL/min, 20% IPA in CO_2, λ = 254 nm): t_R(major) = 3.8 min, t_R(minor) = 4.1 min; t_R(major) = 4.6 min, t_R(minor) = 6.0 min. Spectral data and optical rotation are reported for the mixture of diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 – 8.32 (m, 4H), 7.70 – 7.64 (m, 2H), 7.57 – 7.49 (m, 8H), 7.47 – 7.40 (m, 2H), 7.39 – 7.30 (m, 2H), 5.37 (br d, *J* = 7.4 Hz, 1H), 5.05 (br d, *J* = 8.5 Hz, 1H), 4.33 (dt, *J* = 7.5, 5.5 Hz, 1H), 3.95 (td, *J* = 8.9, 4.0 Hz, 1H), 3.56 (dd, *J* = 14.8, 5.2 Hz, 1H), 3.47 – 3.41 (m, 4H), 3.38 – 3.32 (m, 4H), 3.23 (dd, *J* = 14.6, 9.3 Hz, 1H), 1.45 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 174.8, 170.7, 170.0, 169.4, 169.2, 151.82, 151.76, 139.8, 139.6, 131.6, 131.4, 131.3, 130.5, 130.4, 128.81, 128.80, 128.71, 128.70, 127.2, 126.6, 123.2, 122.5, 121.9, 121.7, 59.16, 59.14, 52.5, 52.3, 50.3, 49.8, 41.6, 41.4, 22.3, 22.0; IR (NaCl/thin film): 3271, 3062, 2952, 2924, 2853, 1747, 1661, 1525, 1444, 1372, 1264, 1216 cm^{-1}; $[\alpha]D^{25}$ = +17.1 (*c* = 0.50, $CHCl_3$). HRMS (MM) calc'd for M^+ 415.0652, found 415.0652.

2.6.6.4 Preparation of 3-hydroxypyrroloindoline 126



A 15 mL flask containing (*S*)-*N*α-acetyl-1-methyl-2-phenyltryptophan methyl ester **121d** (52.5 mg, 0.150 mmol, 1.00 equiv) was flushed with argon and then charged with MeCN (3.3 mL). TFA was added as a solution in MeCN (1.3 M, 125 μL, 0.150 mmol, 1.00 equiv), followed by NCS as a solution in MeCN (0.2 M, 0.75 mL, 0.150 mmol, 1.00 equiv). The flask was then sealed under argon and the solution was stirred in the dark at room temperature. After 3 hours, the reaction was quenched with aqueous ammonia (1.5

mL), poured onto ice, and extracted with DCM (3 x 15 mL). The combined organics were washed (20 mL H_2O, then 20 mL brine), dried (Na_2SO_4), filtered, and concentrated to give the crude mixture of 3-chloropyrroloindoline diastereomers (detected by HRMS direct injection (MM) calc'd for $[M+H]^+$ 385.1313, found 385.1320). The crude residue was redissolved in MeCN (2 mL), then H_2O (1.2 mL) and SiO_2 (2.5 mL) were added. The mixture was vigorously stirred open to air at room temperature for 30 minutes, then filtered through a 1.5 mL silica plug with EtOAc (50 mL), dried (Na_2SO_4), filtered and concentrated. The 3-hydroxypyrroloindoline **126** existed in a 6:1 ratio of diastereomers, favoring the *endo* diastereomer (determined by ^1H NMR analysis of the crude reaction mixture) and was purified by silica gel chromatography (0:100 to 10:90 EtOAc:hexanes) to yield 30.8 mg (contains 18 wt % $CHCl_3$, 46% corrected yield) of the *endo* diastereomer as a yellow oil. The *exo* diastereomer, obtained post chromatography in a mixture with (*S*)-*N*α-acetyl-1-methyl-2- phenyltryptophan methyl ester **XX**, was subjected to reverse phase preparatory HPLC (30:70 to 90:10 MeCN:H_2O) using an Agilent 1200 Series HPLC with an Agilent XDB-C18 5 μM column (9.4 x 250 mm) to yield 3.5 mg (6% yield) of the *exo* diastereomer as a yellow oil.

Endo diastereomer:

The enantiomeric excess was determined to be 84% by chiral SFC analysis (AD-H, 2.5 mL/min, 25% IPA in CO_2, λ = 254 nm): t_R(major) = 7.4 min, t_R(minor) = 4.7 min. The relative stereochemistry was assigned by 2D NMR analysis. ^1H NMR (500 MHz, CD_3CN; compound exists as a 15:1 mixture of rotamers, the major rotamer is reported) δ 7.40 – 7.35 (m, 2H), 7.34 – 7.26 (m, 3H), 7.20 (ddd, *J* = 7.9, 7.5, 1.3 Hz, 1H), 7.12 (ddd, *J* = 7.2, 1.3, 0.5 Hz, 1H), 6.66 (ddd, *J* = 7.3, 7.3, 1.0 Hz, 1H), 6.51 (d, *J* = 7.9 Hz, 1H),

4.79 (d, J = 8.8 Hz, 1H), 3.19 (s, 3H), 2.97 (s, 3H), 2.90 (br s, 1H), 2.82 (d, J = 12.7 Hz, 1H), 2.59 (ddd, J = 12.7, 8.8, 1.1 Hz, 1H), 1.95 (s, 3H); ^{13}C NMR (125 MHz, CD_3CN; compound exists as a 15:1 mixture of rotamers, the major rotamer is reported) δ 172.0, 171.3, 153.1, 138.0, 131.6, 128.9, 128.6, 128.3, 125.2, 118.0, 107.1, 95.3, 88.3, 61.3, 52.7, 39.0, 32.7, 23.6; IR (NaCl/thin film): 3292, 3010, 2948, 1735, 1653, 1648, 1610, 1491, 1448, 1388, 1313, 1220 cm^{-1}; $[\alpha]D^{25}$ = +264.0 (c = 1.35, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 367.1652, found 367.1650.

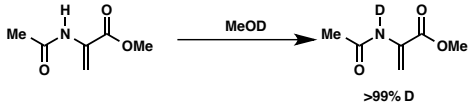
Exo diastereomer:

The enantiomeric excess was determined to be 85% by chiral SFC analysis (OD-H, 2.5 mL/min, 20% IPA in CO_2, λ = 254 nm): t_R(major) = 6.2 min, t_R(minor) = 4.0 min. The relative stereochemistry was assigned by 2D NMR analysis. ^{1}H NMR (500 MHz, CD_3CN; compound exists as a 1.5:1 mixture of rotamers, the major rotamer isdenoted by *, the minor rotamer by§) δ 7.60 – 7.22 (m, 6H*, 7H§), 7.17 (ddd, J = 7.3, 0.6, 0.6 Hz, 1H*), 6.79 (dd, J = 7.5, 7.5 Hz, 1H§), 6.70 (dd, J = 7.5, 7.5 Hz, 1H*), 6.65 (d, J = 7.9 Hz, 1H§), 6.54 (d, J = 7.9 Hz, 1H*), 4.49 (dd, J = 8.0, 6.7 Hz, 1H*), 4.07 (dd, J = 10.0, 6.9 Hz, 1H§), 3.81 (s, 3H*), 3.71 (s, 3H§), 3.34 (s, 1H§), 3.01 (s, 1H*), 2.963 (s, 3H*), 2.958 (s, 3H§)**,** 2.71 (dd, J = 13.0, 8.1 Hz, 1H*), 2.68 (dd, J = 12.6, 7.0 Hz, 1H§)**,** 2.34 (dd, J = 12.9, 6.7 Hz, 1H*), 2.07 (dd, J = 12.7, 10.0 Hz, 1H§), 1.89 (s, 3H*), 1.80 (s, 3H§); ^{13}C NMR (125 MHz, CD_3CN) δ 174.1, 173.6, 172.3, 171.8, 151.2, 151.1, 136.3, 136.2, 131.6, 131.3, 130.3, 129.60, 129.57, 129.4, 128.7, 128.6, 124.4, 123.9, 119.3, 118.2, 108.0, 106.4, 98.8, 96.1, 90.1, 88.5, 61.2, 60.3, 53.3, 52.6, 40.9, 37.2, 33.4, 32.4, 24.6, 23.8; IR (NaCl/thin film): 3305, 2924, 1747, 1646, 1610, 1491, 1448, 1381, 1311, 1207

cm^{-1}; $[\alpha]D^{25}$ = -138.2 (*c* = 0.33, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 367.1652, found 367.1655.

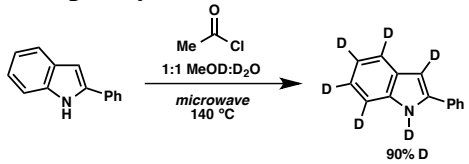
2.6.7 Deuterium Labeling Studies

Preparation of *N*-deuteroacrylate (XX)



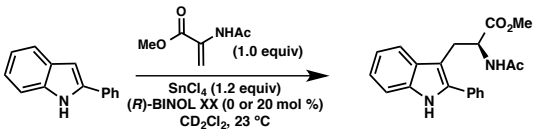
Acrylate **120c** was dissolved in MeOD (1 mL) under nitrogen. After stirring for 1 minute, the solution was concentrated under high vacuum. This procedure was repeated three times to give >99% deuterium incorporation.

Preparation of per-deutero-2-phenylindole



To MeOD (1 mL) in a microwave vial was added acetyl chloride (100 μL), followed by 2-phenylindole (6a, 50 mg) and D_2O (1 mL). The vial was sealed and heated in a microwave to 140 °C for 1 hour. Upon cooling, the heterogenous solution was diluted with DCM. The phases were separated and the aqueous was extracted with DCM (2 x 5 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give per-deutero-2-phenylindole with 90% deuterium incorporation.

2.6.7 ^{1}H NMR Kinetics Studies



An oven-dried vial was charged with 2-phenylindole (19.0 mg, 0.10 mmol, 1.00 equiv), methyl 2-acetamidoacrylate (14.0 mg, 0.10 mmol, 1.00 equiv), (*R*)-BINOL if necessary (6.0 mg, 0.02 mmol, 0.20 equiv) and 1,4-diethylbenzene (4.7 μL, 0.03 mmol, 0.30 equiv) as the internal standard. The vial was pumped into a glove box and charged with CD_2Cl_2 (0.75 mL, to an indole concentration of 0.12 M), then transferred to a screw-cap NMR tube. A ^{1}H NMR spectrum (1 scan) was taken to determine the inital ratio of acrylate and 1,4-diethylbenzene. $SnCl_4$ (1 M in CD_2Cl_2, 120 μL, 0.12 mmol, 1.20 equiv) was then added through the septum of the screw-cap and the NMR tube was inverted once and quickly inserted into the spectrometer. The concentration of acrylate was monitored by ^{1}H NMR over 9 hours and was determined by integration of its resonance at 3.83 ppm relative to 1,4-diethylbenzene's resonance at 2.74 ppm.

2.7 NOTES AND REFERENCES

(1) (a) Zheng, B.-H.; Ding, C.-H.; Hou, X.-L.; Dai, L.-X. *Org. Lett.* **2010**, *12*, 1688. (b) Sui, Y.; Liu, L.; Zhao, J.-L.; Wang, D.; Chen, Y.-J. *Tetrahedron* **2007**, *63*, 5173. (c) Castle, S. L.; Srikanth, G. S. C. *Org. Lett.* **2003**, *5*, 3611. (d) Gentilucci, L.; Cerisoli, L.; Marco, R. D.; Tolomelli, A. *Tetrahedron Letters* **2010**, *51*, 2576. (e) Angelini, E.; Balsamini, C.; Bartoccini, F.; Lucarini, S.; Piersanti, G. *J. Org. Chem.* **2008**, *73*, 5654. (f) Blaser, G.; Sanderson, J. M.; Batsanov, A. S.; Howard,

J. A. K. *Tetrahedron Lett.* **2008**, *49*, 2795. (g) Ruiz-Rodríguez, J.; Albericio, F.; Lavilla, R. *Chem. Eur. J.* **2010**, *16*, 1124.

(2) Townsend, J. M.; Blount, J. F.; Sun, R. C.; Zawoiski, S.; Valentine, D. *J. Org. Chem.* **1980**, *45*, 2995.

(3) Drury, W. J.; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 11006.

(4) Seminal examples of asymmetric Friedel−Crafts conjugate additions of unactivated indoles to set stereogenic centers in the β- position: (a) Boersma, A. J.; Feringa, B. L.; Roelfes, G. *Angew. Chem., Int. Ed*. **2009**, *48*, 3346. (b) Rueping, M.; Nachtsheim, B. J.; Moreth, S. A.; Bolte, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 593. (c) Evans, D. A.; Fandrick, K. R.; Song, H.-J. *J. Am. Chem. Soc.* **2005**, *127*, 8942. (d) Palomo, C.; Oiarbide, M; Kardak, B. G.; Garcia, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154. (e) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780. (f) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (g) Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030. (h) Jensen, K. B.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160.

(5) Repka, L. M.; Ni, J.; Reisman, S. E. *J. Am. Chem. Soc.* **2010**, *132*, 14418.

(6) Improved conditions were published in a follow-up article: Ni, J.; Wang, H.; Reisman, S. E. *Tetrahedron* **2013**, *69*, 5622.

(7) For a racemic variant, see: Lucarini, S.; Bartoccini, F.; Battistoni, F.; Diamantini, G.; Piersanti, G.; Righi, M.; Spadoni, G. *Org. Lett.* **2010**, *12*, 3844.

(8) For reports of asymmetric catalysis by BINOL•SnCl4, see: (a) Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 12854. (b) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 3049. (c) Yu, S. H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808. (d) Rauniyar, V.; Zhai, H. M.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481. For a review, see: (e) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924.

(9) Mohr, J. T.; Hong, A. Y.; Stoltz, B. M. *Nature Chem.* **2009**, *1*, 359.

(10) Navarre, L.; Martinez, R. M.; Genet, J.-P.; Darses, S. *J. Am. Chem. Soc.* **2008**, *130*, 6159.

(11) Sibi, M. P.; Coulomb, J.; Stanley, L. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 9913.

(12) Fu, N.; Zhang, L.; Li, J.; Luo, S.; Cheng, J.-P. *Angew. Chem. Int. Ed.* **2011**, *50*, 11451.

(13) **122i** is easily prepared on multi-gram scale in 3 steps from (R)- BINOL. See: Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139.