CHAPTER 3

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

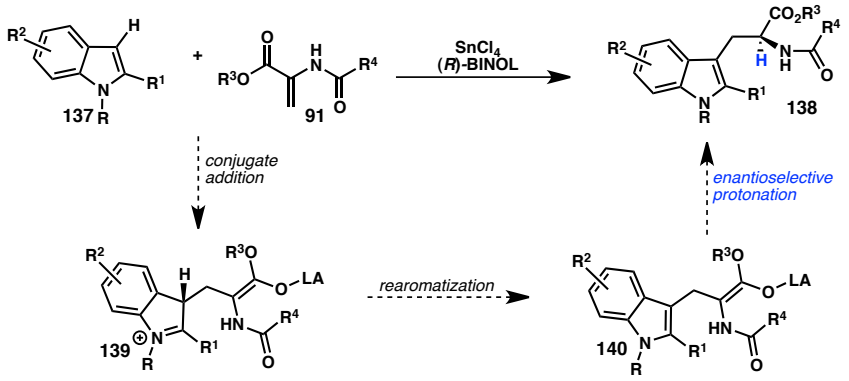
3.1 INTRODUCTION

During the development of the formal (3 + 2) cycloaddition approach to pyrroloindolines, epimerization studies were conducted on the diastereomeric products that strongly suggest that enantioinduction occurs via a highly face-selective, (*R*)-BINOL•$SnCl_4$ controlled protonation event (Chapter 2). We hypothesized that if catalyst-controlled protonation were operative, the related Friedel–Crafts alkylation reaction with C3-unsubstituted indoles should also proceed with high selectivity to provide enantioenriched tryptophan derivatives. Mechanistically, the proposed transformation would involve an initial conjugate addition to generate enolate **139**, which, following rearomatization and asymmetric protonation would give tryptophan derivative **138** (Scheme 3.1.1). This chapter describes the realization of our mechanistic hypothesis in the development of a tandem Friedel–Crafts conjugate addition/enantioselective

[†] Part of this chapter was published as the following article: Kieffer, M. E.; Repka, L. M.; Reisman, S. E. *J. Am. Chem. Soc.* **2012**, *134*, 5131. The research discussed in this chapter was completed in collaboration with Maddi Kieffer, a graduate student in the Reisman lab.

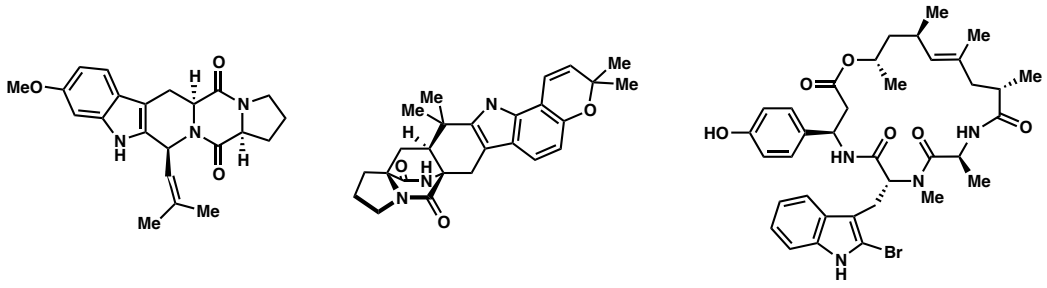
protonation reaction.

Scheme 3.1.1. Proposed mechanism of enantioselective tryptophan derivative formation.



3.1.1 Synthetic and Biological Applications of Tryptophan Derivatives

Figure 3.1.1. Tryptophan-derived biologically active natural products.



fumitremorgin C (**141**)
BCRP inhibitor

stephacidin A (**142**)
testosterone-dependent prostate LNCap inhibitor

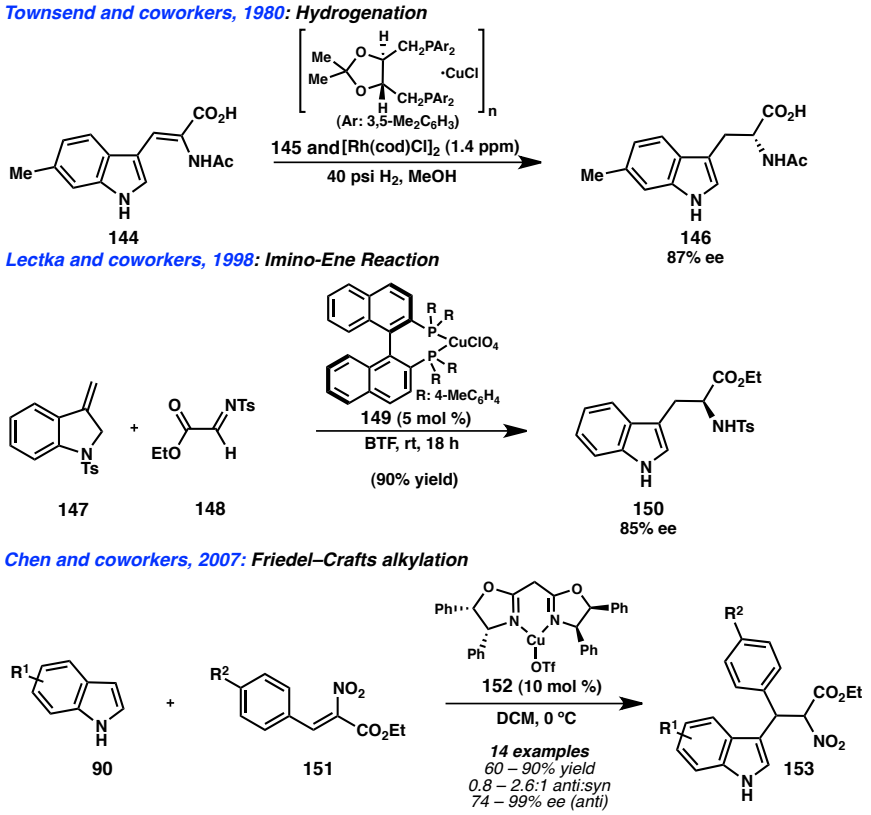
jaspamide (**143**)
MCF-7 and HT-29 cytotoxicity; antimicrofilament activity

Unnatural tryptophan derivatives constitute an important target for synthetic efforts on the basis of their applications. These derivatives are incorporated into a diverse array of biologically active natural products including fumitremorgin C (**141**),[1] stephacidin A (**142**),[2] and the jaspamide family of cyclodepsipeptides (**143**);[3] in particular, **141** has been extensively studied because of its function as an inhibitor of the breast cancer resistance protein (BCRP) (*Figure 3.1.1*). Furthermore, tryptophan derivatives have found applications as chiral catalysts[4] and as biological probes. For example, these molecules have been used in protein detection and design on the basis of their fluorescent

properties,[5] and in linear free energy relationship studies that have identified a key cation-π binding interaction for acetylcholine and the nicotinic acetylcholine receptors.[6]

3.1.2 Catalytic, Enantioselective Approaches to Tryptophan Derivatives

Scheme 3.1.2. Selected enantioselective, catalytic approaches to tryptophan derivatives.



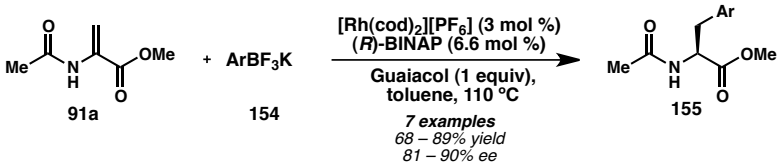
Due to the applications of tryptophan derivatives, the synthesis of these molecules has been the subject of extensive research. However, there are few convergent, enantioselective approaches to tryptophan derivatives (*Scheme 3.1.2*).[7] In a seminal 1980 report, Townsend and coworkers disclosed a hydrogenation catalyst prepared from tartrate-derived ligand **145**, [Rh(cod)Cl_2], and H_2 that efficiently converts enamide **144** to the corresponding (*R*)-6-methyltryptophan **146** in 87% ee.[7a] More recently, Lectka and coworkers developed the first enantioselective imino-ene reaction using an (*R*)-BINAP-

derived copper complex (**149**) that enables access to tryptophan **150** in 85% ee from 3-methylideneindole **147** and α-imino ester **148**.[7b] When we initiated research directed toward tryptophan synthesis, one Friedel–Crafts approach had also been reported; Liu, Chen and coworkers disclosed a Cu-catalyzed enantioselective conjugate addition involving C3-unsubstituted indoles (**90**) and β-aryl-nitroacrylates (**151**) that provides β–substituted tryptophan derivatives (e.g. **153**).[7d]

3.1.3 Tandem Conjugate Addition/Enantioselective Protonation Reactions

Throughout the past decade, many tandem conjugate addition/enantioselective protonation reactions have been developed for a variety of nucleophiles.[8] For example, Genet and Darses reported the synthesis of phenylalanine derivatives (**155**) by a Rh-catalyzed reaction of methyl 2-acetamidoacrylate (**91a**) and potassium aryltrifluoroborates (**154**) that employs guaiacol as the stoichiometric proton source (*Scheme 3.1.3*).[8h]

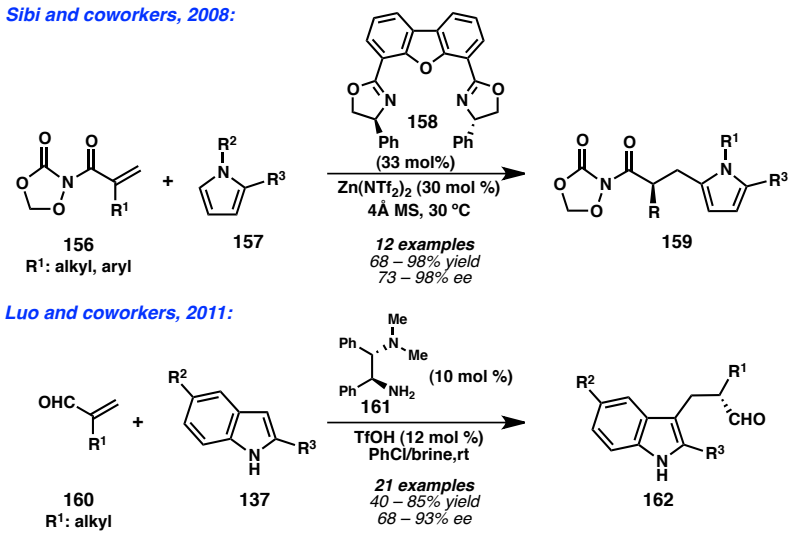
Scheme 3.1.3. Access to amino acids by tandem conjugate addition/enantioselective protonation (Genet and Darses, 2004).



Despite considerable research, examples of tandem *Friedel–Crafts* conjugate addition/enantioselective protonation reactions are rare and were first reported in 2008. Sibi and coworkers developed an oxazolidinone-derived acrylamide (**156**) for conjugate addition of pyrroles (**157**) catalyzed by $Zn(NTf_2)_2$ and dibenzofuran-derived BOX ligand **158** (*Scheme 3.1.4*).[8k] The selectivity is thought to arise by bischelation of the catalyst with

the carbonyls of **156**. The pyrrole products were prepared in excellent yield and ee; however, no examples of this reaction using indole nucleophiles have been reported. Concomitant with our work in this area, Luo and coworkers developed a related diamine **161**-catalyzed tandem conjugate addition/enantioselective protonation reaction involving C2-substituted indoles (**137**) and acrolein derivatives (**160**).[81] However, to our knowledge, the research discussed in this chapter constitutes the only enantioselective protonation approach to tryptophan derivatives.[9]

Scheme 3.1.4. Tandem Friedel–Crafts conjugate addition/enantioselective protonation reactions.



3.2 $SnCl_4$-PROMOTED ASYMMETRIC PROTONATION APPROACH TO TRYPTOPHAN DERIVATIVES

3.2.1 Optimization Studies

Our studies began with the investigation of 2-phenylindole (**137a**) using our previously optimized conditions for asymmetric pyrroloindoline synthesis. Surprisingly, these conditions resulted in formation of trifluoroacetamido ester **138a** in poor yield and

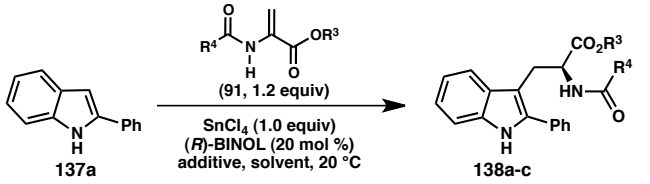
ee (Table 3.2.1, entry 1). Alternatively, treatment of **137a** and methyl 2-acetamidoacrylate (**91a**) with 1 equivalent $SnCl_4$ and 20 mol % (*R*)-BINOL in DCM delivers acetamido ester **138c** in 73% yield and 78% ee (entry 3).[10] Importantly, we found it critical to quench these reactions with saturated aqueous $NaHCO_3$; a quench with 1 M aqueous NaOH consistently results in partial racemization and under otherwise identical conditions, **138c** was isolated in 75% ee (entry 6). We also hypothesized that adventitious HCl generated under the reaction conditions might artificially reduce the ee by serving as an achiral proton source for enolate protonation; therefore, a screen of acid and water scavenging additives was conducted. 2,6-lutidine inhibited the reaction, presumably through coordination of $SnCl_4$, and no effect was observed with the inorganic bases such as K_2CO_3 (entries 7-8). However, we were pleased to find that in the presence of 4Å molecular sieves, the reaction of 2-phenylindole (**137a**) furnishes acetamido ester **138c** in an improved 86% yield and 81% ee (entry 9). As observed for pyrroloindoline formation, halogenated solvents are optimal with DCM providing the highest enantioselectivity (entries 9-11).

As observed for the formal (3 + 2) cycloaddition reaction, BINOL significantly increases the rate of the reaction, with $SnCl_4$ alone providing **138c** in only 13% yield (entry 4).[‡] Likewise, no reaction is observed in the absence of $SnCl_4$ (entry 5). Although BINOL cannot independently facilitate this transformation, it is notable that exposure to HCl results in a reaction of 2-phenylindole (**137a**) and **91a**; however, in this case **91a** preferentially reacts via the imine tautomer to give quaternary amide **165** in 38% yield (Scheme 3.2.1). By contrast, diphenylphosphate only promotes trace conversion to **165**.

[‡] For kinetics experiments involving in situ monitoring by ^{1}H NMR spectroscopy, see Section 3.4.10.

The reactivity promoted by HCl appears unique to **137a**; Piersanti and coworkers reported that subjection of indole and **91a** to two equivalents of HCl at 0 ºC gave no reaction.[9b] A possible explanation for this divergent reactivity is the enhanced stability of the imine intermediate resulting from conjugate addition with **137a** that derives from conjugation with the C2-phenyl substituent.

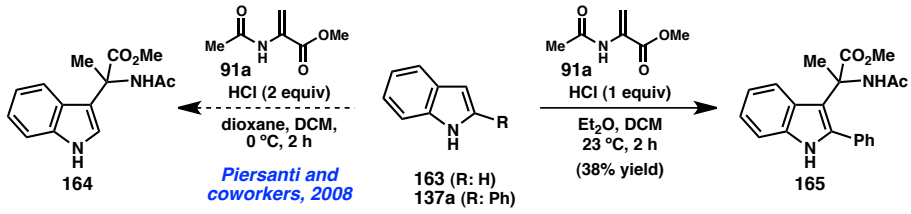
Table 3.2.1. Optimization of reaction parameters.[a]



Entry	R^3, R^4	pdt	Solvent	Additive	Yield (%)[b]	ee (%)[c]
1	Bn, CF_3 (**91d**)	**138a**	DCM	--	12	35
2	Me, CF_3 (**91b**)	**138b**	DCM	--	12	42
3	Me, Me (**91a**)	**138c**	DCM	--	73	78
4	Me, Me (**91a**)	**138c**	DCM	[d]	13	--
5	Me, Me (**91a**)	**138c**	DCM	[e]	0	--
6	Me, Me (**91a**)	**138c**	DCM	[f]	75	75
7	Me, Me (**91a**)	**138c**	DCM	K_2CO_3	73	78
8	Me, Me (**91a**)	**138c**	DCM	2,6-lutidine	0	--
9	Me, Me (**91a**)	**138c**	DCM	4Å MS	86	81
10	Me, Me (**91a**)	**138c**	DCE	4Å MS	87	79
11	Me, Me (**91a**)	**138c**	$CHCl_3$	4Å MS	80	72

[a] Reactions conducted in a glovebox on 0.2 mmol scale for 2 h. Reactions worked up using saturated aqueous $NaHCO_3$. [b] Isolated yield. [c] Determined by chiral stationary phase SFC. [d] Reaction run without (*R*)-BINOL. [e] Reaction run without $SnCl_4$. [f] Reaction worked up using 1 M aqueous NaOH.

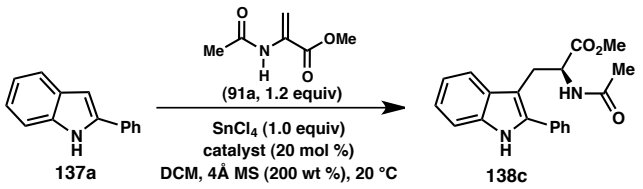
*Scheme 3.2.1. Bronsted acid-promoted reactivity of 2-phenylindole (**137a**).*



The enantioselectivity of the tandem conjugate addition/enantioselective protonation reaction was further improved through catalyst optimization. Investigation of 6,6'-disubstituted BINOL derivatives did not identify more selective catalysts and indicated

that the selectivity could not be tuned soley based on electronic perturbation (Table 3.2.2, entries 8-10). Sterically hindered (*R*)-3,3'-diphenyl-BINOL (**102g**) provided acetamido ester **138c** in low yield and only 37% ee, while (*R*)-3,3'-dimethoxy-BINOL (**102l**) gave the product as a racemate possibly due to alternate binding modes for $SnCl_4$ that result in an unselective reaction (entries 1 and 7). We were pleased to find that 3,3'-dihalogenated derivatives of BINOL provided improved selectivity, with (*R*)-3,3'-dibromo-BINOL (**102k**) affording ester **138c** in 76% yield and 93% ee (entry 6). Notably, although our initial screening was conducted in a glovebox, this reaction can be conducted on gram scale on the benchtop without any significant effect on the yield or ee (Scheme 3.2.2).

Table 3.2.2. Catalyst optimization.[a]



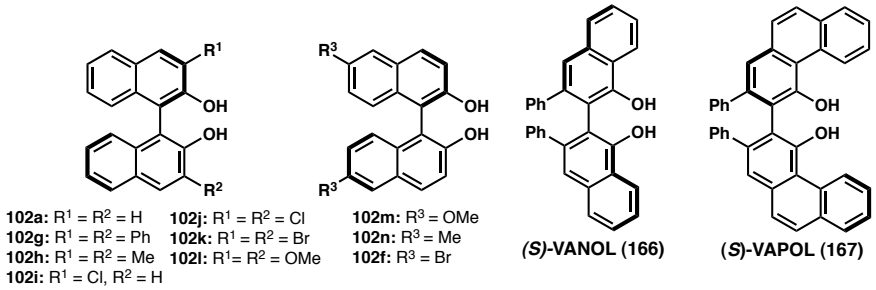
Entry	Catalyst	Loading (mol %)	Yield (%)[b]	ee (%)[c]
1	**102a**	20	86	81
2	**102g**	20	17	37
3	**102h**	20	83	87
4	**102i**	20	76	84
5	**102j**	20	85	90
6	**102k**	20	76	93
7	**102l**	20	7	1
8	**102m**	20	86	54
9	**102n**	20	88	78
10	**102f**	20	82	78
11	**166**	20	86	–95
12	**167**	20	9	–32

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

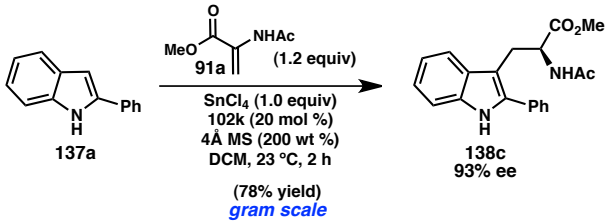
Interestingly, (*S*)-VANOL (**166**), a vaulted chiral diol developed by Wulff and coworkers,[11] provided the highest yield and ee we have observed to date, furnishing **138c** in 86% yield and –95% ee (Table 3.2.2, entry 11). Although 2-phenylindole (**137a**) gave

optimal results with **166**, we elected to use (*R*)-3,3'-dibromo BINOL (**102k**) in the evaluation of substrate scope. While both **102k** and **166** are commercially available, **102k** is much less expensive and readily accessible in three steps from BINOL. Furthermore, although **166** proved optimal for **137a**, this trend was not consistently observed with other indole substrates (Table 3.2.5).

Figure 3.2.1 Catalysts.

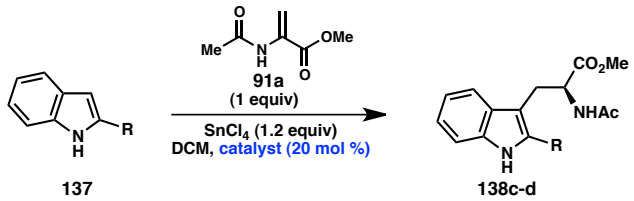


*Scheme 3.2.2. Gram-scale, benchtop synthesis of tryptophan methyl ester **138c**.*



A variety of other chiral diols were also evaluated during the course of our optimization studies (Table 3.2.3). As observed for the formal (3 + 2) cycloaddition reaction, non-BINOL-derived chiral diols, including (*R*)-5,5',6,6',7,7',8,8'-octahydro-BINOL (**168**), TADDOLs **103** and **169**, and hydrobenzoin (**104**) provided tryptophan products either in low ee (entries 2,5,14) or as a racemate (entries 3-4). In addition, (*R*)-2-alkoxy-BINOL derivatives gave reduced ee, which is indicative of the key role played by the hydroxyl protons in the enantioselective protonation (entries 15-18).

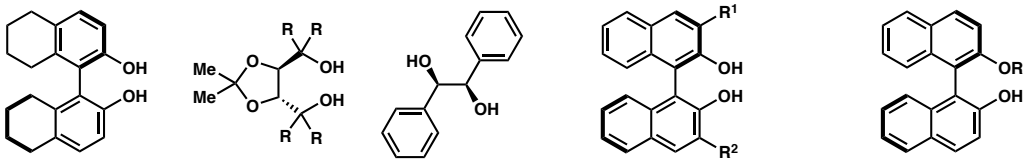
Table 3.2.3. Initial catalyst optimization studies.[a]



Entry	R	pdt	Catalyst	ee (%)[b]
1[c]	Me (**137b**)	**138d**	**102a**	71
2[c,d]	Me (**137b**)	**138d**	**168**	2
3[c]	Me (**137b**)	**138d**	**103**	0
4[c]	Me (**137b**)	**138d**	**169**	0
5[c]	Me (**137b**)	**138d**	**104**	9
6[c]	Ph (**137a**)	**138c**	**102a**	78
7[c]	Ph (**137a**)	**138c**	**102k**	80
8[c]	Ph (**137a**)	**138c**	**102o**	85
9[c]	Ph (**137a**)	**138c**	**102q**	84
10[c]	Ph (**137a**)	**138c**	**102r**	81
11[c]	Ph (**137a**)	**138c**	**102s**	86
12[e]	Ph (**137a**)	**138c**	**102a**	72
13[e]	Ph (**137a**)	**138c**	**102p**	50
14[e]	Ph (**137a**)	**138c**	**168**	23
15[e]	Ph (**137a**)	**138c**	**102b**	20
16[e]	Ph (**137a**)	**138c**	**102t**	39
17[e]	Ph (**137a**)	**138c**	**102u**	7
18[e]	Ph (**137a**)	**138c**	**102v**	1

[a] Reactions conducted under inert atmosphere on the benchtop on 0.1 to 0.2 mmol scale. [b] Determined by chiral stationary phase SFC. [c] Reaction worked up using saturated aqueous $NaHCO_3$. [d] 2.0 equivs $SnCl_4$ was employed. [e] Reaction worked up using 1M aqueous NaOH.

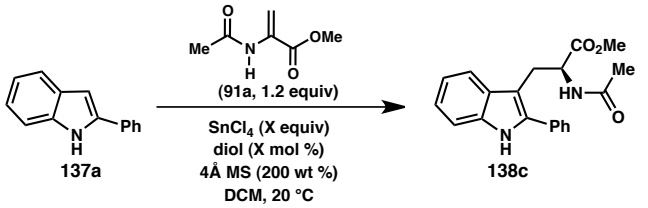
Figure 3.2.2. Catalysts for initial optimization.



With optimal conditions for tryptophan synthesis in hand, we evaluated the possibility of reducing the loading of both (*R*)-3,3'-dibromo-BINOL (**102k**) and $SnCl_4$ (Table 3.2.4). The loading of **102k** can be reduced as low as 10 mol % without significant erosion of ee; **138c** is obtained in reduced ee (88%) when 5 mol % **102k** is employed (entries 4-5).

However, it appears that the reaction requires a full equivalent of $SnCl_4$. Unlike in the formal (3 + 2) cycloaddition and the $EtAlCl_2$-promoted tryptophan synthesis by Piersanti and coworkers wherein the reactions barely proceed with substoichiometric Lewis acid loadings (Chapter 2),[9b] we observed that the loading of $SnCl_4$ is directly proportional to yield; for example, use of 0.6 equiv $SnCl_4$ provides 66% yield of **138c**.

*Table 3.2.4. Catalytic loadings of **102k** and $SnCl_4$.*[a]



Entry	Diol	Diol (mol %)	$SnCl_4$ (equiv)	Yield (%)[b]	ee (%)[c]
1	**102k**	20	1.0	76	93
2	**102k**	40	1.0	76	93
3	**102k**	15	1.0	77	93
4	**102k**	10	1.0	75	92
5	**102k**	5	1.0	72	88
6	**102a**	20	1.0	86	81
7	**102a**	20	0.8	80	79
8	**102a**	20	0.6	66	77

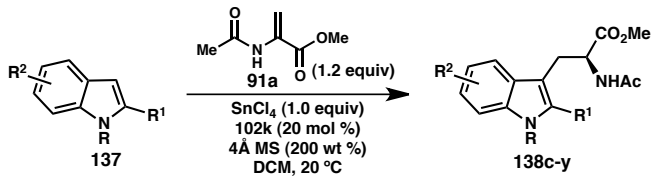
[a] Reactions conducted in a glovebox on 0.2 mmol scale for 2 h. [b] Isolated yield. [c] Determined by chiral stationary phase SFC.

3.2.2 Substrate Scope of Tryptophan Synthesis

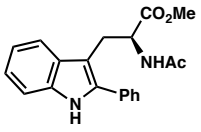
The substrate scope was explored under the optimized conditions using a 20 mol % loading of (*R*)-3,3'-dibromo-BINOL (**102k**) to ensure optimal results for all substrates (Table 3.2.5). In contrast to the trend observed in the formal (3 + 2) cycloaddition reaction (Chapter 2), *N*-alkylated indoles react in lower yield than (1*H*)-derivatives, with tryptophans **138e** and **138f** both accessed in 85% ee (entries 2-3). Electronically diverse indoles functionalized at C4, C5, C6, and C7 provided uniformly high ees; however, electron-poor indoles furnished tryptophan products in lower yields (e.g. **138l**). A variety

of alkyl and aryl substituents were tolerated at C2 of the indole although *ortho*-functionalized aryl substituents (e.g. **138t**) and very small or bulky alkyl substitution resulted in lower yields and ee (entries 18-23).

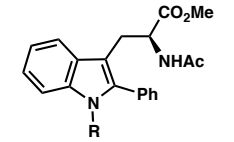
Table 3.2.5. Substrate scope.[a]



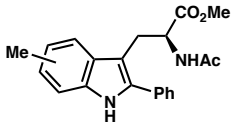
entry

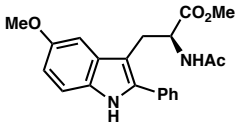
1) 
138c
76% yield, 93% ee

2) R = Me (138e) 63% yield, 85% ee
3) R = allyl (138f) 68% yield, 85% ee

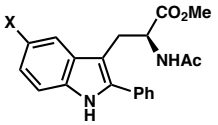


4) 4-Me (138g): 88% yield, 96% ee
5) 5-Me (138h): 83% yield, 95% ee
6) 6-Me (138i): 80% yield, 89% ee
7) 7-Me (138j): 94% yield, 94% ee

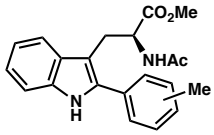



138k
8) 85% yield, 91% ee

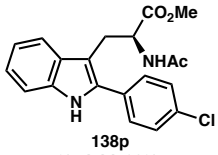
entry

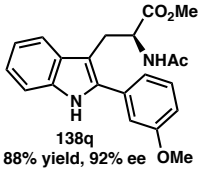


9)[b] Br (138l): 60% yield, 93% ee
10)[b] F (138m): 63% yield, 92% ee

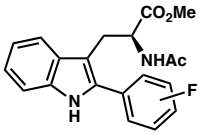


11) 4-Me (138n): 86% yield, 94% ee
12) 2-Me (138o): 26% yield, 87% ee

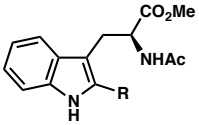

138p
13) 75% yield, 93% ee


138q
14) 88% yield, 92% ee

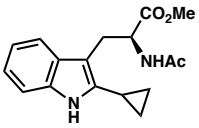
entry

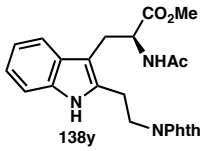


15) 4-F (138r): 78% yield, 93% ee
16) 3-F (138s): 76% yield, 92% ee
17) 2-F (138t): 35% yield, 92% ee



18) R = Me (138d): 61% yield, 85% ee
(63% yield, –75% ee)[c]
19) R = *n*-Bu (138u): 72% yield, 91% ee
20) R = *i*-Pr (138v): 66% yield, 92% ee
21) R = *t*-Bu (138w): 29% yield, 84% ee


138x
22) 24% yield, 75% ee
(7% yield, –80% ee)[c]


138y
23) 80% yield, 90% ee

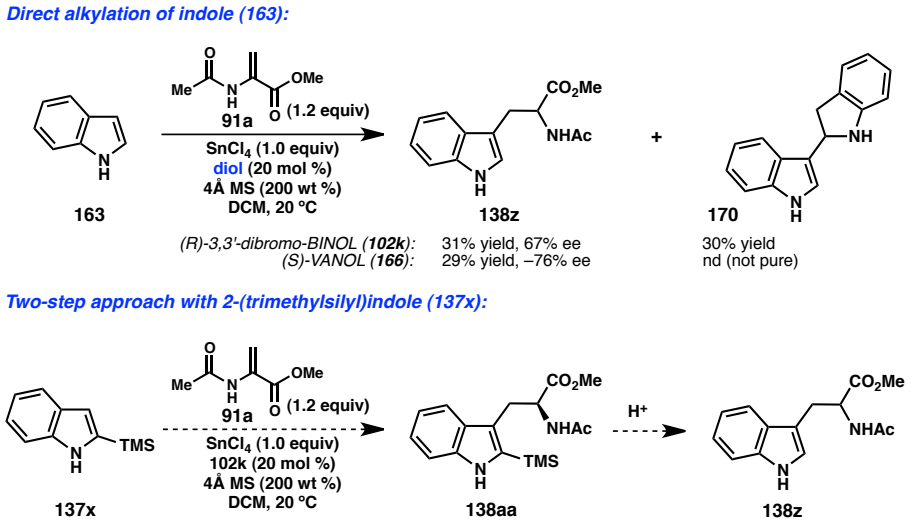
[a] Reaction conducted in a glovebox for 2 h on 0.1 or 0.2 mmol scale. Isolated yields are reported. Enantiomeric excess determined by chiral SFC analysis. [b] 1.6 equivs $SnCl_4$ was employed. [c] Reaction run with (*S*)-VANOL (**166**).

For a few cases where low yield and ee was observed, the reactions were also conducted using (*S*)-VANOL (**166**) as the catalyst (entries 18 and 22). Unfortunately, the trend observed with 2-phenylindole, wherein higher yield and ee was observed with **166**,

was found to be substrate specific. For example, reaction of 2-cyclopropylindole using **166** as the catalyst gave **138x** in 80% ee, compared to 75% with **102k**; however, the yield was reduced from 24% to 7% using **166** as the catalyst.

Although the tandem conjugate addition/enantioselective protonation reaction is tolerant of diverse functionalization, substitution at C2 of the indole is required to enable a highly enantioselective, efficient transformation. Exposure of indole to the standard reaction conditions results in competitive dimerization, with tryptophan **138z** formed in only 31% yield and 67% ee (Scheme 3.2.3). Unfortunately, low yields are also observed using (*S*)-VANOL (**166**) as the catalyst, although the ee is improved to –76%. As an alternative approach to C2-unsubstituted tryptophan derivatives, we have investigated the alkylation of 2-(trimethylsilyl)indole (**137x**); however, as experienced with the formal (3 + 2) cycloaddition (Scheme 2.3.1), exposure of **137x** to $SnCl_4$ on the benchtop resulted in rapid protodesilylation and attempts at this alkylation under strictly anhydrous conditions were unsuccessful.

Scheme 3.2.3. Efforts to access C2-unsubstituted tryptophan derivatives.[a]

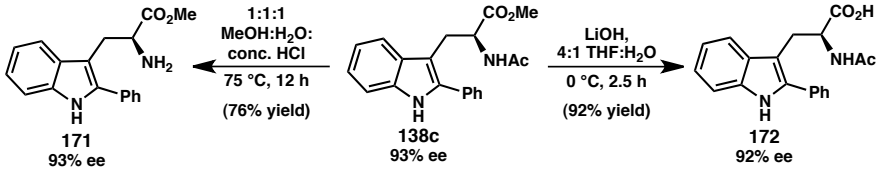


[a]Reactions conducted in a glovebox on 0.1 or 0.2 mmol scale. Isolated yields are reported. Enantiomeric excess was determined by chiral stationary phase SFC.

3.2.3 Derivatization of Tryptophan Products

Following the development of the tandem conjugate addition/enantioselective protonation reaction, our attention turned to investigating the functionalization of the products. Importantly, both the acetamide and ester functionalities could be selectively hydrolyzed without erosion of ee. Heating of **138c** with methanolic HCl gives primary amine **171**, whereas exposure of **138c** to LiOH cleanly affords carboxylic acid **172** (*Scheme 3.2.4*). For more information regarding derivatization and the development of an oxidative cyclization reaction of *N*-methyl tryptophan derivative **138e**, refer to Chapter 4.

*Scheme 3.2.4. Selective hydrolysis conditions for acetamide and methyl ester of **138c**.*

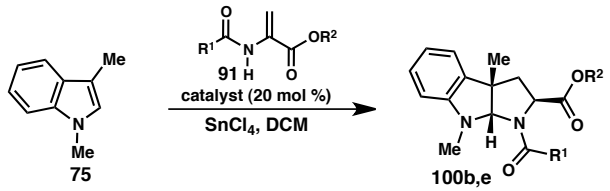


3.2.4 Comparison of New Conditions for Pyrroloindoline Formation

On the basis of mechanistic similarities, we envisioned that the optimal conditions for the tandem conjugate addition/protonation reaction might afford improved yields and selectivities for the formal (3 + 2) cycloaddition reaction. When methyl 2-acetamidoacrylate (**91a**)–the optimal partner for tryptophan synthesis–is employed, 1,3-dimethylindole (**75**) reacts in the presence of (*R*)-BINOL•$SnCl_4$ to give pyrroloindoline **100b** in 5:1 dr, with the major diastereomer formed in 65% ee (Table 3.2.6, entry 1). Alternatively, exposure of a mixture of **91a** and **75** to (*R*)-3,3'-dibromo-BINOL and 4Å MS furnished **100b** in an improved 8:1 dr and 87% ee for the *exo* diastereomer, albeit in lower yield (entry 2). We observed a similar trend with the benzyl 2-trifluoroacetamidoacrylate (**91d**)–the optimal partner for pyrroloindoline synthesis. The

reaction of **75** and benzyl 2-trifluoroacetamidoacrylate (**91d**) using (*R*)-3,3'-dibromo-BINOL and 4Å MS gave improved dr and the *exo* diastereomer was formed in an exceptional 98% ee, but the yield was dramatically reduced to only 39% (entry 4). Thus, an appropriate matching of acrylate and catalyst is required to obtain both high yields and selectivities.

Table 3.2.6. Comparison of conditions for pyrroloindoline formation.

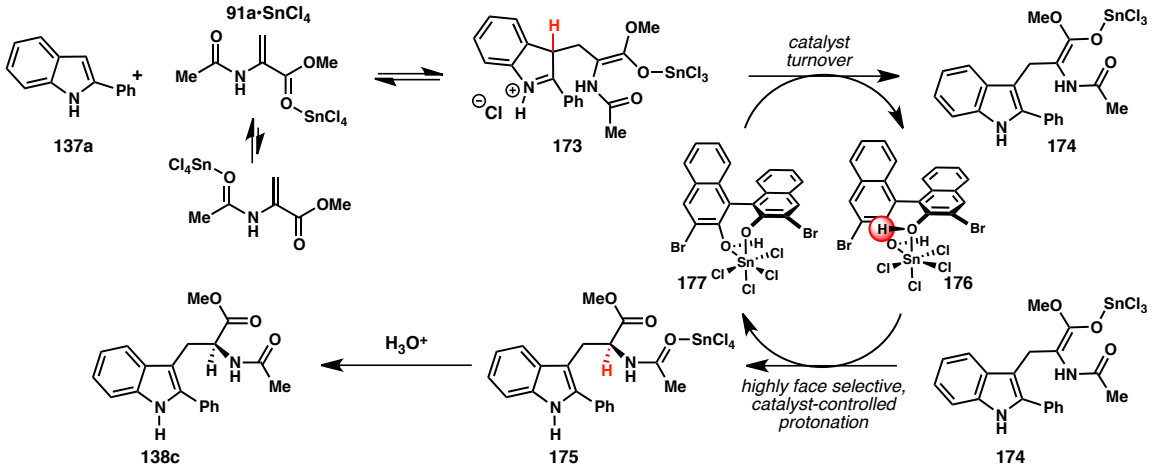


Entry	Conditions	R^1, R^2	pdt	Yield (%)[a]	dr[b]	ee (%)[c]
1[d]	**102a**	Me, Me (**91a**)	**100b**	70	5:1	65/80
2[e]	**102k**, 4Å MS	Me, Me (**91a**)	**100b**	58	8:1	87/85
3[d]	**102a**	CF_3, Bn (**91d**)	**100e**	86	4:1	94/91
4[e]	**102k**, 4Å MS	CF_3, Bn (**91d**)	**100e**	39	7:1	98/92

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis of 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 $SnCl_4$.

These results are suggestive of subtle mechanistic differences between the tandem conjugate addition/enantioselective protonation reaction and the formal (3 + 2) cycloaddition reaction. For example, in the tryptophan synthesis it is proposed that the stoichiometric proton source required for catalyst turnover derives from C3 of the indole, which is lost during rearomatization (Scheme 3.2.5). In contrast, in the pyrroloindoline formation, the stoichiometric proton is hypothesized to derive from the Lewis acid-coordiated trifluoroacetamide group (Scheme 2.3.2). Unfortunately, deuterium labeling studies aimed at identifying the stoichiometric proton source have been inconclusive, as exposure of deuterated indoles to BINOL•$SnCl_4$ results in rapid deuterium scrambling (3.4.9).

Scheme 3.2.5. Proposed catalytic cycle for tryptophan synthesis.



3.3 CONCLUDING REMARKS

In summary, the first tandem Friedel–Crafts conjugate addition/enantioselective protonation approach to tryptophan derivatives has been developed. This reaction proceeds optimally using $SnCl_4$•(*R*)-3,3'-dibromo BINOL as the catalyst and has allowed for the preparation of many C2-substituted tryptophan derivatives in excellent yields and ees. These derivatives have proven amenable to further functionalization, including selective hydrolysis and oxidative cyclization reactions (Chapter 4). In addition to enabling efficient access to tryptophan derivatives, the successful development of this reaction has provided further support for the mechanism of the formal (3 + 2) cycloaddition reaction. However, despite the shared enantiodetermining step for tryptophan and pyrroloindoline syntheses, the contrasting optimal conditions for each is suggestive of subtle differences in their mechanistic pathways. Further research is focused on mechanistic analysis and the application of this asymmetric protonation strategy in the design of new methodologies.

3.4 EXPERIMENTAL SECTION

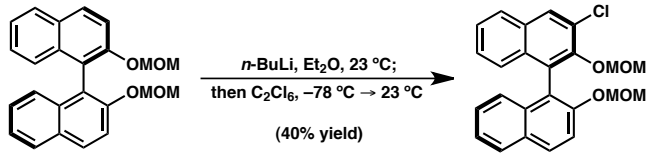
3.4.1 Materials and Methods

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 (**102a**), 2-phenylindole (**137a**) and 2-methylindole (**137b**) were purchased from Alfa Aesar, *N*-methyl-2-phenylindole (**137c**) was obtained from Sigma-Aldrich, and 1 M $SnCl_4$ in DCM was purchased from Acros Organics. (*R*)-3,3'-diphenyl-BINOL (**102g**),[12] (*R*)-3,3'-dimethyl-BINOL (**102h**),[13] (*R*)-3,3'-dichloro-BINOL (**102j**),[14] (*R*)-3,3'-dibromo-BINOL (**102k**),[15] (*R*)-3,3'-dimethoxy-BINOL (**102l**),[15] (*R*)-6,6'-dimethyl-BINOL (**102n**),[16] (*R*)-6,6'-dibromo-BINOL (**102f**),[17] (*R*)-2'-methoxy-[1,1'-binaphthalen]-2-ol (**102b**),[18] (*R*)-2'-isopropoxy-[1,1'-binaphthalen]-2-ol (**102u**),[19] (*R*)-3,3'-difluoro-BINOL (**102o**),[20] (*R*)-3-phenyl-BINOL (**102p**),[21] (*R*)-5,5',6,6',7,7',8,8'-octahydro-BINOL (**168**)[22], (*R*)-2'-benzoyl-[1,1'-binaphthalen]-2-ol (**102v**),[23] (*R*)-3-bromo-BINOL (**102q**) and (*R*)-3-iodo-BINOL (**102r**),[24] TADDOL (**103**),[25] Napthyl-TADDOL (**169**),[26] and 2-(trimethylsilyl)indole (**137x**),[27] 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.

3.4.2 Catalyst and Substrate Preparation

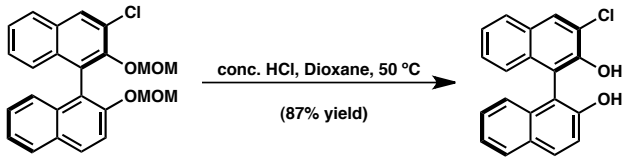
Preparation of (*R*)-3-chloro-BINOL (102i)



178 179

To a flame-dried 100 mL flask containing MOM–protected (*R*)-BINOL **178**[13] (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 **179** 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

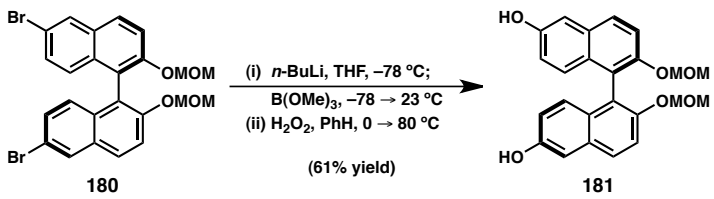
cm^{-1}; $[\alpha]_D^{25}$ = +69.1º (*c* = 0.90, $CHCl_3$). HRMS (FAB+) calc'd for M^+ 408.1128, found 408.1128.



179 **102i**

A 10 mL flask was charged with **179** (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 (**102i**) 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}; $[\alpha]_D^{25}$ = +55.4º (*c* = 1.01, $CHCl_3$). HRMS (MM) calc'd for $[M-H]^-$ 319.0531, found 319.0549.

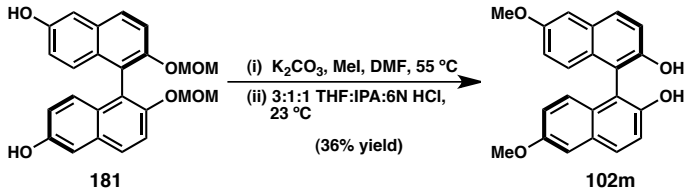
Preparation of (*R)*-6,6'-dimethoxy-BINOL (102m)



180 181

(*R*)-6,6'-dimethoxy-BINOL (**102m**) was prepared following a procedure adapted from a reported synthesis of (*R*)-3,3'-dimethoxy-BINOL (**102l**).[15] To a 25 mL flask containing MOM–protected (*R*)-6,6'-dibromo-BINOL **180**[17] (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 **181** 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,

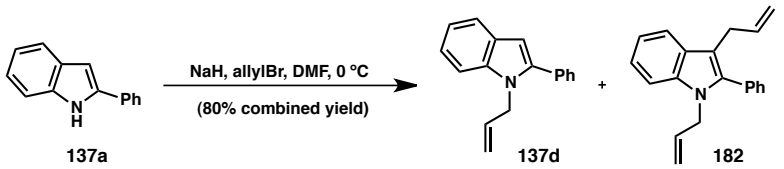
119.6, 118.7, 110.1, 96.0, 56.1; IR (NaCl/thin film): 3368, 2914, 1624, 1599, 1511, 1240, 1196, 1148, 1023 cm^{-1}; $[\alpha]_D^{25}$ = +87.1° (*c* = 1.00, MeCN). HRMS (MM) calc'd for $[M-H]^-$ 405.1344, found 405.1350.



181 **102m**

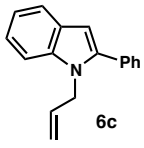
A 15 mL flask was charged with **181** (200 mg, 0.493 mmol, 1.00 equiv) and K_2CO_3 (177 mg, 1.28 mmol, 2.60 equiv). DMF (2 mL) was added, followed by MeI (123 μL, 1.97 mmol, 4.00 equiv) dropwise. The reaction was then heated to 55 ºC for 22 hours, then cooled to room temperature and quenched with saturated 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 (**102m**) as a light brown solid, which was dried over P_2O_5 under hi-vacuum. Spectral data are in agreement with the literature.[28]

Preparation of 1-allyl-2-phenylindole (137d)



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 **137a** (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 (**137d**) as a yellow solid and 331 mg (23% yield) of 1,3-diallyl-2-phenylindole (**182**) as a yellow oil.

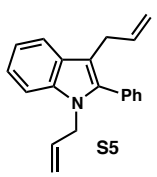
1-allyl-2-phenylindole (137d):



^{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

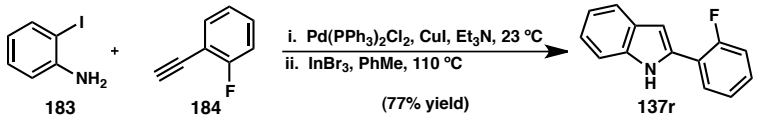
Hz, 1H), 5.00 (dtd, *J* = 17.1, 2.0, 1.2 Hz, 1H), 4.74 (dt, *J* = 4.2, 1.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.5, 137.8, 133.8, 132.7, 129.1, 128.5, 128.1, 128.0, 121.7, 120.5, 120.0, 116.5, 110.3, 102.0, 46.5; IR (NaCl/thin film): 3055, 2917, 1602, 1462, 1443, 1392, 1345, 1317, 1162 cm^{-1}; HRMS (APCI) calc'd for $[M+H]^+$ = 234.1277, found 234.1284.

1,3-diallyl-2-phenylindole (182):



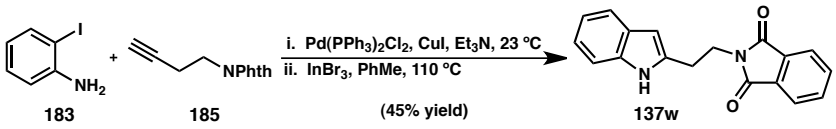
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (ddd, *J* = 7.8, 1.2, 0.7 Hz, 1H), 7.50 – 7.40 (m, 5H), 7.33 (ddd, *J* = 8.1, 0.9, 0.9 Hz, 1H), 7.24 (ddd, *J* = 7.0, 7.0, 1.2 Hz, 1H), 7.16 (ddd, *J* = 7.0, 7.0, 1.1 Hz, 1H), 6.05 (ddt, *J* = 17.0, 10.1, 5.9 Hz, 1H), 5.91 (ddt, *J* = 17.1, 10.4, 4.7 Hz, 1H), 5.14 (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 (137r)



2-(2-fluorophenyl)indole (**137r**) was prepared by an analogous procedure to that reported by Sakai et al.[29] A flame-dried flask was charged with 2-iodoaniline (**183**, 200 mg, 0.90 mmol, 1.00 equiv), ethynyl-2-fluorobenzene (**184**, 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 (**137r**) 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 (137w)



183 185 137w

2-(ethylphthalimide)indole (**137w**) was prepared by an analogous procedure to that reported by Sakai et al.[29] A flame-dried flask was charged with 2-iodoaniline (**183**, 500 mg, 2.30 mmol, 1.00 equiv), 2-(but-3-yn-1-yl)isoindoline-1,3-dione (**185**, 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 (**137w**) 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.

3.4.3 Optimization of Reaction Parameters

3.4.3.1 General Procedure 1

An oven-dried vial was charged with 2-phenylindole (**137a**, 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 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.

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:

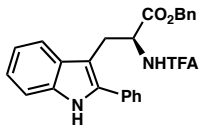
- flame-dried powdered 4Å molecular sieves (200 wt % relative to indole)
- K_2CO_3 (1.00 equiv)
- 2,6-lutidine (1.00 equiv)

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.

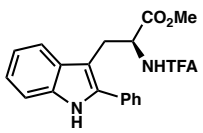
3.4.3.2 Characterization Data

(*S*)-N_α-Trifluoroacetyl-2-phenyltryptophan benzyl ester (138a)



Prepared from benzyl 2-trifluoroacetamidoacrylate[30] (**91d**, 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 **138a** 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, $J_{C\text{-}F}$ = 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, $J_{C\text{-}F}$ = 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 (138b)



Prepared from methyl 2-trifluoroacetamidoacrylate[31] (**91b**, 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 **138b** 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, $J_{C\text{-}F}$ = 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, $J_{C\text{-}F}$= 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.

3.4.4 Optimized Conjugate Addition/Asymmetric Protonation

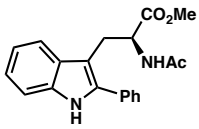
3.4.4.1 General Procedure 2

An oven-dried vial was charged with the indole (1.00 equiv), methyl 2-acetamidoacrylate (**91a**, 1.20 equiv)[32] and (*R*)-3,3'-dibromo-BINOL (**102k**, 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.

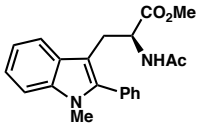
3.4.4.2 Characterization Data

(*S*)-*N*$_\alpha$-Acetyl-2-phenyltryptophan methyl ester (138c)



Prepared from 2-phenylindole (**137a**, 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 **138c** 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.[33]

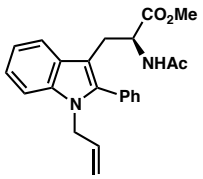
(*S*)-*N*$_\alpha$-Acetyl-1-methyl-2-phenyltryptophan methyl ester (138e)



Prepared from 1-methyl-2-phenylindole (**137c**, 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 **138e** 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.

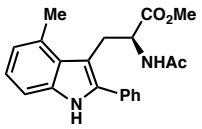
(*S*)-N_α-Acetyl-1-allyl-2-phenyltryptophan methyl ester (138f)



Prepared from 1-allyl-2-phenylindole (**137d**, 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 **138f** 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,

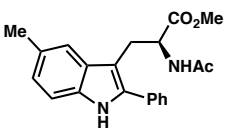
2851, 1744, 1658, 1538, 1500, 1408, 1367, 1219, 1196, 1134; $[\alpha]_D^{25}$ = +13.8º (*c* = 2.96, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 377.1860, found 377.1865.

(*S*)-N_α-Acetyl-4-methyl-2-phenyltryptophan methyl ester (138g)



Prepared from 4-methyl-2-phenylindole[34] (**137e**, 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 **138g** 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; $[\alpha]_D^{25}$ = -29.0º (*c* = 0.63, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 351.1703, found 351.1698.

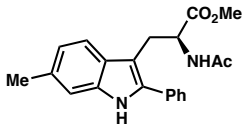
(*S*)-N_α-Acetyl-5-methyl-2-phenyltryptophan methyl ester (138h)



Prepared from 5-methyl-2-phenylindole[29] (**137f**, 42.0 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 58.0 mg (83% yield) of **138h** as a white foam. The enantiomeric excess was determined to be 95% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO_2, λ = 254 nm): t_R(major) =

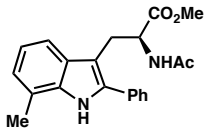
4.9 min, t_R(minor) = 6.4 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 7.54 (ddd, *J* = 10.1, 6.1, 4.2 Hz, 2H), 7.50 – 7.43 (m, 2H), 7.40 – 7.33 (m, 2H), 7.24 (d, *J* = 8.3 Hz, 1H), 7.06 – 7.00 (m, 1H), 5.78 (br d, *J* = 8.1 Hz, 1H), 4.83 (dt, *J* = 8.1, 5.4 Hz, 1H), 3.53 – 3.51 (m, 2H), 3.31 (s, 3H), 2.46 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 169.5, 136.1, 134.0, 133.3, 129.7, 129.2, 129.1, 128.2, 128.0, 124.1, 118.6, 110.6, 106.3, 52.7, 51.2, 26.5, 22.8, 21.5; IR (NaCl/thin film): 3379, 3365, 2948, 1737, 1658, 1439, 1372, 1306, 1217 cm^{-1}; $[\alpha]_D^{25}$ = +33.8° (*c* = 0.26, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 351.1703, found 351.1680.

(*S*)-N_α-Acetyl-6-methyl-2-phenyltryptophan methyl ester (138i)



Prepared from 6-methyl-2-phenylindole[34] (**137g**, 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 **138i** 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.

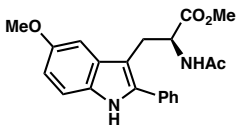
(*S*)-N_α-Acetyl-7-methyl-2-phenyltryptophan methyl ester (138j)



Prepared from 7-methyl-2-phenylindole[34] (**137h**, 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 **138j** 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),

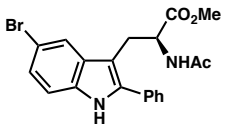
7.03 – 6.97 (m, 1H), 5.79 (br d, J = 8.1 Hz, 1H), 4.82 (dt, J = 8.1, 5.7 Hz, 1H), 2.55 (dd, J = 12.5, 3.1 Hz, 1H), 3.51 (dd, J = 12.5, 3.1 Hz, 1H), 3.30 (s, 3H), 2.50 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 169.6, 135.8, 135.3, 133.3, 129.1, 128.9, 128.4, 128.0, 123.1, 120.20, 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_α-Acetyl-5-methoxy-2-phenyltryptophan methyl ester (138k)



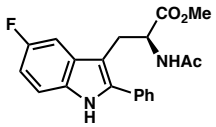
Prepared from 5-methoxy-2-phenylindole[34] (**137i**, 45.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 62.0 mg (85% yield) of **138k** as a colorless oil. The enantiomeric excess was determined to be 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_α-Acetyl-5-bromo-2-phenyltryptophan methyl ester (138l)



Prepared from 5-bromo-2-phenylindole[35] (**137j**, 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 **138l** 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.

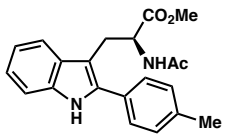
(*S*)-N_α-Acetyl-5-fluoro-2-phenyltryptophan methyl ester (138m)



Prepared from 5-fluoro-2-phenylindole[34] (**137k**, 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 **138m** 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,

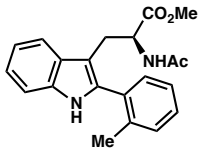
1H), 7.21 (dd, *J* = 9.8, 2.6 Hz, 1H), 6.94 (ddd, *J* = 9.0, 9.0, 2.6 Hz, 1H), 5.77 (br d, *J* = 7.8 Hz, 1H), 4.82 (dt, *J* = 8.1, 5.4 Hz, 1H), 3.53 (dd, J = 14.9, 5.6 Hz, 1H), 3.47 (dd, J = 14.9, 5.0 Hz, 1H), 3.35 (s, 3H), 1.64 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 169.8, 168.3, 135.6, 134.2, 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 (138n)



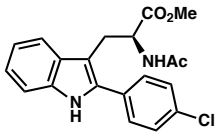
Prepared from 2-(4-methylphenyl)indole[36] (**137l**, 41.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 60.1 mg (86% yield) of **138n** as a white foam. The enantiomeric excess was determined to be 94% 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*$_\alpha$-Acetyl-2-(2-methylphenyl)tryptophan methyl ester (138o)



Prepared from 2-(2-methylphenyl)indole[37] (**137m**, 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 **138o**. 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.

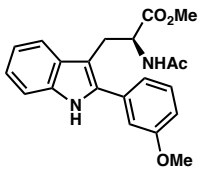
(*S*)-*N*α-Acetyl-2-(4-chlorophenyl)tryptophan methyl ester (138p)



Prepared from 2-(4-chlorophenyl)indole[34] (**137n**, 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 **138p** 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,

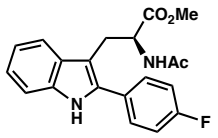
1H), 7.49 – 7.43 (m, 2H), 7.43 – 7.37 (m, 2H), 7.33 (ddd, J = 8.1, 8.1, 1.0 Hz, 1H), 7.23 – 7.18 (m, 1H), 7.14 (ddd, J = 8.0, 7.1, 1.1 Hz, 1H), 5.85 (br d, J = 8.1 Hz, 1H), 4.83 (dt, J = 8.1, 5.5 Hz, 1H), 3.55 – 3.38 (m, 2H), 3.34 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 169.6, 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}; $[\alpha]_D^{25}$ = +40.8º (*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 (138q)



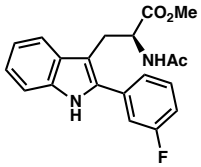
Prepared from 2-(3-methoxyphenyl)indole[38] (**137o**, 45.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (30:70 to 100:0 EtOAc:hexanes) to yield 65.0 mg (88% yield) of **138q** as a colorless oil. The enantiomeric excess was determined to be 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; $[\alpha]_D^{25}$ = +40.3º (*c* = 1.16, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 367.1652, found 367.1656.

(*S*)-*N*$_\alpha$-Acetyl-2-(4-fluorophenyl)tryptophan methyl ester (138r)



Prepared from 2-(4-fluorophenyl)indole[29] (**137p**, 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 **138r** 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.

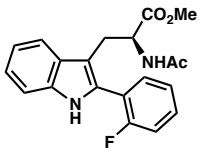
(*S*)-*N*$_\alpha$-Acetyl-2-(3-fluorophenyl)tryptophan methyl ester (138s)



Prepared from 2-(3-fluorophenyl)indole[36] (**137q**, 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 **138s** 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, $J_{C\text{-}F}$ = 246.3 Hz), 135.8, 135.2 (d, $J_{C\text{-}F}$ = 7.5 Hz), 134.5 (d, $J_{C\text{-}F}$ = 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.

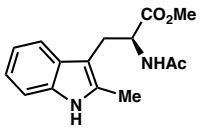
(*S*)-N_α-Acetyl-2-(2-fluorophenyl)tryptophan methyl ester (138t)



Prepared from 2-(2-fluorophenyl)indole (**137r**, 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 **138t**. 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

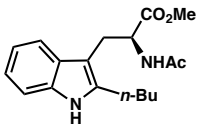
(NaCl/thin film): 3275, 3058, 2925, 2853, 1734, 1653, 1523, 1490, 1457, 1437, 1374, 1245, 1216, 1130, 1104; $[\alpha]_D^{25}$ = +39.8° (*c* = 0.41, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 355.1452, found 355.1463.

(*S*)-*N*$_\alpha$-Acetyl-2-methyltryptophan methyl ester (138d)



Prepared from 2-methylindole (**137b**, 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 **138d** 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.[33]

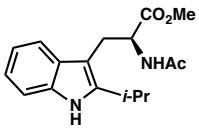
(*S*)-*N*$_\alpha$-Acetyl-2-butyltryptophan methyl ester (138u)



Prepared from 2-butylindole[39] (**137s**, 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 **138u** 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

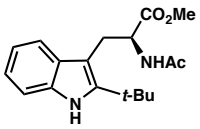
(125 MHz, $CDCl_3$) δ 172.6, 169.6, 137.4, 135.2, 128.8, 121.3, 119.5, 117.9, 110.4, 105.26, 105.29, 53.0, 52.3, 31.8, 26.8, 25.7, 23.2, 22.6, 13.9; IR (NaCl/thin film): 3296, 3058, 2955, 2871, 1737, 1658, 1562, 1530, 1463, 1439, 1376, 1217, 1129; $[\alpha]_D^{25}$ = -+16.3º (*c* = 0.83, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 317.1860, found 317.1855.

(*S*)-*N*α-Acetyl-2-isopropyltryptophan methyl ester (138v)



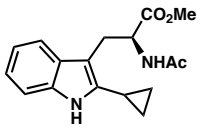
Prepared from 2-isopropylindole[40] (**137t**, 32.0 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (40:60 to 100:0 EtOAc:hexanes) to yield 39.6 mg (66% yield) of **138v** as a colorless oil. The enantiomeric excess was determined to be 92% by 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}; $[\alpha]_D^{25}$ = +22.2º (*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 (138w)



Prepared from 2-(tert-butyl)indole[33] (**137u**, 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 **138w** 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; $[\alpha]_D^{25}$ = +12.4º (*c* = 0.36, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 317.1860, found 317.1856.

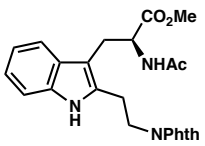
(*S*)-*N*$_\alpha$-Acetyl-2-cyclopropyltryptophan methyl ester (138x)



Prepared from 2-cyclopropylindole[41] (**137v**, 16.0 mg, 0.10 mmol) following General Procedure 2 except that 1.0 equiv methyl 2-acetamidoacrylate (**91a**) was employed. The crude residue was purified by silica gel chromatography (50:50 EtOAc:hexanes) to yield 4.6 mg (24% yield) of **138x** as a colorless oil. The enantiomeric excess was determined to be 75% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO_2, λ = 254 nm). t_R(major) = 2.6 min t_R(minor) = 2.3 min. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (br s, 1H), 7.41 (ddt, *J* = 7.5, 1.5, 0.7 Hz, 1H), 7.24 (ddd, *J* = 7.9, 1.3, 0.8 Hz, 1H), 7.10 (ddd, *J* = 7.9, 7.1, 1.5 Hz, 1H), 7.10 – 7.03 (m,

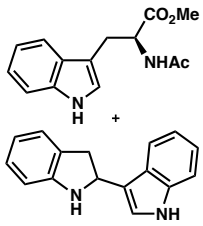
1H), 6.03 (br d, *J* = 8.0 Hz, 1H), 4.93 (dt, *J* = 8.0, 5.6 Hz, 1H), 3.67 (s, 3H), 3.36 (d, *J* = 5.6 Hz, 2H), 2.02 (tt, *J* = 8.4, 5.3 Hz, 1H), 1.94 (s, 3H), 1.05 – 1.01 (m, 2H), 0.79 – 0.76 (m, 2H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 169.6, 137.6, 134.6, 129.1, 121.5, 119.7, 117.6, 110.4, 106.9, 53.0, 52.4, 26.8, 23.3, 7.4, 7.10, 7.06.; IR (NaCl/thin film): 3297, 3058, 3006, 2952, 2926, 1736, 1654, 1523, 1468, 1439, 1375, 1339, 1309, 1217 cm^{-1}; HRMS (ESI) calc'd for $[M+H]^+$ 301.1547, found 301.1546.

(*S*)-N_α-Acetyl-2-(ethylphthalimide)tryptophan methyl ester (138y)



Prepared from 2-(ethylphthalimide)indole (**137w**, 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 **138y** 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.

(*S*)-*N*α-Acetyltryptophan methyl ester (138z) and indole dimer (170)

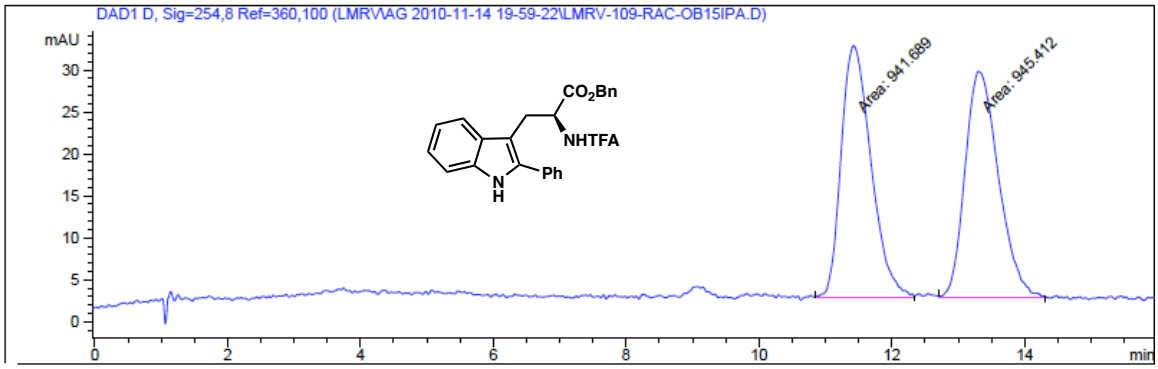


Prepared from indole (**163**, 23.4 mg, 0.20 mmol) following General Procedure 2. The crude residue was purified by silica gel chromatography (0:100 to 100:0 EtOAc:hexanes) to yield 17.9 mg (contains 9 wt % EtOAc, 31% corrected yield) of **138z** as a light pink oil and 7.0 mg (30% yield) of **170** as a light yellow oil. The enantiomeric excess of **138z** was determined to be 67% by chiral SFC analysis (OD-H, 2.5 mL/min, 15% IPA in CO_2, λ = 254 nm): t_R(major) = 11.4 min, t_R(minor) = 10.6 min. $[\alpha]_D^{25}$ = +39.3° (*c* = 0.83, $CHCl_3$). Spectral data for both (*S*)-N_α-acetyltryptophan methyl ester[42] and the indole dimer[43] are in agreement with the literature.

3.4.5 SFC Traces for Racemic and Enantioenriched Tryptophan Derivatives

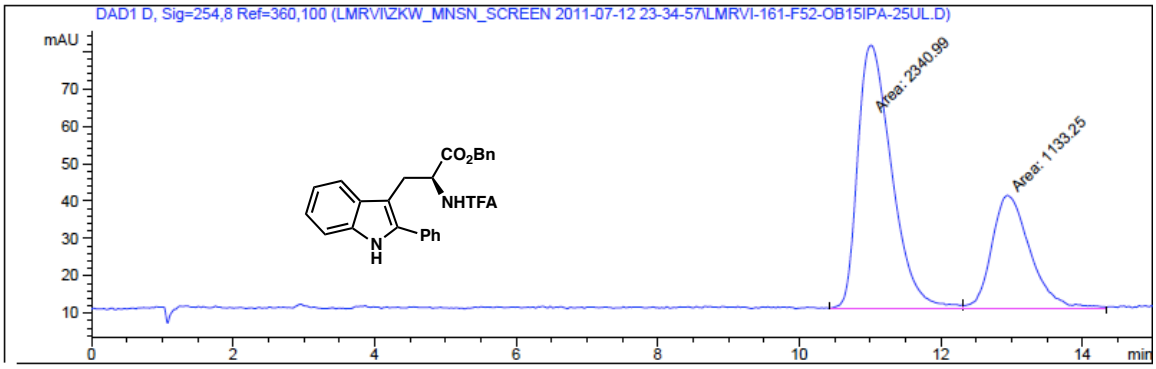
Optimization of Reaction Parameters

138a (Table 3.2.1, **entry 1**): racemic



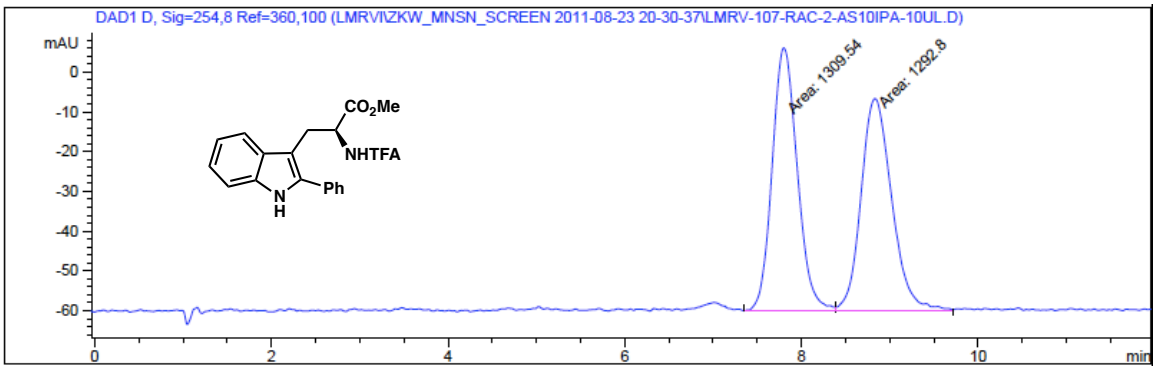
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.427	MM	0.5219	941.68884	30.07461	49.9014
2	13.305	MM	0.5837	945.41193	26.99413	50.0986

138a (Table 3.2.1**, entry 1**): enantioenriched, 35% ee



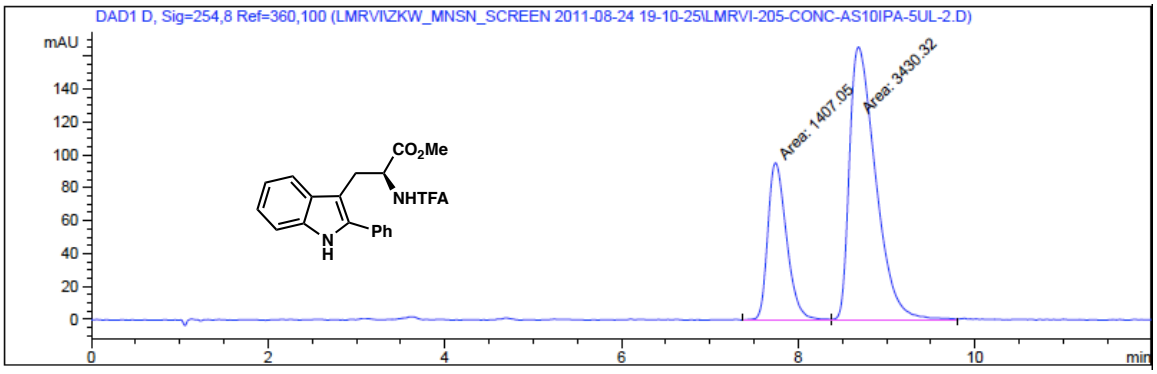
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.016	MM	0.5552	2340.98975	70.28041	67.3814
2	12.949	MM	0.6247	1133.24951	30.23348	32.6186

138b (Table 3.2.1, **entry 2**): racemic



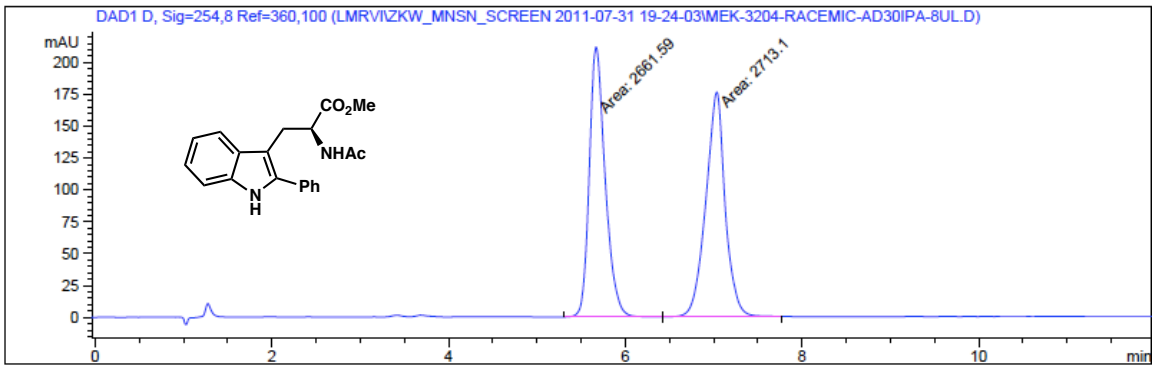
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.800	MM	0.3300	1309.54053	66.13437	50.3216
2	8.832	MM	0.4035	1292.80322	53.39447	49.6784

138b (Table 3.2.1, **entry 2**): enantioenriched, 42% ee



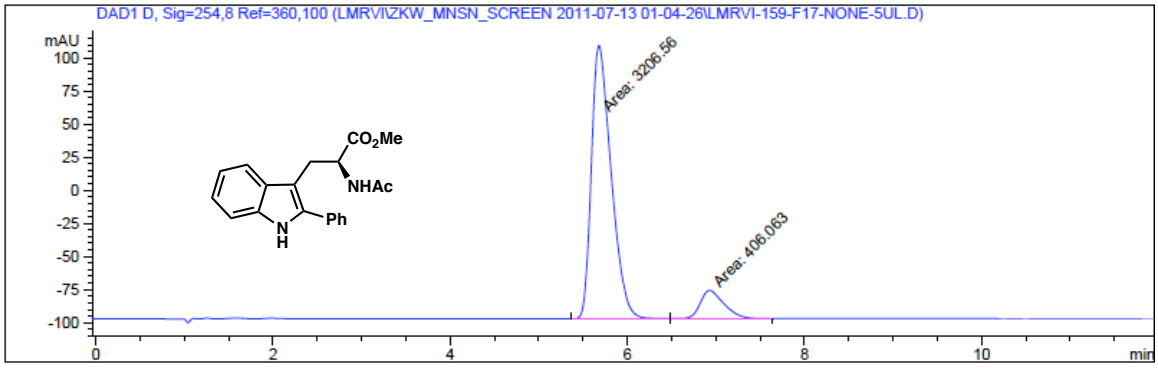
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.744	MM	0.2458	1407.04663	95.40716	29.0870
2	8.683	MM	0.3450	3430.32251	165.69673	70.9130

138c: racemic



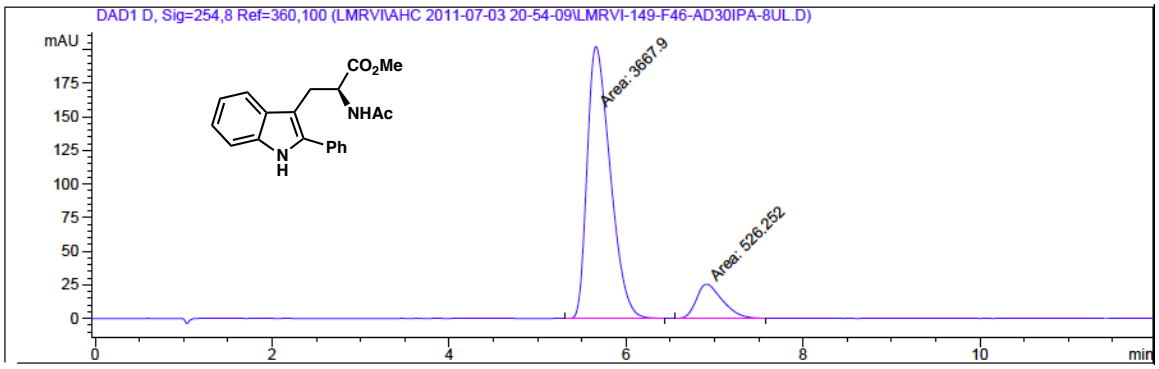
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.669	MM	0.2091	2661.59399	212.13072	49.5208
2	7.035	MM	0.2559	2713.10010	176.69841	50.4792

138c (Table 3.2.1, **entry 3**, no additive, DCM as solvent): enantioenriched, 78% ee



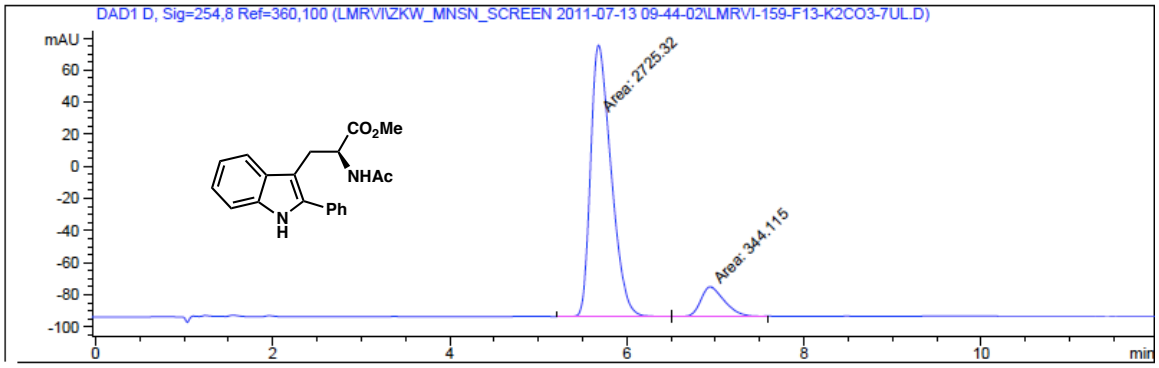
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.680	MM	0.2586	3206.56348	206.67487	88.7599
2	6.931	MM	0.3155	406.06302	21.44969	11.2401

138c (Table 3.2.1, **entry 6**, no additive, 1M NaOH workup): enantioenriched, 75% ee



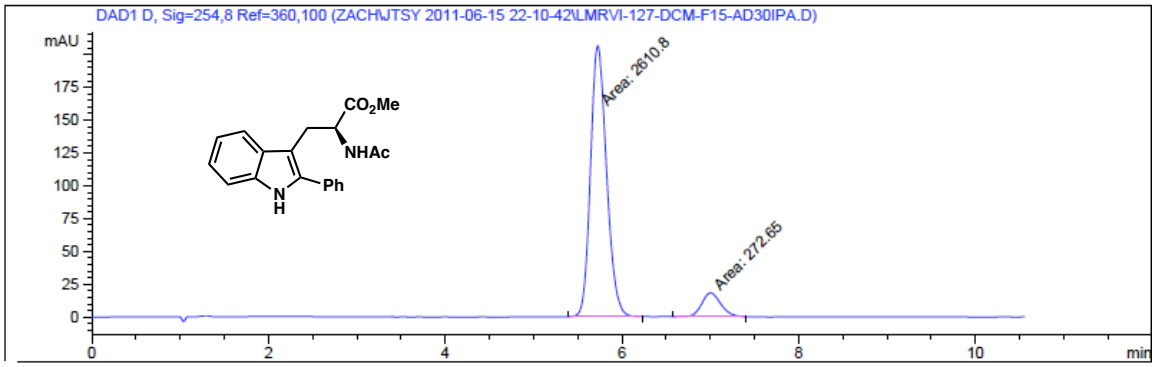
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.661	MM	0.3023	3667.89795	202.25258	87.4527
2	6.909	MM	0.3432	526.25208	25.55660	12.5473

138c (Table 3.2.1, **entry 7**, with K_2CO_3, DCM as solvent): enantioenriched, 78% ee



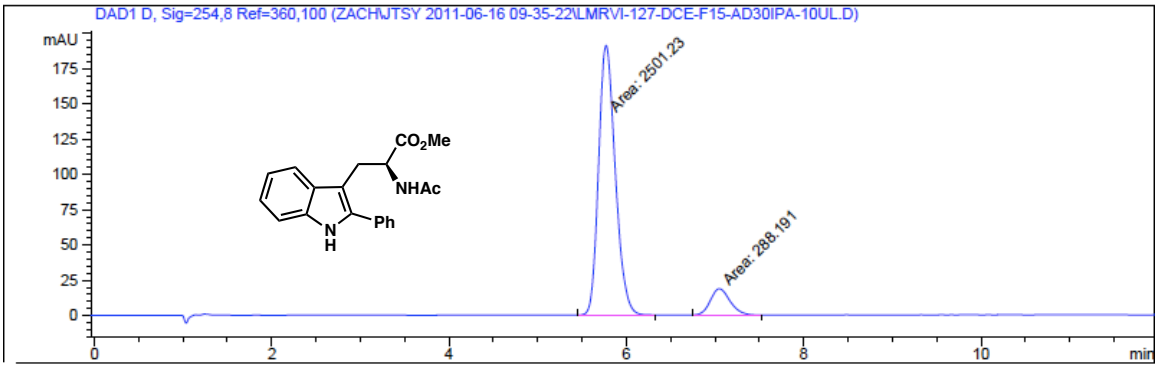
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.680	MM	0.2687	2725.31787	169.06570	88.7890
2	6.940	MM	0.3096	344.11493	18.52597	11.2110

138c (Table 3.2.1, **entry 9**, with 4Å MS, DCM as solvent): enantioenriched, 81% ee



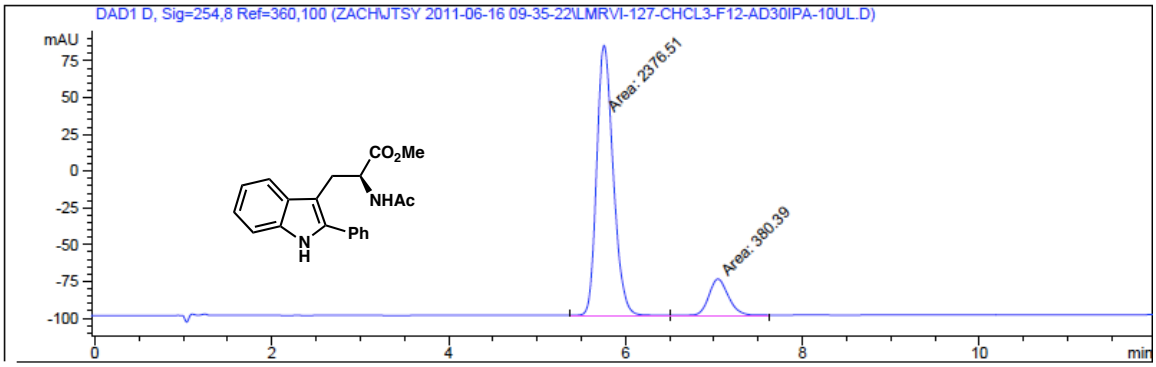
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.727	MM	0.2106	2610.80005	206.59111	90.5443
2	7.003	MM	0.2491	272.64963	18.24538	9.4557

138c (Table 3.2.1, **entry 10**, with 4Å MS, DCE as solvent): enantioenriched, 79% ee



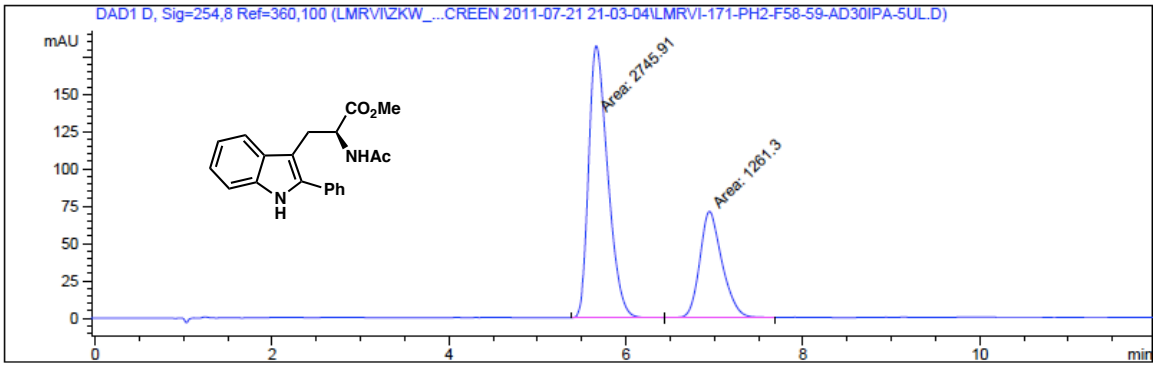
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.770	MM	0.2179	2501.22583	191.34946	89.6684
2	7.046	MM	0.2574	288.19092	18.66254	10.3316

138c (Table 3.2.1, **entry 11**, with 4Å MS, $CHCl_3$ as solvent): enantioenriched, 72% ee



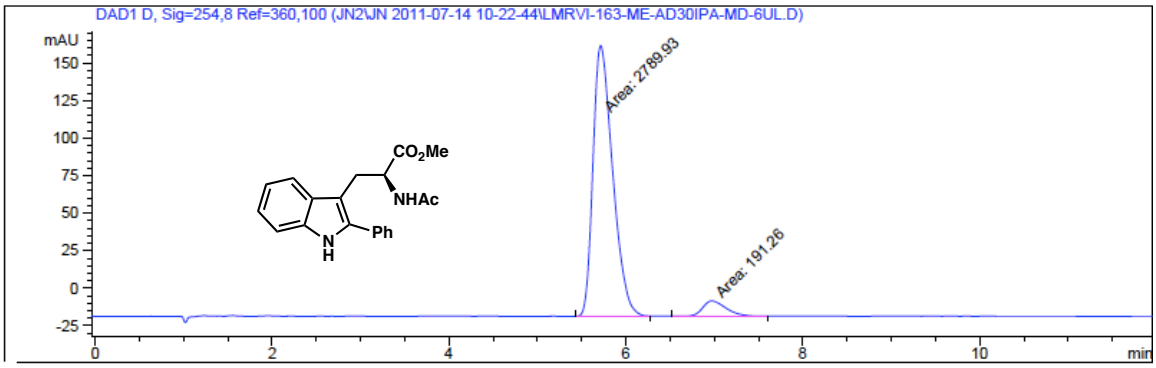
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.758	MM	0.2156	2376.51440	183.68063	86.2023
2	7.046	MM	0.2564	380.39029	24.72798	13.7977

138c (Table 3.2.2, **entry 2**, (*R*)-3,3'-diphenyl-BINOL (**102g**)): enantioenriched, 37% ee



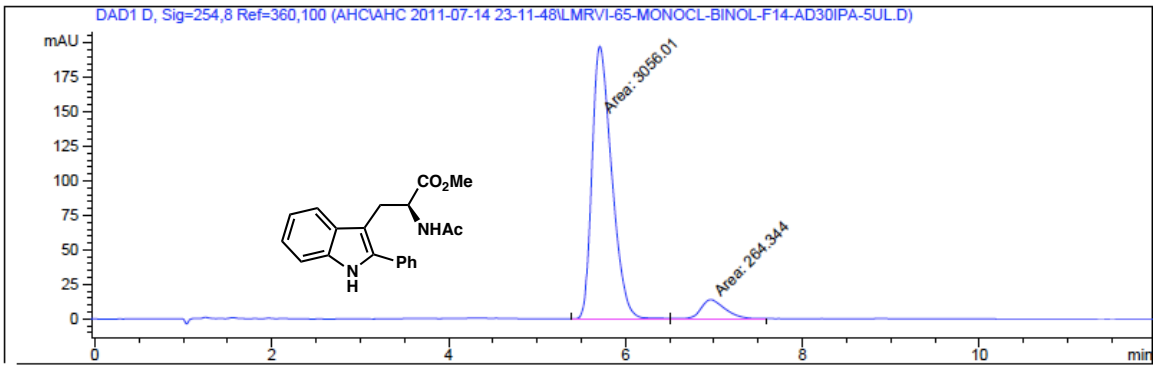
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.665	MM	0.2511	2745.91113	182.26123	68.5243
2	6.944	MM	0.2946	1261.29749	71.36543	31.4757

138c (Table 3.2.2, **entry 3**, (*R*)-3,3'-dimethyl-BINOL (**102h**)): enantioenriched, 87% ee



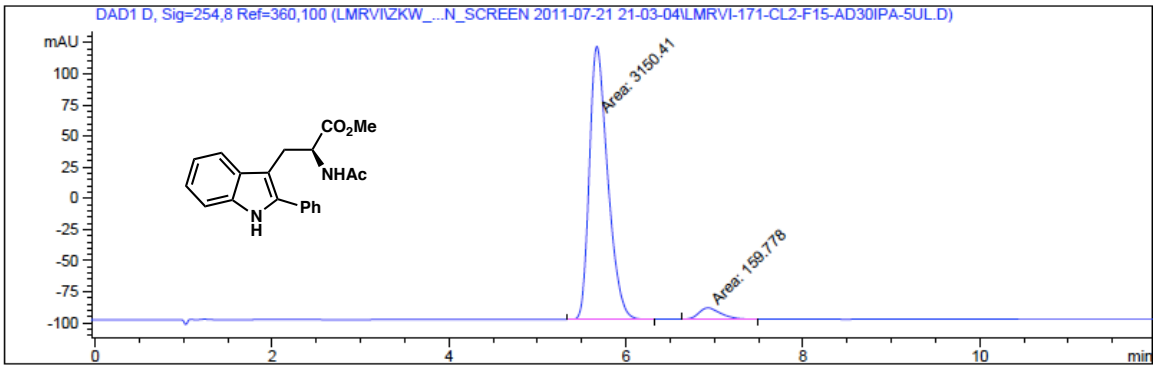
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.716	MM	0.2577	2789.92920	180.42043	93.5844
2	6.976	MM	0.3109	191.26035	10.25464	6.4156

138c (Table 3.2.2, **entry 4**, (*R*)-3-chloro-BINOL (**102i**)): enantioenriched, 84% ee



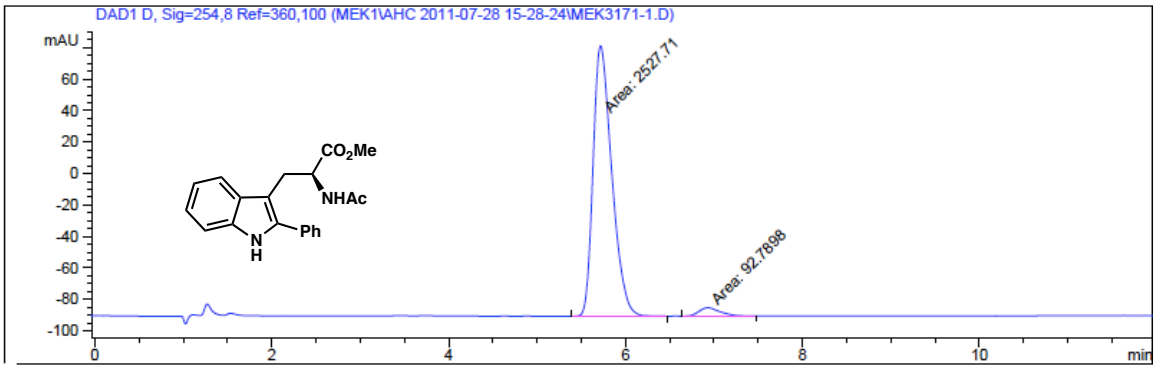
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.709	MM	0.2580	3056.00586	197.42212	92.0387
2	6.963	MM	0.3156	264.34421	13.95930	7.9613

138c (Table 3.2.2, **entry 5**, (*R*)-3,3'-dichloro-BINOL (**102j**)): enantioenriched, 90% ee



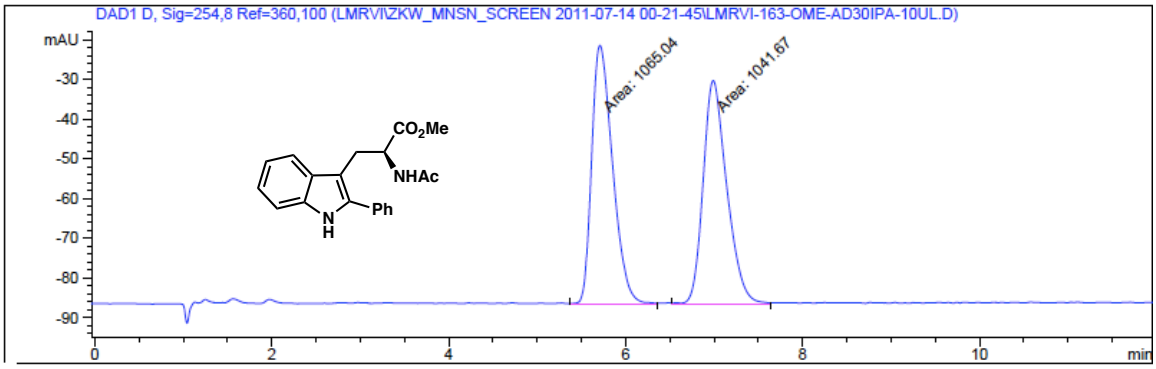
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.671	MM	0.2398	3150.40820	218.99393	95.1731
2	6.928	MM	0.2902	159.77843	9.17721	4.8269

138c (Table 3.2.2, **entry 6**, (*R*)-3,3'-dibromo-BINOL (**102k**)): enantioenriched, 93% ee



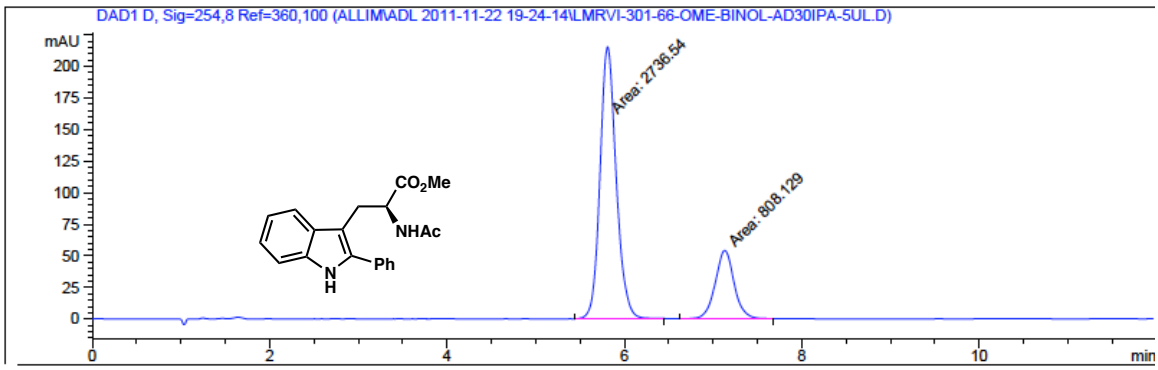
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.718	MM	0.2447	2527.71191	172.14331	96.4591
2	6.930	MM	0.2860	92.78983	5.40752	3.5409

138c (Table 3.2.2, **entry 7**, (*R*)-3,3'-dimethoxy-BINOL (**102l**)): enantioenriched, 1% ee



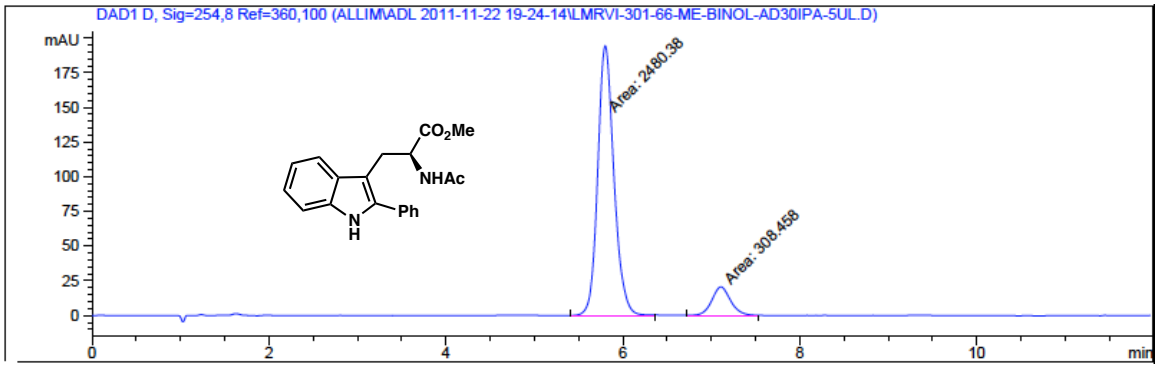
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.709	MM	0.2729	1065.04150	65.04519	50.5546
2	6.989	MM	0.3090	1041.67273	56.18153	49.4454

138c (Table 3.2.2, **entry 8**, (*R*)-6,6'-dimethoxy-BINOL (**102m**)): enantioenriched, 54% ee



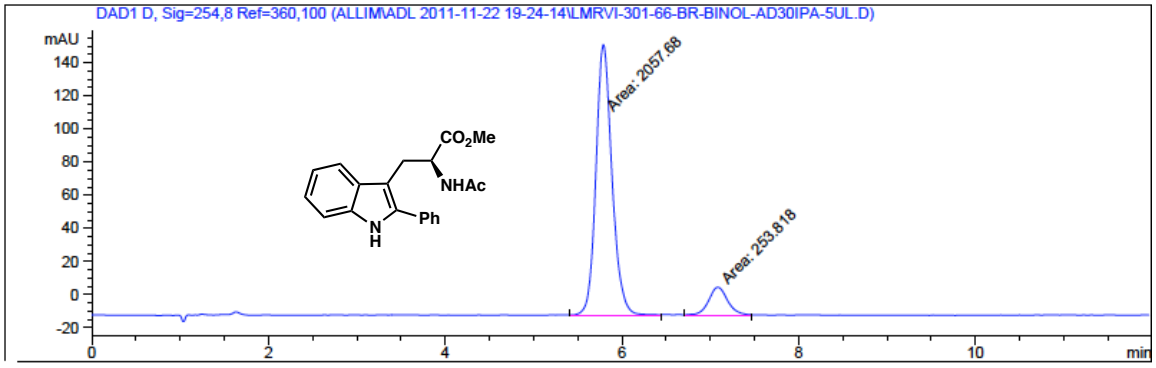
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.811	MM	0.2116	2736.53906	215.56961	77.2016
2	7.134	MM	0.2481	808.12903	54.27740	22.7984

138c (Table 3.2.2, **entry 9**, (*R*)-6,6'-dimethyl-BINOL (**102n**)): enantioenriched, 78% ee



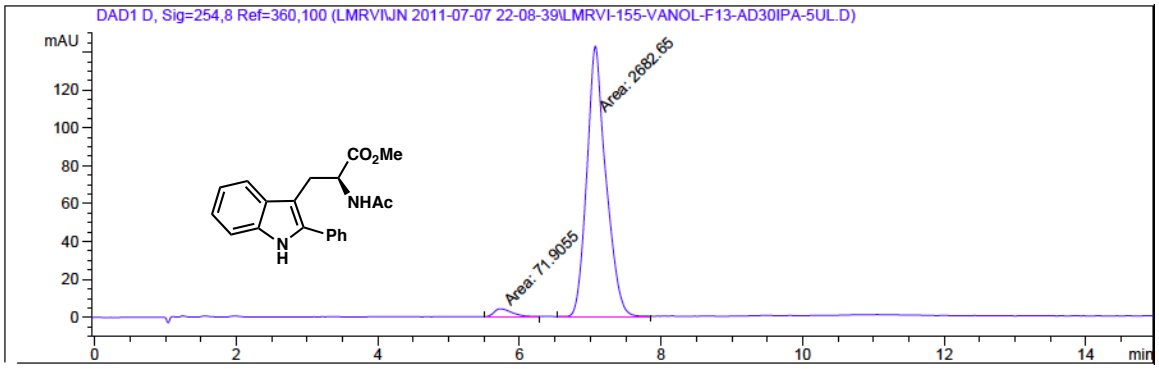
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.801	MM	0.2122	2480.38086	194.82515	88.9395
2	7.108	MM	0.2484	308.45816	20.69525	11.0605

138c (Table 3.2.2, **entry 10**, (*R*)-6,6'-dibromo-BINOL (**102f**)): enantioenriched, 78% ee



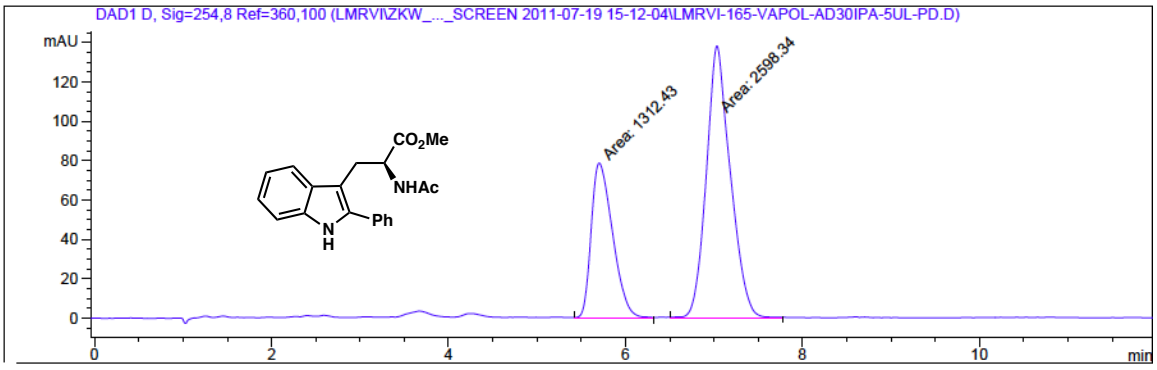
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.791	MM	0.2099	2057.68115	163.40929	89.0193
2	7.089	MM	0.2512	253.81812	16.83896	10.9807

138c (Table 3.2.2, **entry 11**, (*S*)-VANOL (**166**)): enantioenriched, –95% ee



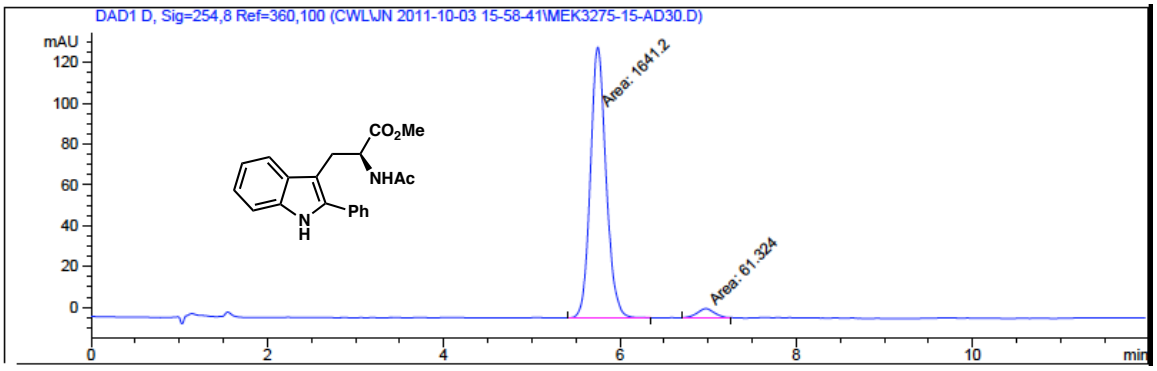
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.731	MM	0.2917	71.90548	4.10848	2.6104
2	7.071	MM	0.3130	2682.65479	142.86838	97.3896

138c (Table 3.2.2, **entry 12**, (*S*)-VAPOL (**167**)): enantioenriched, –33% ee



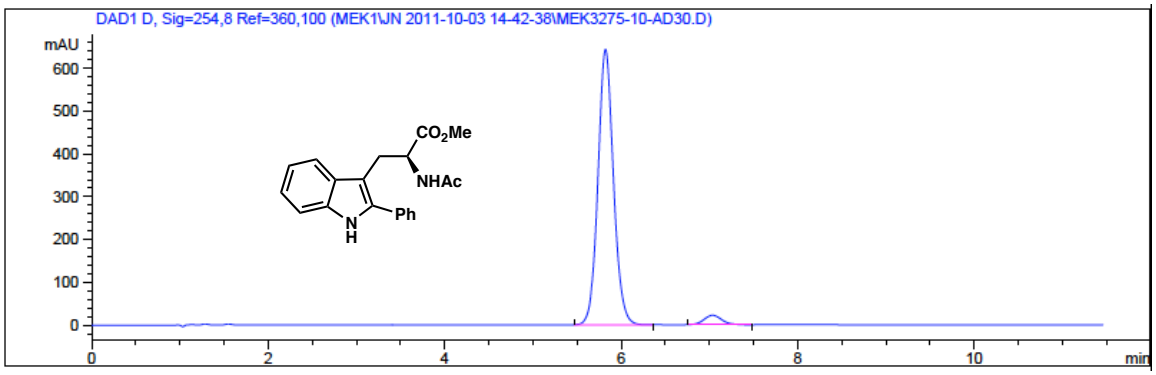
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.703	MM	0.2786	1312.42859	78.50554	33.5593
2	7.034	MM	0.3137	2598.34058	138.04201	66.4407

138c (Table 3.2.4, **entry 3**, 15 mol % **102k**): enantioenriched, 93% ee



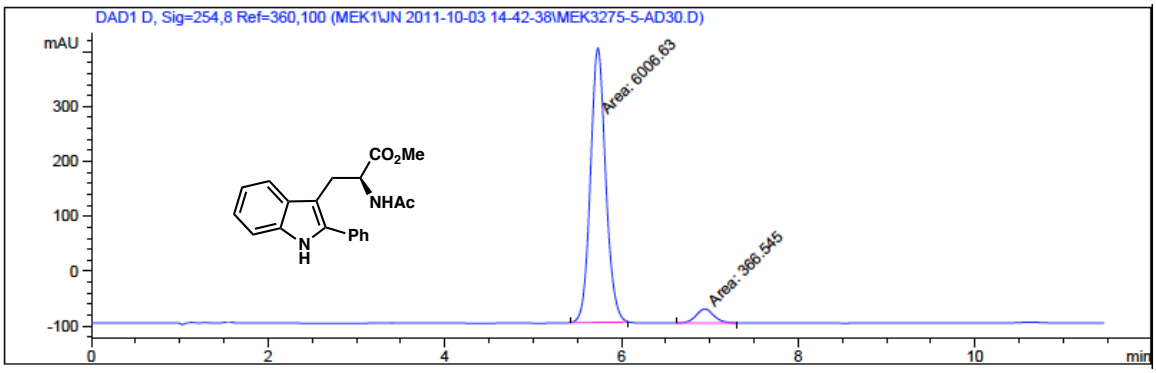
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.749	MM	0.2058	1641.20337	132.90843	96.3981
2	6.976	MM	0.2267	61.32397	4.50806	3.6019

138c (Table 3.2.4, **entry 4**, 10 mol % **102k**): enantioenriched, 92% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.823	BB	0.1872	7899.69922	643.65857	96.1676
2	7.036	BB	0.2153	314.81149	22.49169	3.8324

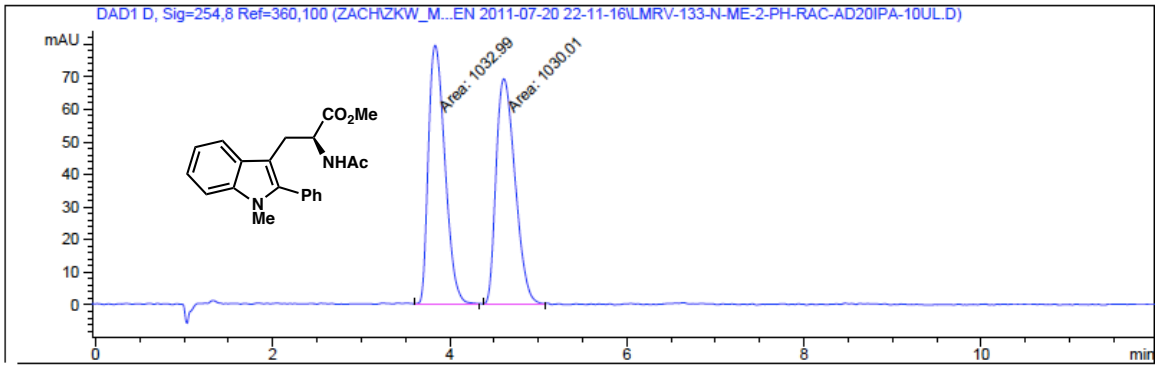
138c (Table 3.2.4, **entry 5**, 5 mol % **102k**): enantioenriched, 88% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.732	MM	0.1999	6006.63232	500.90204	94.2486
2	6.943	MM	0.2375	366.54471	25.72305	5.7514

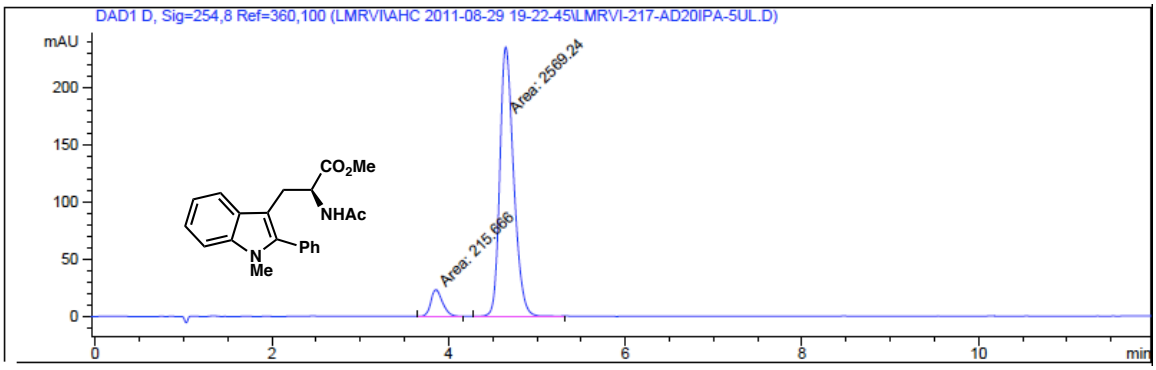
Substrate scope of the conjugate addition/asymmetric protonation

138e (Table 3.2.5, **entry 2**): racemic



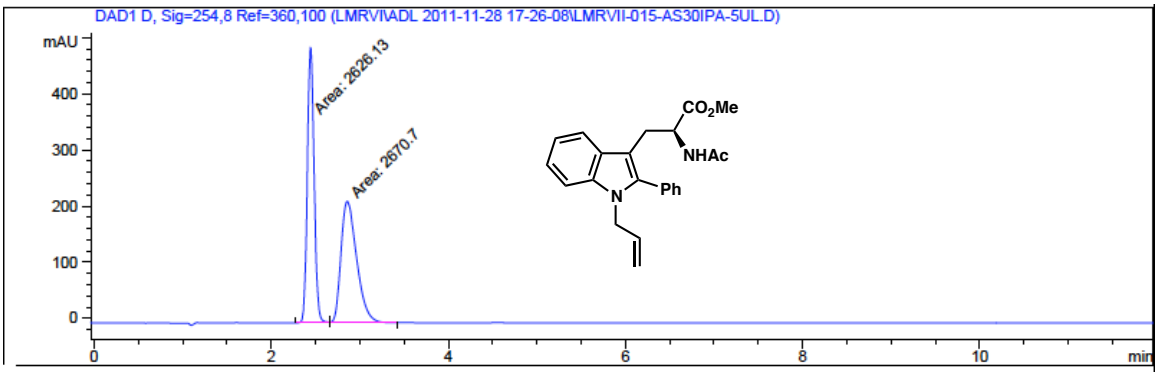
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.836	MM	0.2168	1032.99182	79.40057	50.0722
2	4.612	MM	0.2483	1030.01440	69.12988	49.9278

138e (Table 3.2.5, **entry 2**): enantioenriched, 85% ee



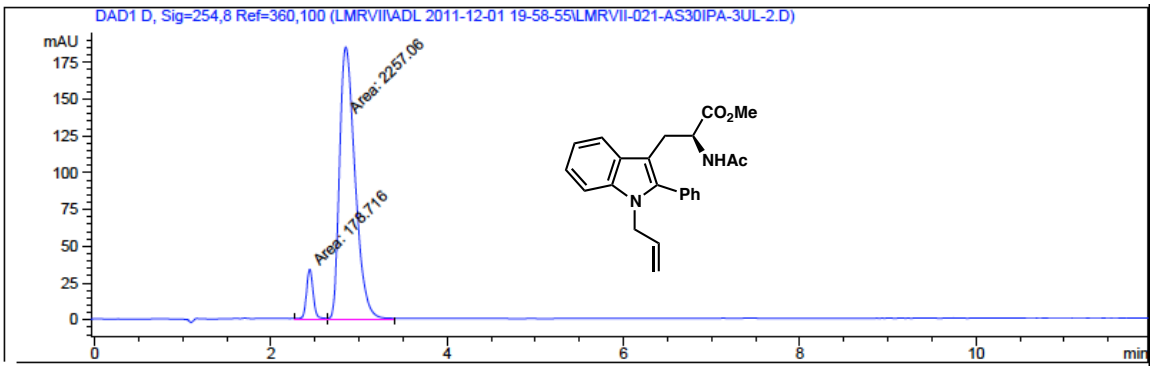
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.857	MM	0.1536	215.66585	23.40283	7.7441
2	4.648	MM	0.1816	2569.23853	235.83917	92.2559

138f (Table 3.2.5, **entry 3**): racemic



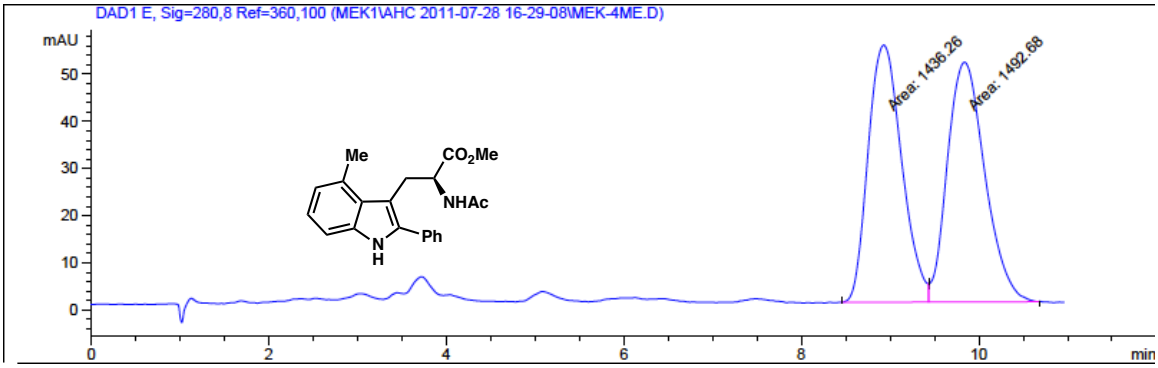
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.445	MM	0.0885	2626.12964	494.64706	49.5793
2	2.860	MM	0.2054	2670.69971	216.69223	50.4207

138f (Table 3.2.5, **entry 3**): enantioenriched, 85% ee



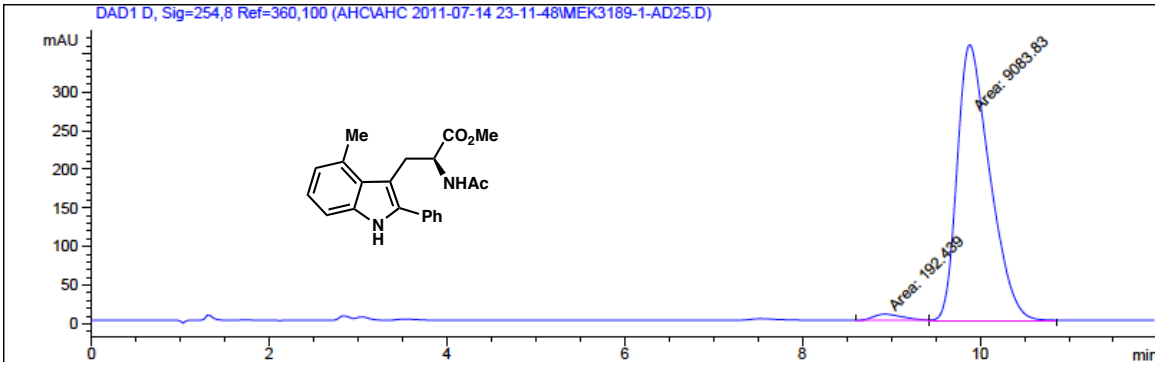
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.440	MM	0.0877	178.71585	33.96154	7.3371
2	2.850	MM	0.2033	2257.05518	185.04457	92.6629

138g (Table 3.2.5, **entry 4**): racemic



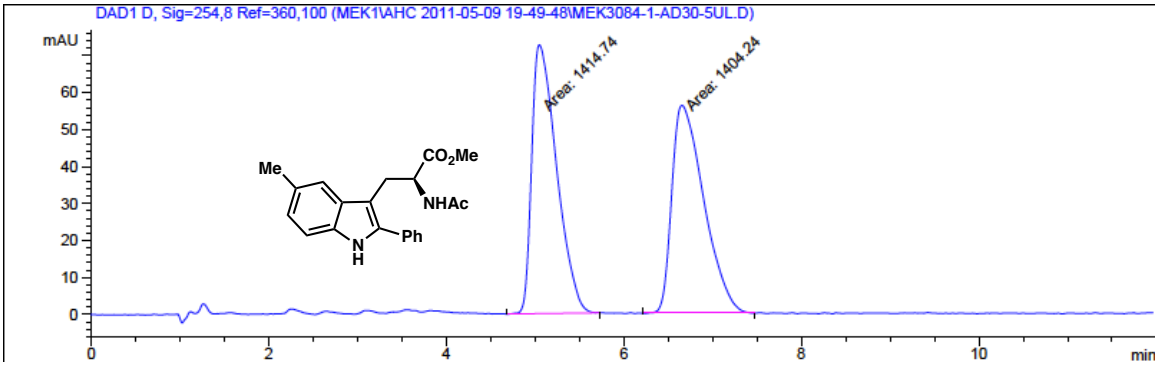
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.929	MF	0.4389	1436.26184	54.54070	49.0370
2	9.840	FM	0.4892	1492.67529	50.85297	50.9630

138g (Table 3.2.5, **entry 4**): enantioenriched, 96% ee



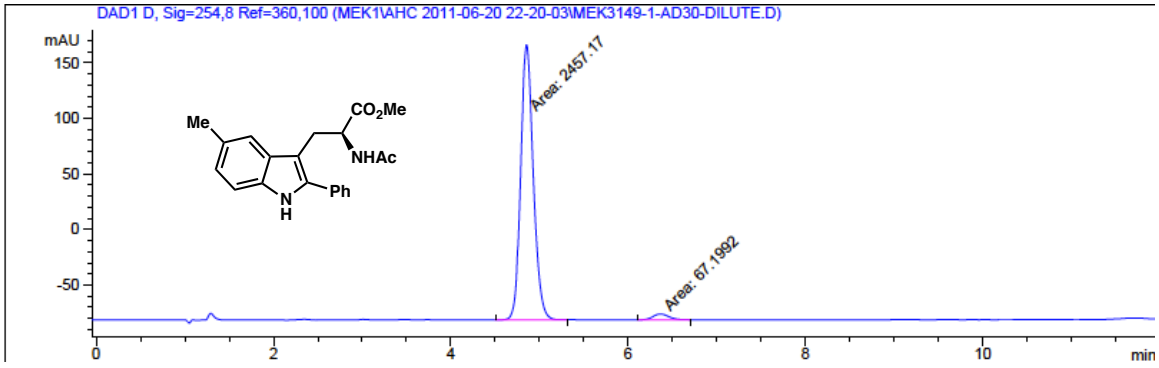
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.934	MF	0.3836	192.43893	8.36206	2.0745
2	9.884	FM	0.4243	9083.83105	356.81247	97.9255

138h (Table 3.2.5, **entry 5**): racemic



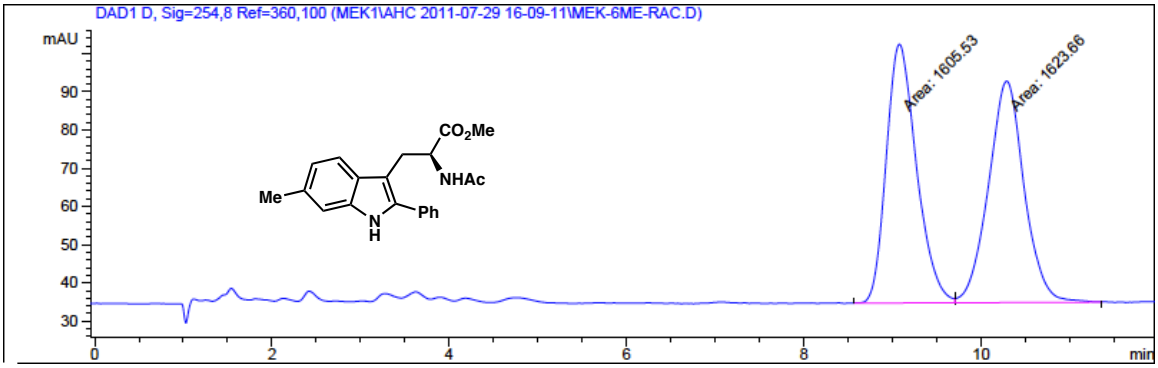
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.050	MM	0.3239	1414.74487	72.79134	50.1863
2	6.656	MM	0.4167	1404.24048	56.16964	49.8137

138h (Table 3.2.5, **entry 5**): enantioenriched, 95% ee



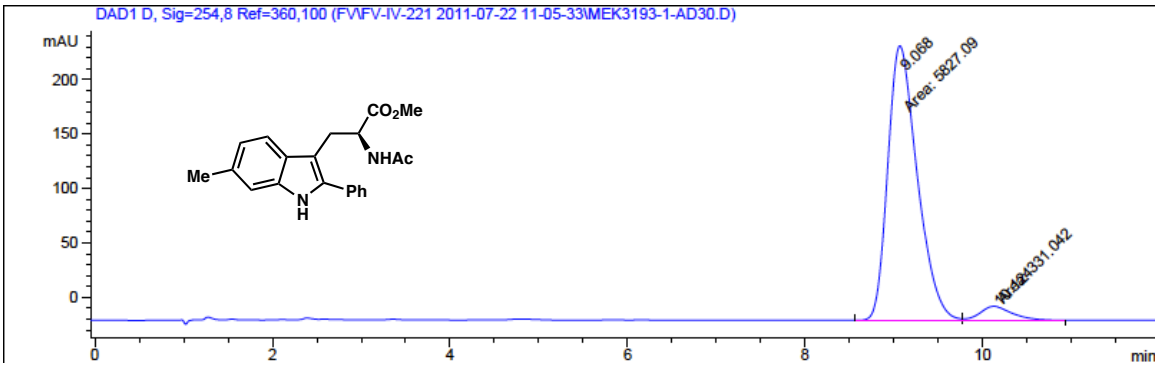
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.854	MM	0.1651	2457.17432	248.06091	97.3380
2	6.363	MM	0.2091	67.19923	5.35534	2.6620

138i (Table 3.2.5, **entry 6**): racemic



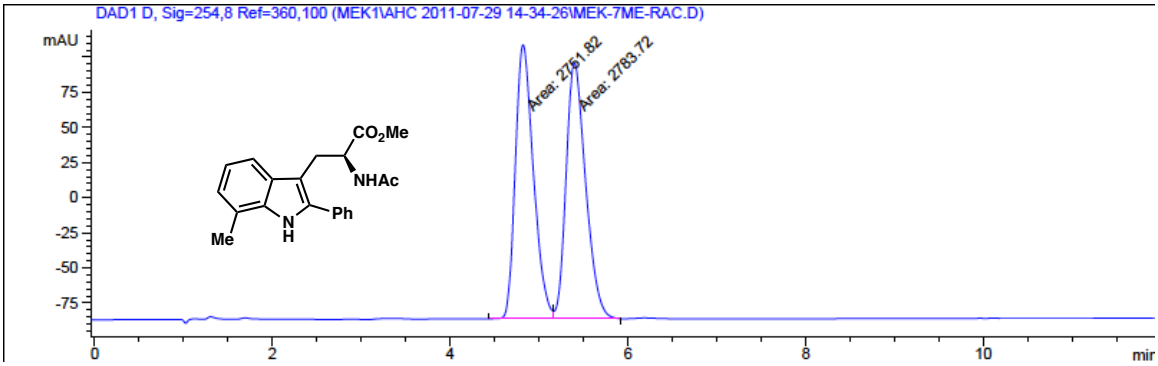
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.077	MF	0.3956	1605.53394	67.64597	49.7194
2	10.287	FM	0.4674	1623.65698	57.89628	50.2806

138i (Table 3.2.5, **entry 6**): enantioenriched, 89% ee



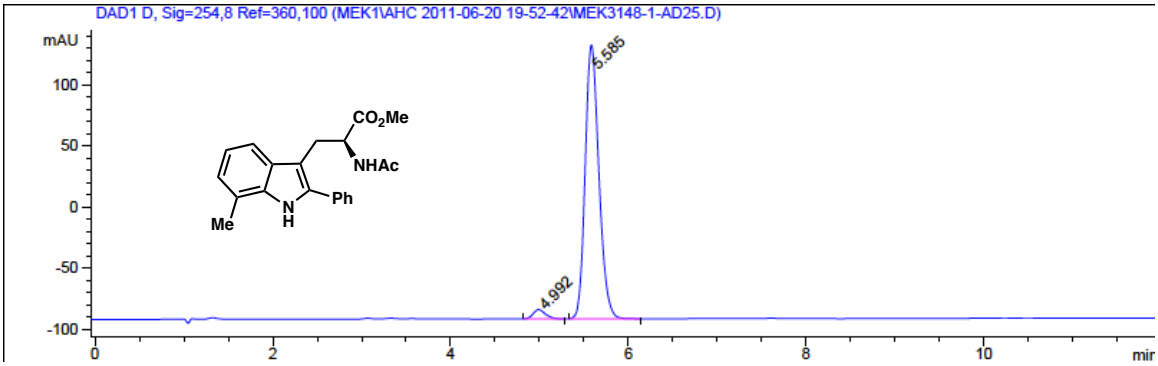
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.068	MF	0.3850	5827.08984	252.25751	94.6243
2	10.124	FM	0.4240	331.04230	13.01276	5.3757

138j (Table 3.2.5, **entry 7**): racemic



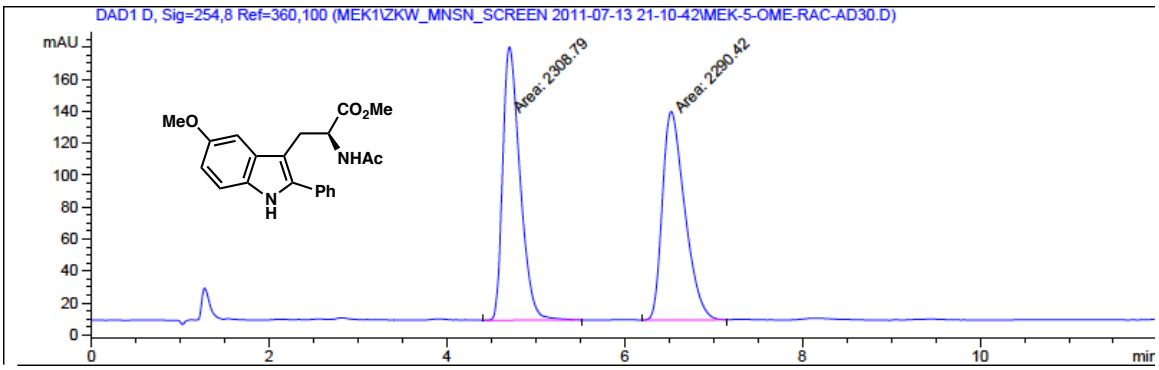
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.820	MF	0.2351	2751.81982	195.09174	49.7119
2	5.397	FM	0.2547	2783.71802	182.13214	50.2881

138j (Table 3.2.5, **entry 7**): enantioenriched, 94% ee



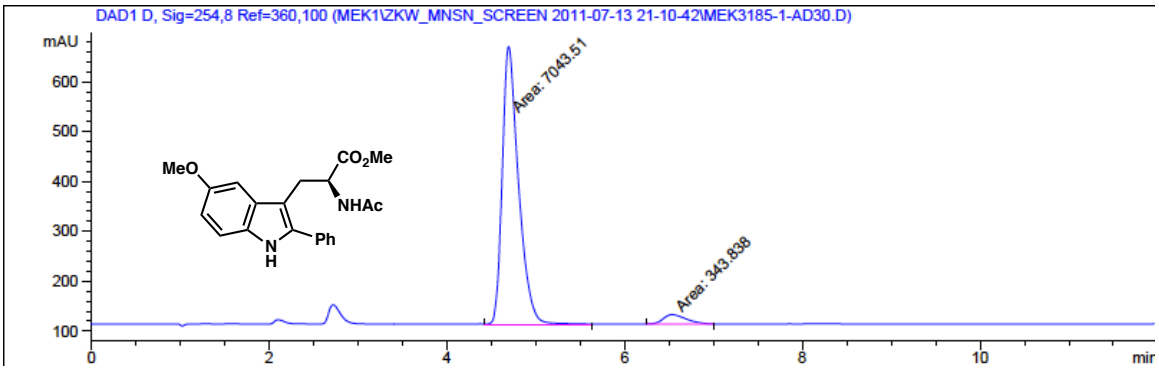
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.992	BB	0.1485	73.50820	7.62170	2.9637
2	5.585	BB	0.1651	2406.73779	224.39053	97.0363

138k (Table 3.2.5, **entry 8**): racemic



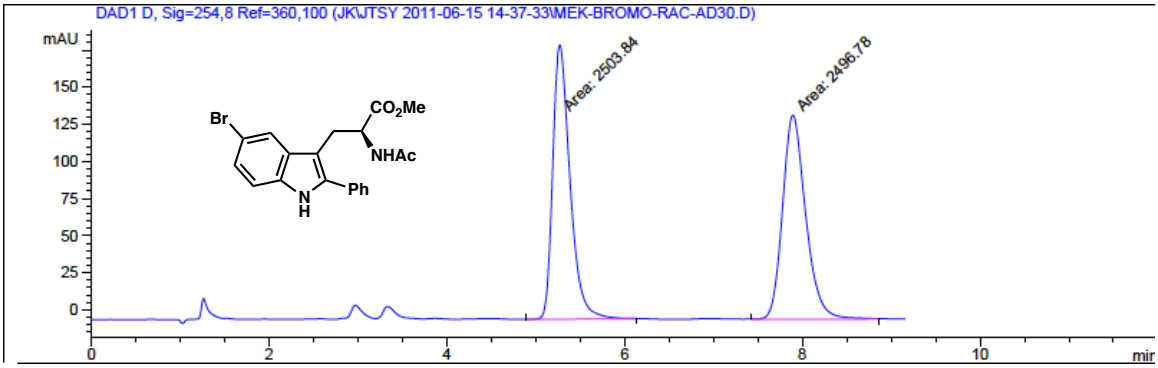
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.705	MM	0.2251	2308.79272	170.98026	50.1998
2	6.524	MM	0.2925	2290.41650	130.51103	49.8002

138k (Table 3.2.5, **entry 8**): enantioenriched, 91% ee



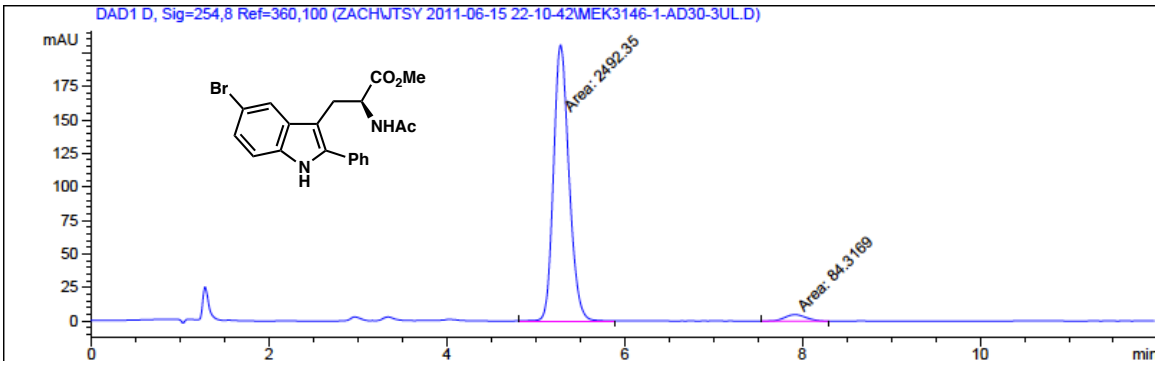
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.696	MM	0.2109	7043.50879	556.51990	95.3456
2	6.537	MM	0.3008	343.83807	19.05145	4.6544

138l (Table 3.2.5, **entry 9**): racemic



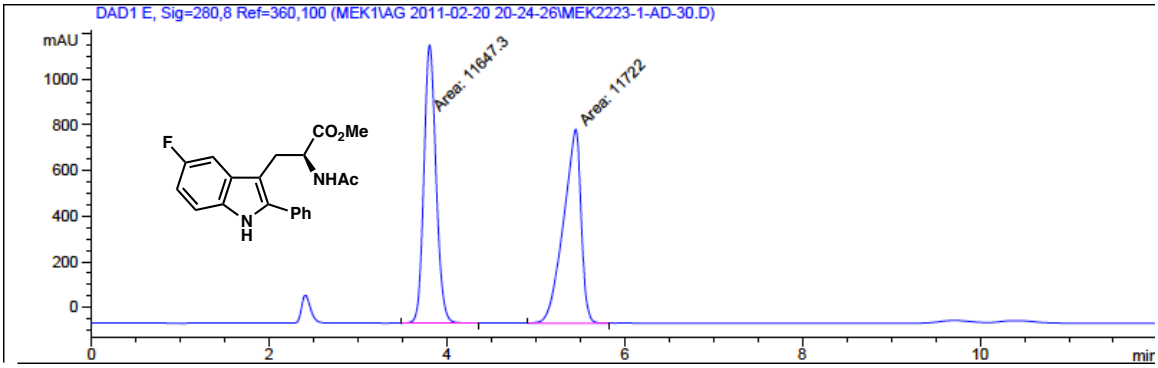
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.271	MM	0.2255	2503.83789	185.02051	50.0705
2	7.894	MM	0.3023	2496.78491	137.64893	49.9295

138l (Table 3.2.5, **entry 9**): enantioenriched, 93% ee



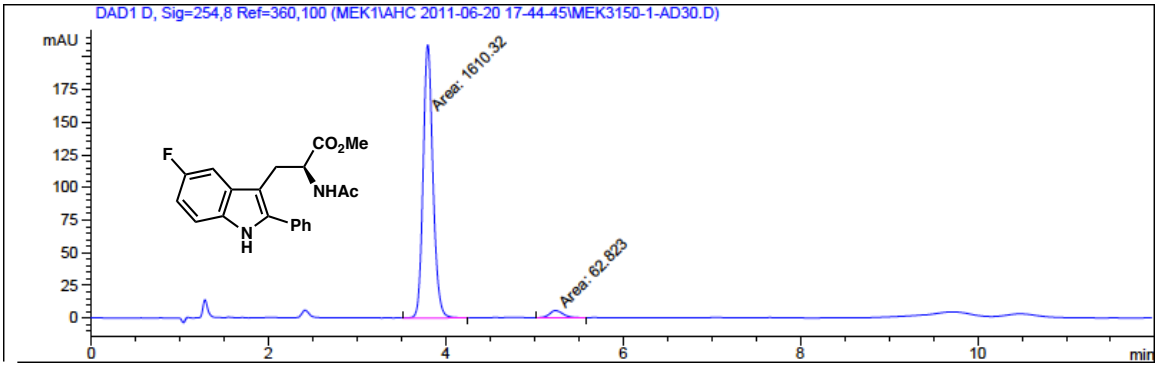
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.280	MM	0.2015	2492.35010	206.16266	96.7277
2	7.908	MM	0.2847	84.31690	4.93608	3.2723

138m (Table 3.2.5, **entry 10**): racemic



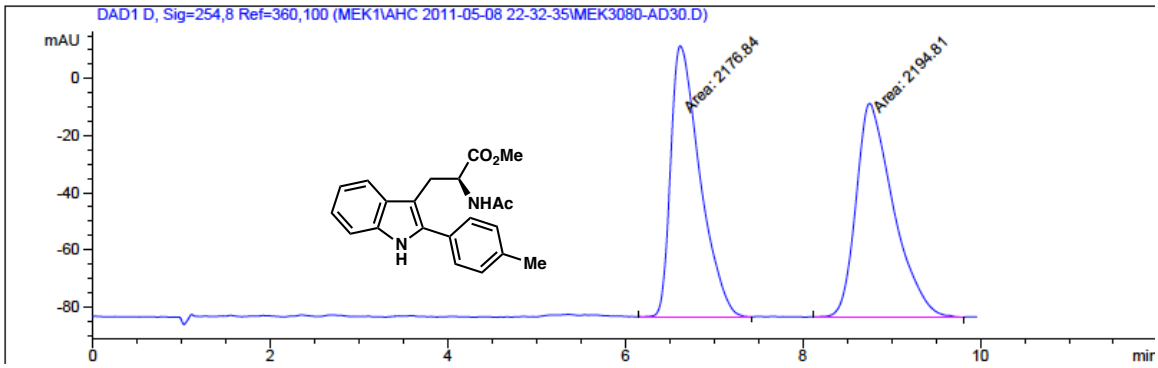
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.808	MM	0.1587	1.16473e4	1223.43835	49.8401
2	5.451	MM	0.2288	1.17220e4	853.89844	50.1599

138m (Table 3.2.5, **entry 10**): enantioenriched, 92% ee



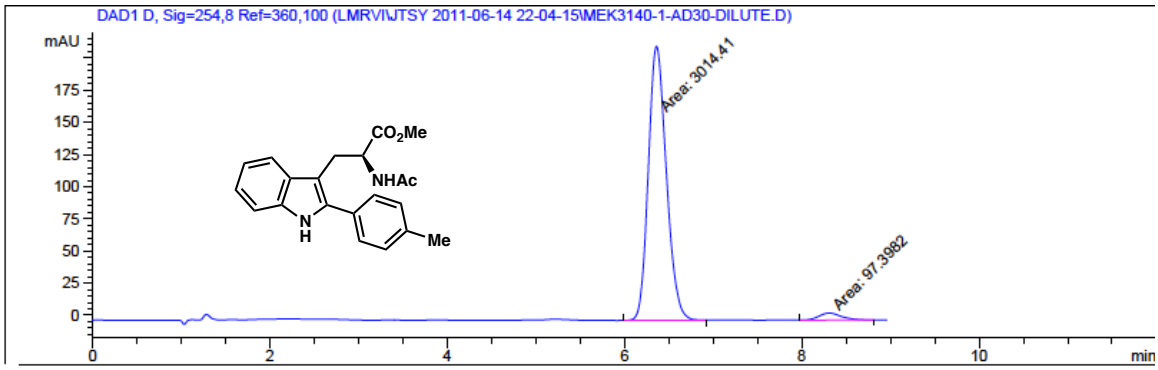
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.798	MM	0.1277	1610.32483	210.17332	96.2452
2	5.237	MM	0.1839	62.82299	5.69236	3.7548

138n (Table 3.2.5, **entry 11**): racemic



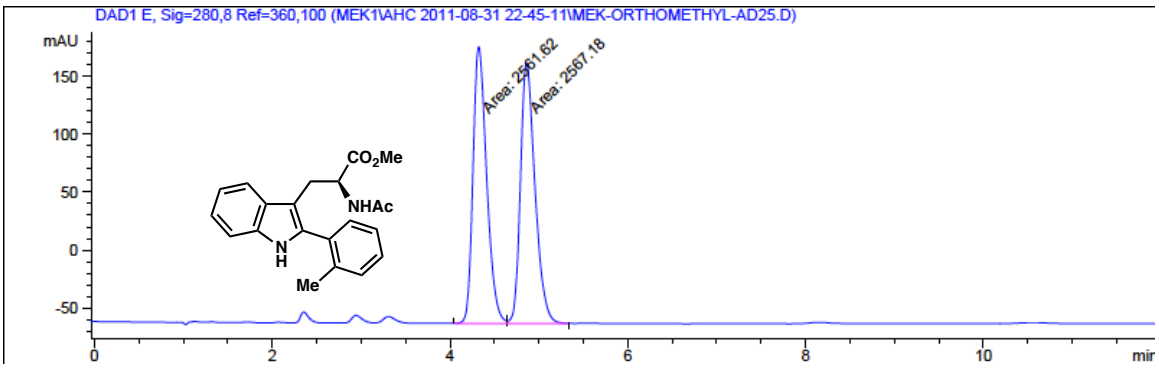
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.621	MM	0.3814	2176.84033	95.11774	49.7945
2	8.753	MM	0.4879	2194.80835	74.98085	50.2055

138n (Table 3.2.5, **entry 11**): enantioenriched, 94% ee



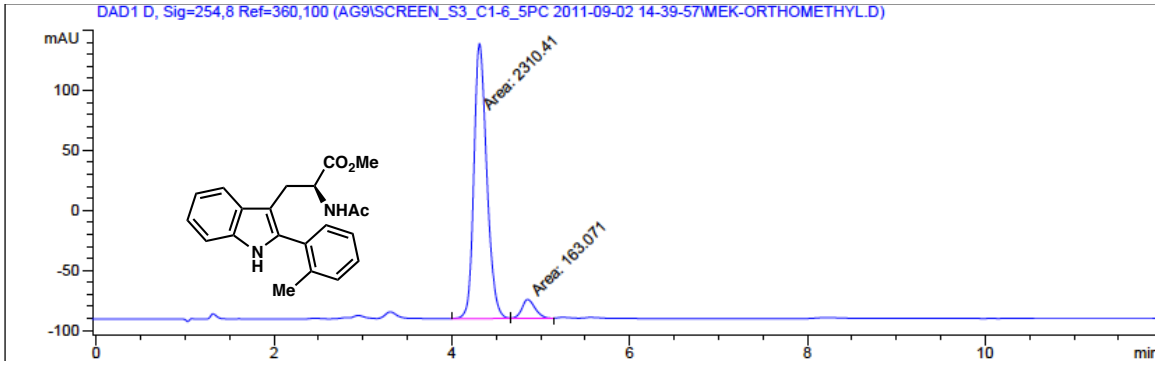
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.362	MM	0.2356	3014.40527	213.28644	96.8700
2	8.308	MM	0.2940	97.39824	5.52150	3.1300

138o (Table 3.2.5**, entry 12)**: racemic



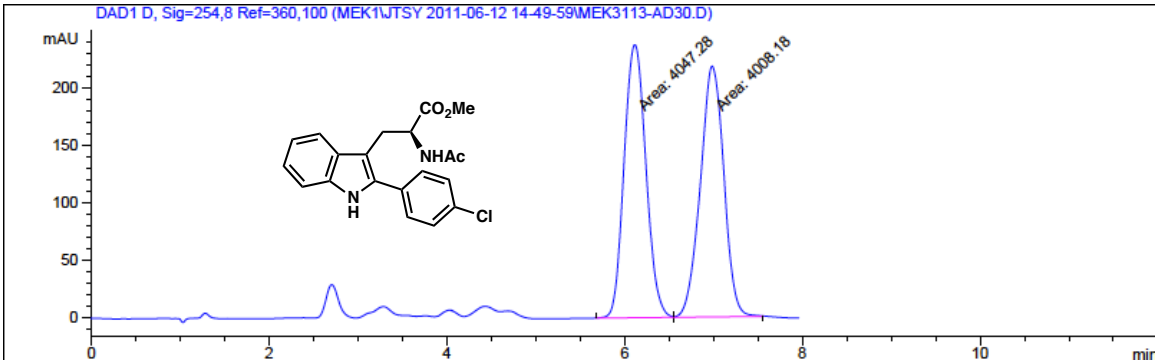
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.324	MF	0.1781	2561.61523	239.71214	49.9458
2	4.862	FM	0.1897	2567.17676	225.56844	50.0542

138o (Table 3.2.5, **entry 12**): enantioenriched, 87% ee



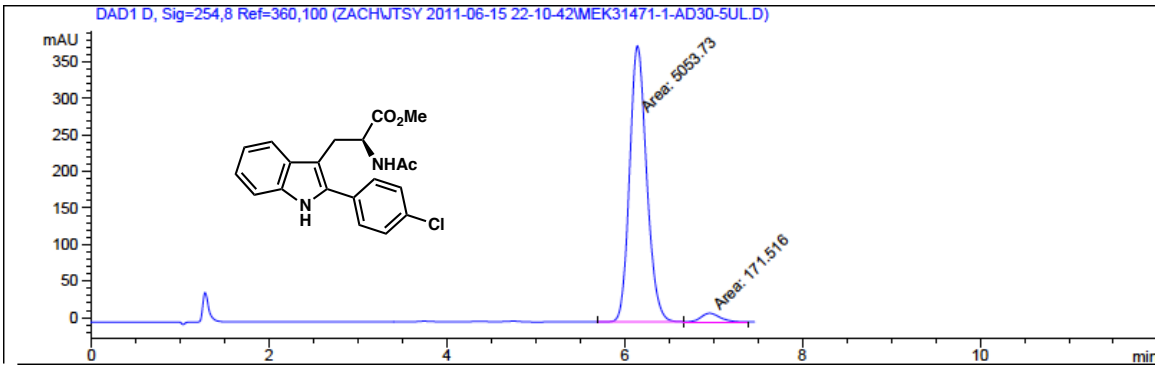
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.312	MF	0.1680	2310.40869	229.23323	93.4072
2	4.854	FM	0.1724	163.07098	15.76543	6.5928

138p (Table 3.2.5, **entry 13**): racemic



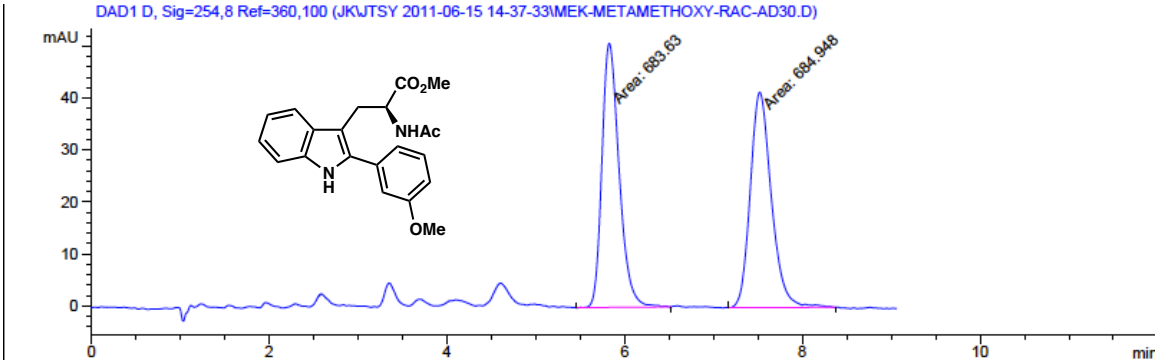
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.115	MF	0.2839	4047.27661	237.58223	50.2427
2	6.986	FM	0.3061	4008.18091	218.21001	49.7573

138p (Table 3.2.5, **entry 13**): enantioenriched, 93% ee



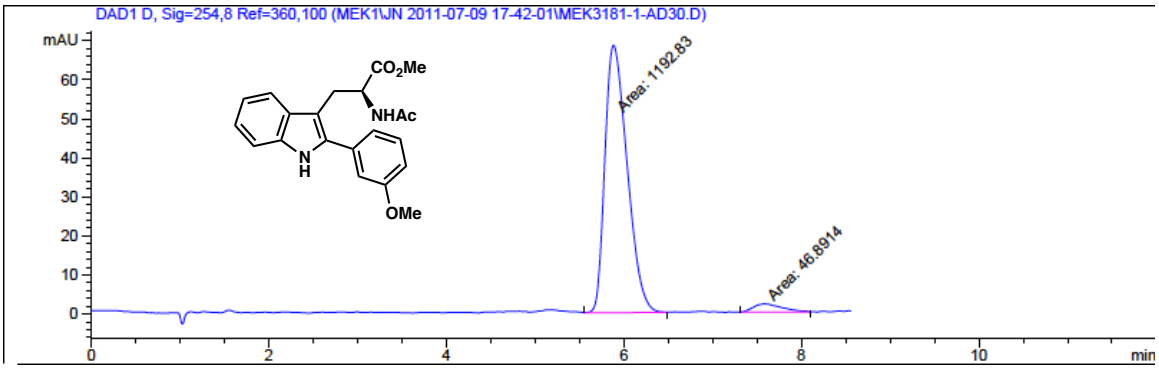
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.146	MF	0.2229	5053.73291	377.91241	96.7176
2	6.960	FM	0.2433	171.51614	11.74924	3.2824

138q (Table 3.2.5, **entry 14**): racemic



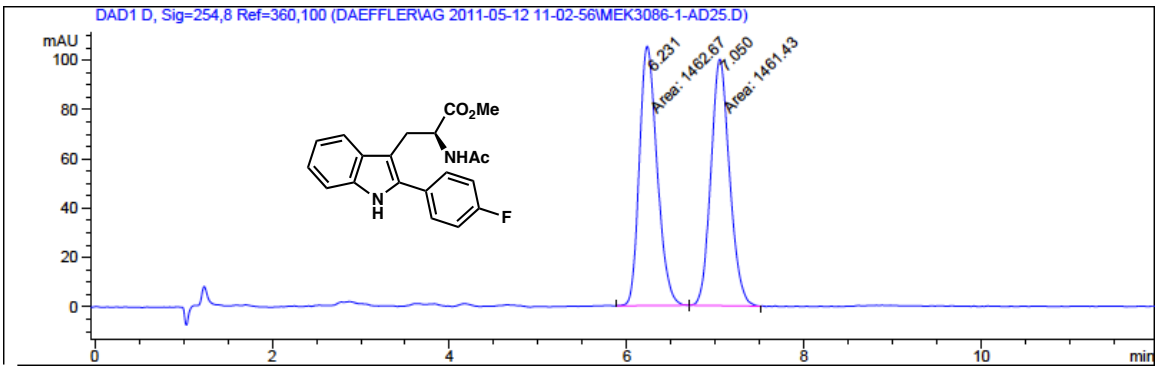
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.829	MM	0.2242	683.62952	50.82516	49.9518
2	7.521	MM	0.2756	684.94781	41.42142	50.0482

138q (Table 3.2.5, **entry 14**): enantioenriched, 92% ee



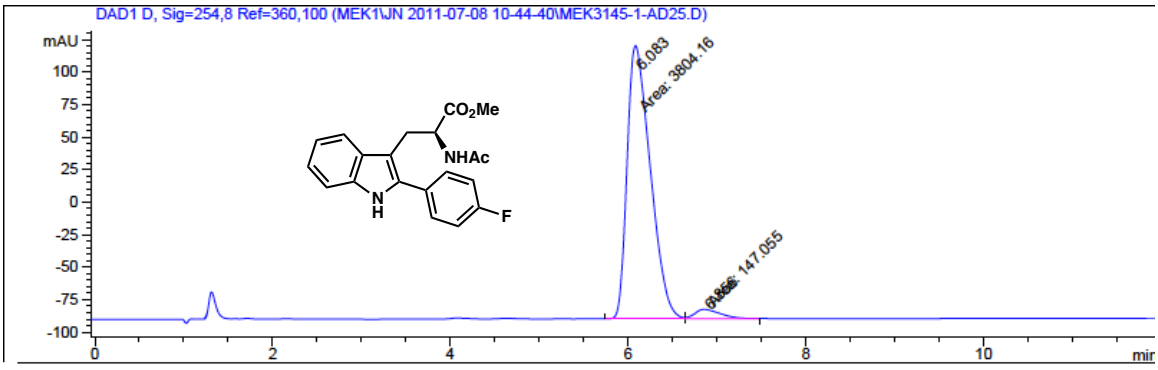
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.885	MM	0.2902	1192.82666	68.51757	96.2176
2	7.580	MM	0.3706	46.89137	2.10879	3.7824

138r (Table 3.2.5, **entry 15**): racemic



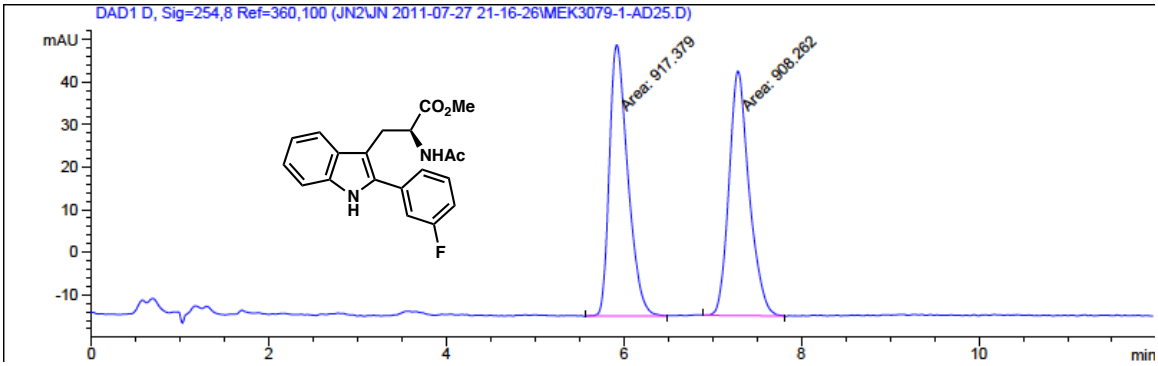
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.231	MM	0.2319	1462.67285	105.12125	50.0213
2	7.050	MM	0.2437	1461.42761	99.94221	49.9787

138r (Table 3.2.5, **entry 15**): enantioenriched, 93% ee



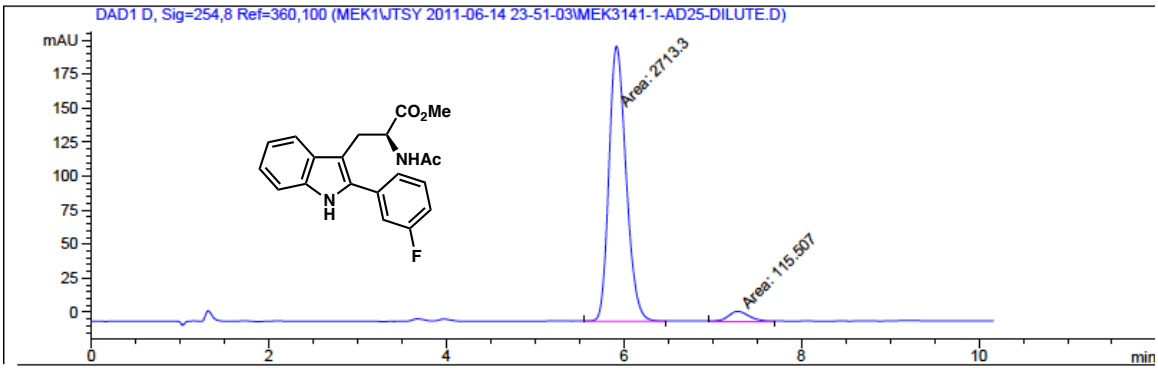
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.083	MF	0.3018	3804.16431	210.09053	96.2782
2	6.856	FM	0.3379	147.05510	7.25396	3.7218

138s (Table 3.2.5**, entry 16)**: racemic



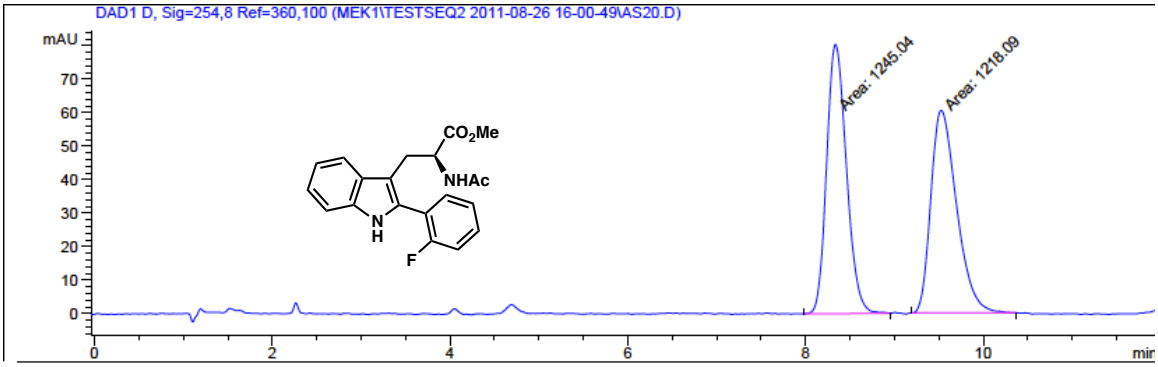
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.921	MM	0.2396	917.37872	63.80575	50.2497
2	7.287	MM	0.2632	908.26233	57.51292	49.7503

138s (Table 3.2.5, **entry 16**): enantioenriched, 92% ee



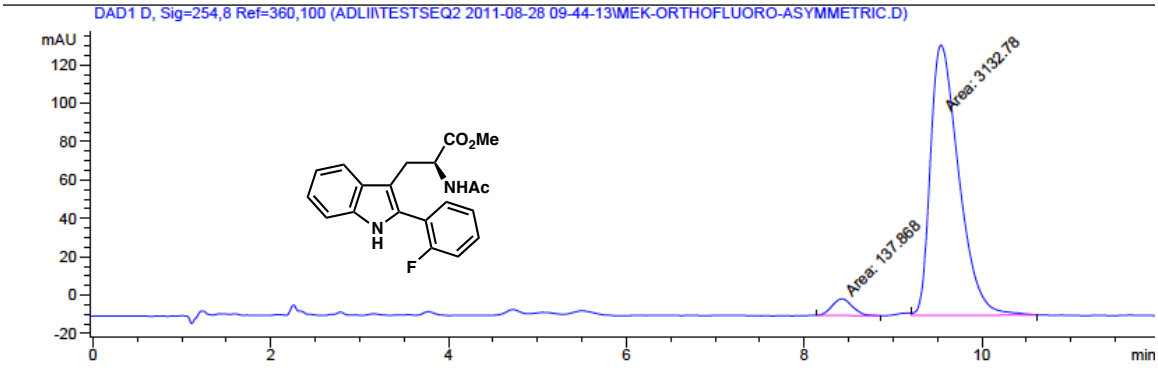
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.919	MM	0.2233	2713.30493	202.51631	95.9167
2	7.288	MM	0.2660	115.50748	7.23739	4.0833

138t (Table 3.2.5, **entry 17**): racemic



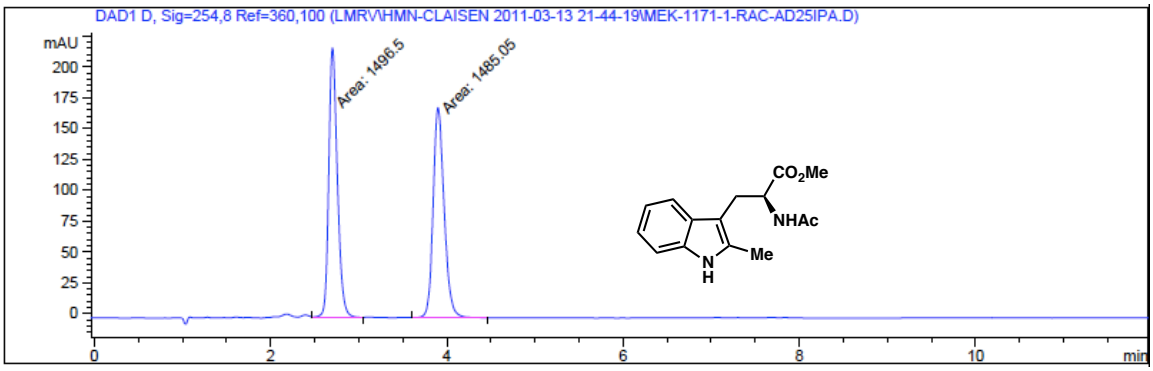
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.337	MM	0.2581	1245.03833	80.40385	50.5471
2	9.527	MM	0.3356	1218.08643	60.50121	49.4529

138t (Table 3.2.5, **entry 17**): enantioenriched, 92% ee



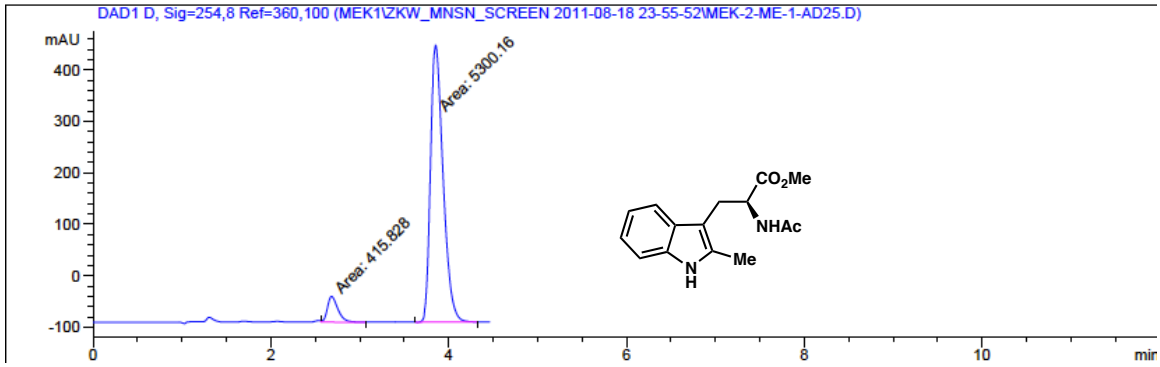
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.424	MM	0.2645	137.86769	8.68627	4.2153
2	9.540	MM	0.3705	3132.78320	140.94464	95.7847

138d (Table 3.2.5, **entry 18**): racemic



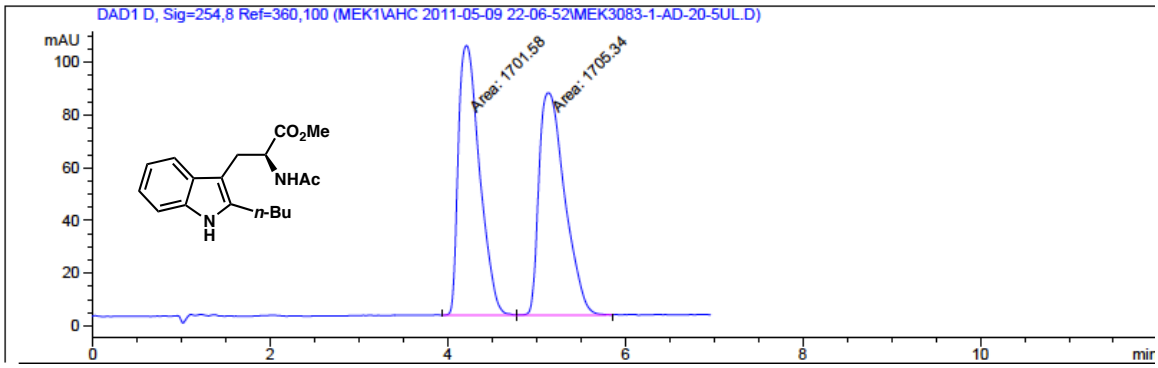
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.704	MM	0.1135	1496.50342	219.75923	50.1920
2	3.902	MM	0.1449	1485.05188	170.80902	49.8080

138d (Table 3.2.5, **entry 18**): enantioenriched, 85% ee



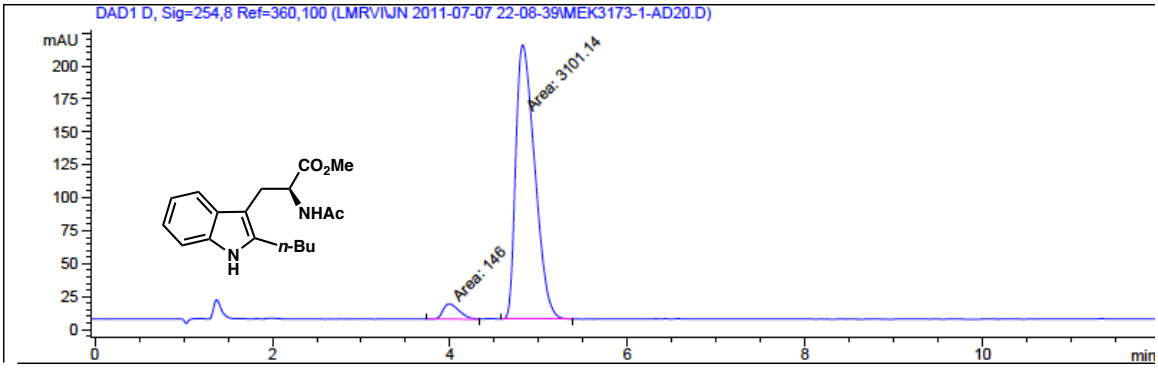
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.683	MM	0.1386	415.82819	49.99455	7.2748
2	3.853	MM	0.1639	5300.16357	538.95465	92.7252

138u (Table 3.2.5, **entry 19**): racemic



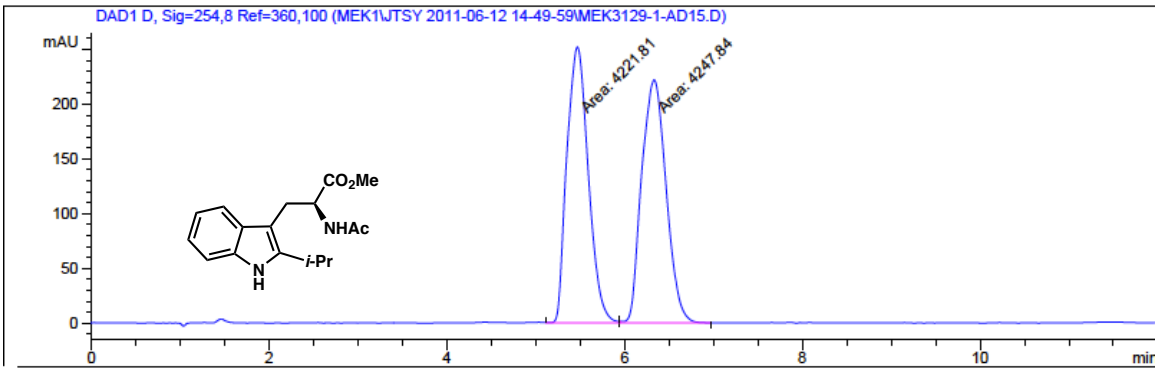
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.212	MM	0.2768	1700.02417	102.35526	50.0010
2	5.137	MM	0.3361	1699.95459	84.29318	49.9990

138u (Table 3.2.5, **entry 19**): enantioenriched, 91% ee



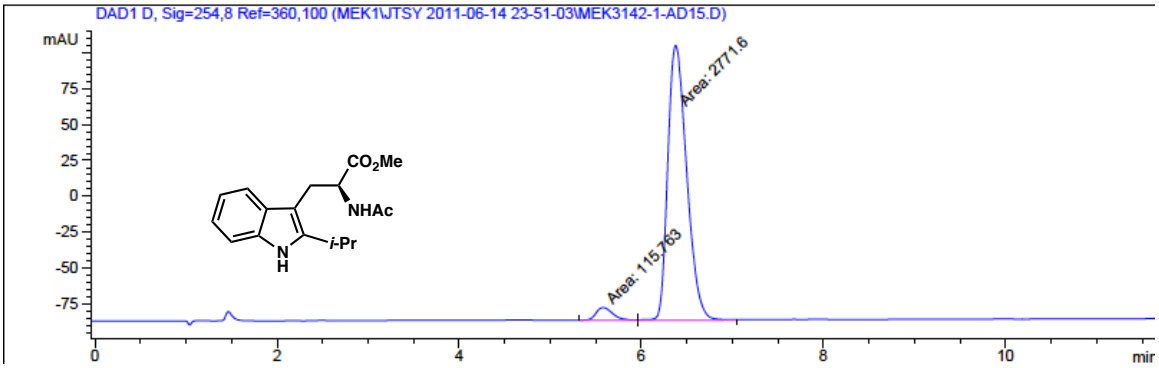
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.989	MM	0.2108	145.99951	11.54476	4.4962
2	4.820	MM	0.2481	3101.14380	208.34941	95.5038

138v (Table 3.2.5, **entry 20**): racemic



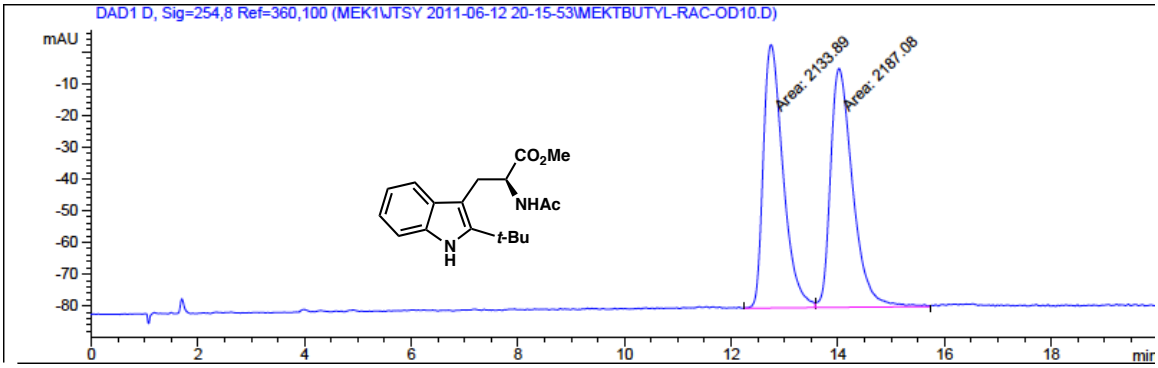
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.470	MF	0.2791	4221.81055	252.11853	49.8463
2	6.333	FM	0.3188	4247.84424	222.08144	50.1537

138v (Table 3.2.5, **entry 20**): enantioenriched, 92% ee



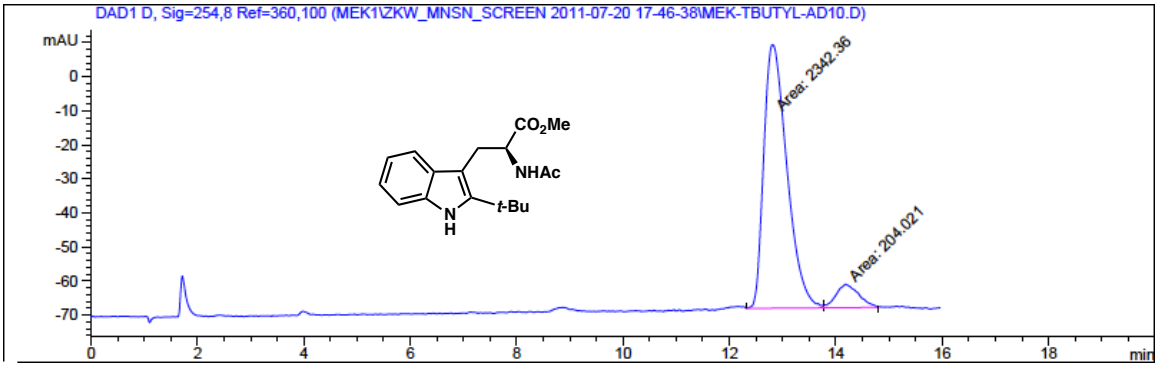
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.579	MF	0.2157	115.76347	8.94554	4.0093
2	6.378	FM	0.2407	2771.60327	191.88481	95.9907

138w (Table 3.2.5, **entry 21**): racemic



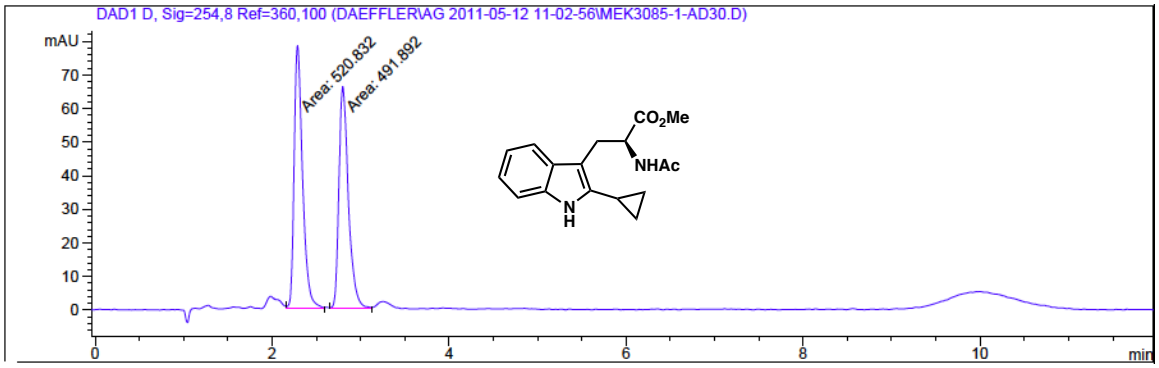
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.747	MF	0.4289	2133.88867	82.91142	49.3845
2	14.022	FM	0.4846	2187.08203	75.22533	50.6155

138w (Table 3.2.5, **entry 21**): enantioenriched, 84% ee



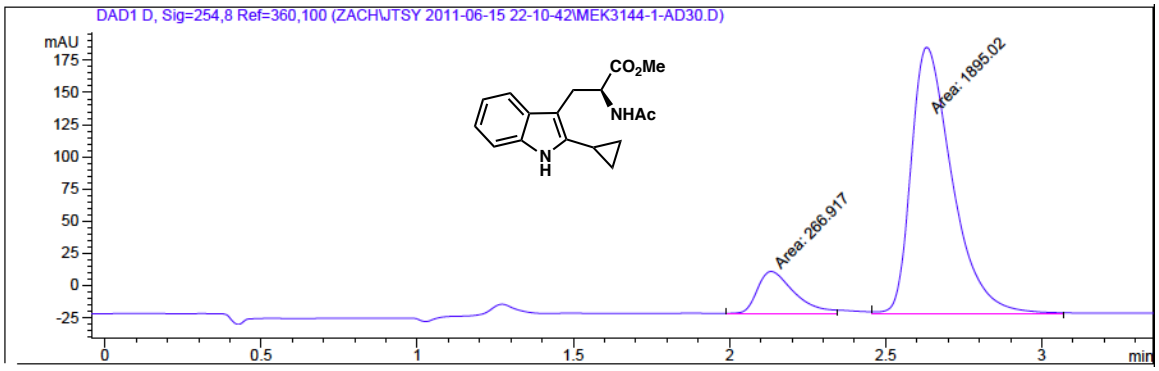
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.811	MF	0.5042	2342.36499	77.42957	91.9878
2	14.185	FM	0.4960	204.02127	6.85510	8.0122

138x (Table 3.2.5, **entry 22**): racemic



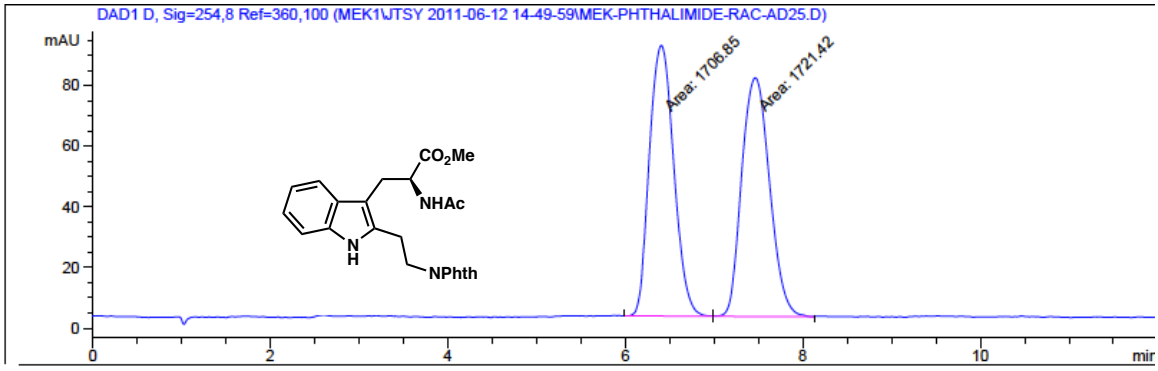
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.287	MM	0.1108	520.83179	78.37215	51.4288
2	2.799	MM	0.1237	491.89221	66.25817	48.5712

138x (Table 3.2.5, **entry 22**): enantioenriched, 75% ee



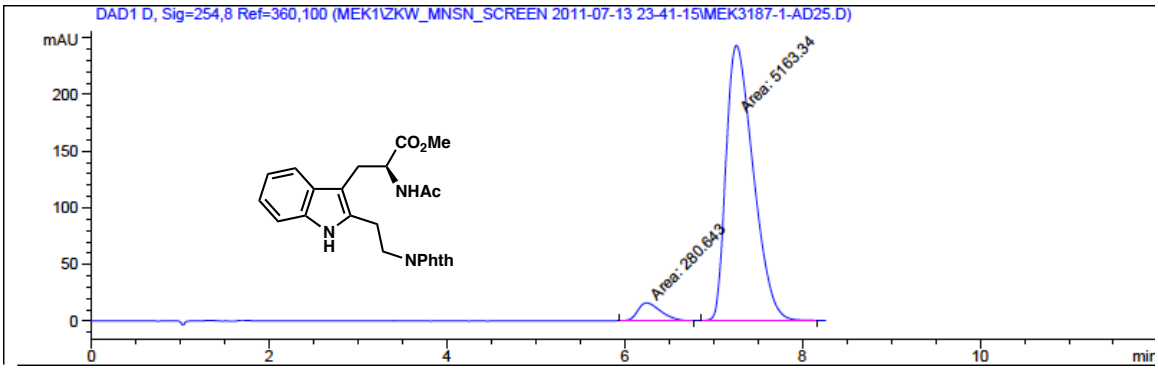
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.133	MM	0.1362	266.91724	32.65373	12.3462
2	2.632	MM	0.1524	1895.02393	207.30278	87.6538

138y (Table 3.2.5, **entry 23**): racemic



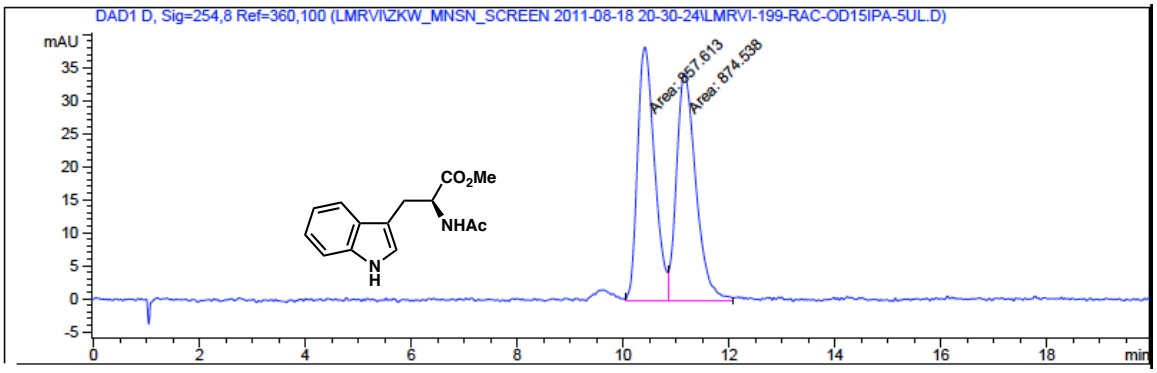
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.408	MF	0.3187	1706.84790	89.26434	49.7874
2	7.465	FM	0.3642	1721.42261	78.76897	50.2126

138y (Table 3.2.5, **entry 23**): enantioenriched, 90% ee



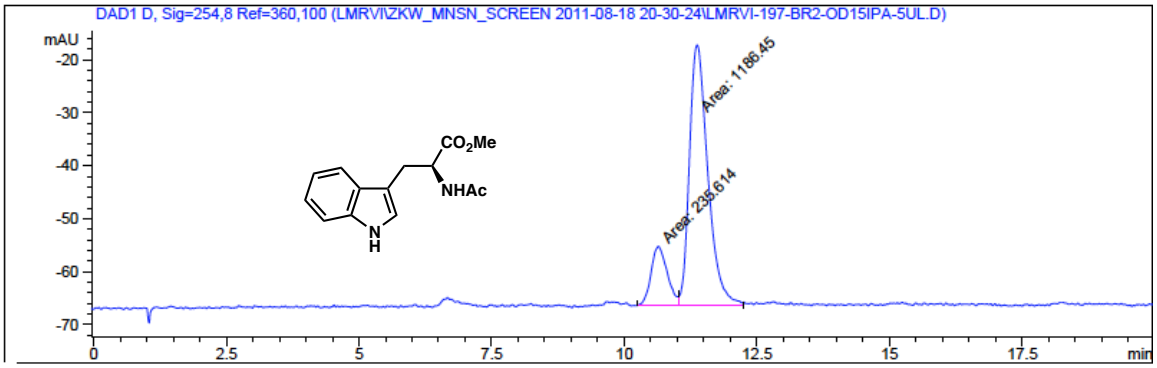
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.251	MM	0.2975	280.64285	15.72261	5.1551
2	7.260	MM	0.3544	5163.33643	242.81979	94.8449

138z (Scheme 3.2.3): racemic



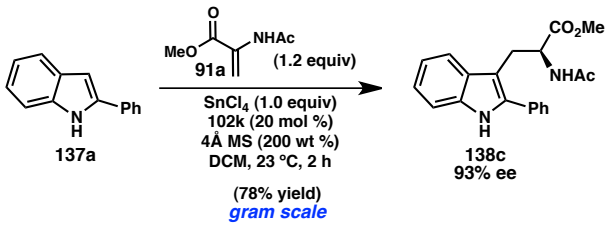
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.415	MM	0.3727	857.61285	38.35357	49.5114
2	11.162	MM	0.4245	874.53839	34.33775	50.4886

138z (Scheme 3.2.3): enantioenriched, 67% ee

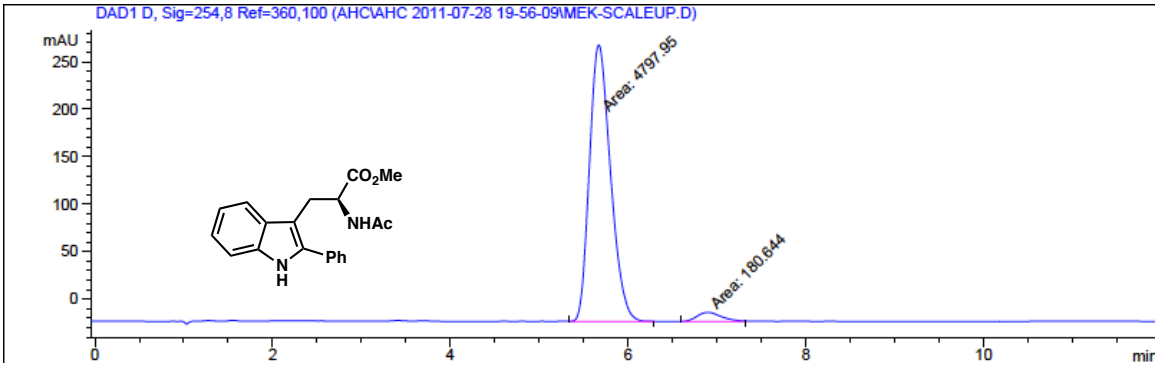


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.642	MM	0.3525	235.61412	11.14041	16.5685
2	11.371	MM	0.4028	1186.44934	49.09745	83.4315

3.4.6 Scale-up Procedure

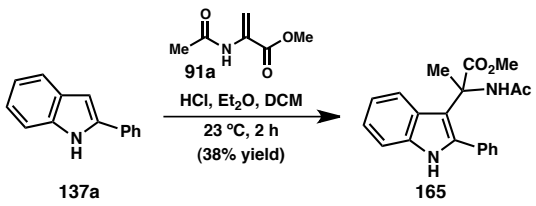


To a flame-dried flask under nitrogen containing freshly activated powdered 4Å molecular sieves (200 wt %) was added 2-phenylindole (**137a**, 1.00 g, 5.20 mmol, 1.00 equiv), methyl 2-acetamidoacrylate (**91a**, 890 mg, 6.20 mmol, 1.20 equiv), and (*R*)-3,3'-dibromo-BINOL (**102k**, 457 mg, 1.00 mmol, 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 **138c** 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

3.4.7 Preparation of Methyl 2-acetamido-2-(2-phenyl-1H-indol-3-yl)propanoate (165)

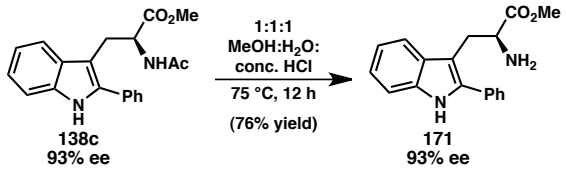


To a flame-dried flask charged with 2-phenylindole (**137a**, 38.6 mg, 0.200 mmol, 1.00 equiv) and methyl 2-acetamidoacrylate (**91a**, 34.3 mg, 0.240 mmol, 1.20 equiv) was added 1.5 mL DCM, followed by HCl dropwise (2 M in Et_2O, 100 µL, 0.200 mmol, 1.00 equiv). After stirring in the dark 2 hours at room temperature, the dark yellow reaction solution was diluted with 10 mL EtOAc and quenched with 10 mL saturated aqueous $NaHCO_3$. The aqueous layer was extracted with 10 mL EtOAc and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude oil was purified by silica gel column chromatography (gradient, 0:100 to 100:0 EtOAc:hexanes) to yield 25.8 mg (38% yield) of methyl 2-acetamido-2-(2-phenyl-1*H*-indol-3-yl)propanoate (**165**) as a pale yellow foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (br s, 1H), 7.79 (d, *J* = 8.0 Hz,

1H), 7.56 – 7.48 (m, 2H), 7.45 – 7.37 (m, 3H), 7.30 (ddd, *J* = 8.1, 0.9, 0.9 Hz, 1H), 7.20 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.15 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 6.70 (br s, 1H), 3.48 (s, 3H), 1.96 (s, 3H), 1.70 (s, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 168.8, 135.5, 135.4, 133.5, 130.6, 128.7, 128.0, 126.1, 122.2, 120.5, 120.1, 111.4, 111.1, 59.8, 52.7, 24.4, 23.3.; FTIR (NaCl/thin film): 3271, 3054, 2948, 1734, 1663, 1507, 1489, 1458, 1445, 1432, 1370, 1295, 1253, 1126 cm^{-1}; HRMS (MM) calc'd for $C_{20}H_{21}N_2O_3$ $[M+H]^+$ 337.1547, found 337.1545.

3.4.8 Functionalization of Tryptophan 138c

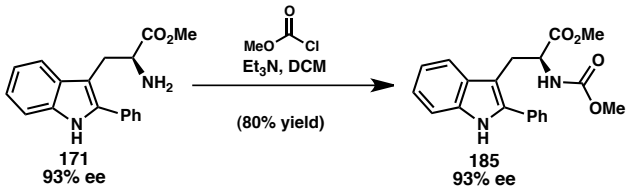
3.4.8.1 Acetamide Hydrolysis[44]



A vial was charged with (*S*)-*N*α-acetyl-2-phenyltryptophan methyl ester (**138c**, 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 DCM:MeOH) to yield 20.0 mg (76% yield) of **171** as a light yellow oil. The enantiomeric excess was determined by chiral SFC analysis of the corresponding methylcarbamate **185** (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.

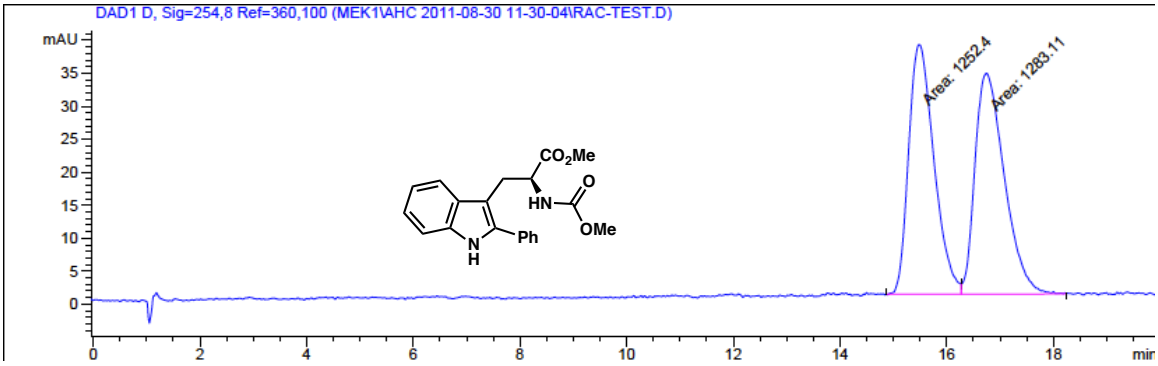
Methylcarbamate Protection



A flame-dried flask was charged with free amine **171** (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 **185** 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. ^1H 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

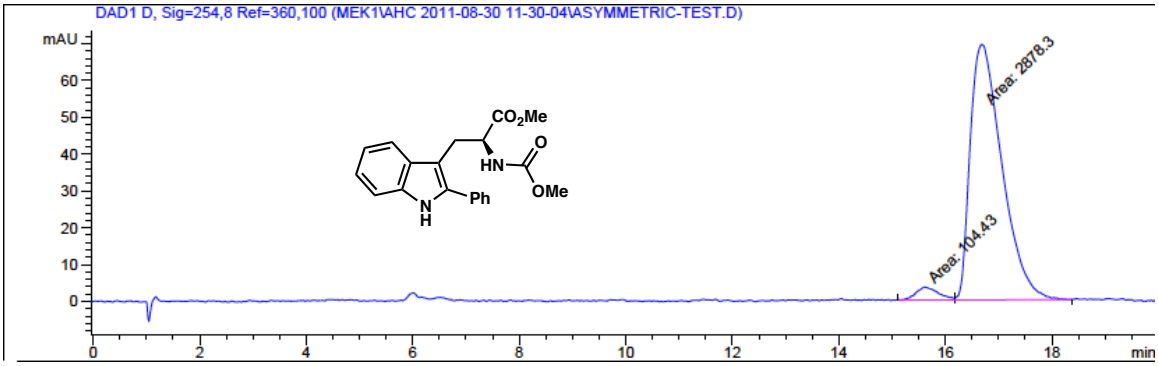
= 7.7 Hz, 1H), 4.63 – 4.59 (m, 1H), 3.54 (s, 3H), 3.50 (m, 2H), 3.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 156.1, 136.2, 135.7, 132.9, 129.2, 129.0, 128.3, 128.0, 122.5, 120.0, 118.9, 110.9, 106.7, 54.5, 52.12, 52.07, 27.1; IR (NaCl/thin film) 3338, 2953, 2923, 2852, 1718, 1701, 1507, 1457, 1363, 1213, 1072 cm^{-1}; $[\alpha]_D^{25}$ = +22.6º (*c* = 0.10, $CHCl_3$). HRMS (MM) calc'd for $[M+H]^+$ 353.1496, found 353.1497.

Methylcarbamate (185): racemic



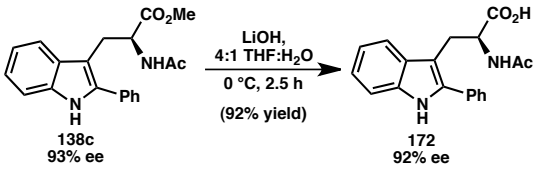
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.480	MF	0.5516	1252.40308	37.84099	49.3945
2	16.749	FM	0.6385	1283.11060	33.49063	50.6055

Methylcarbamate (185): 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

3.4.8.2 Methyl Ester Hydrolysis[45]

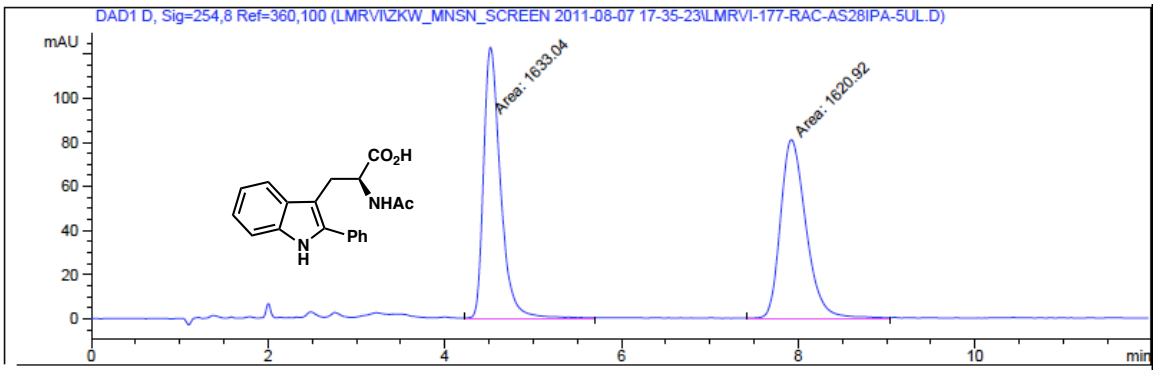


138c
93% ee

172
92% ee

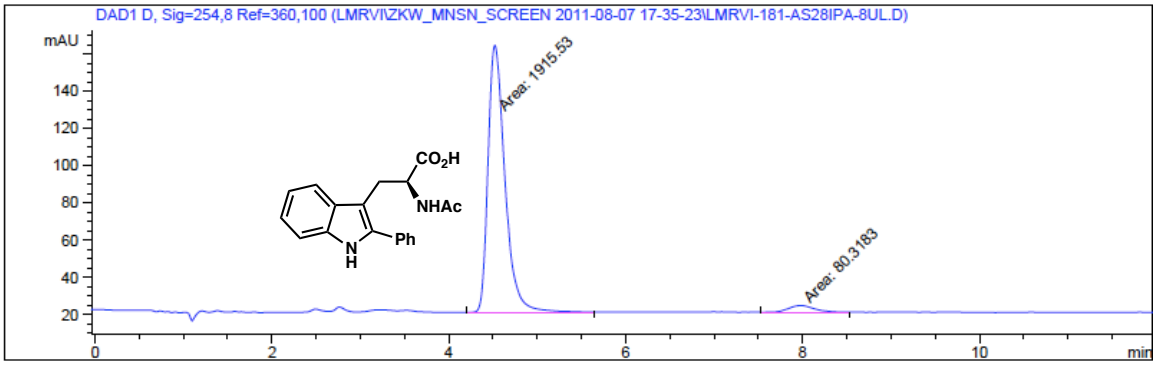
A 10 mL flask was charged with (*S*)-*N*α-acetyl-2-phenyltryptophan methyl ester **138c** (67.2 mg, 0.20 mmol, 1.00 equiv) and THF (0.9 mL) then cooled to 0 ºC, followed by dropwise addition of aqueous LiOH (1.75 M, 230 μL, 0.40 mmol, 2.00 equiv). The reaction was vigorously stirred at 0 ºC for 2 hours, 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 **172** 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}; $[\alpha]_D^{25}$ = +9.2º (*c* = 1.05, MeCN). HRMS (MM) calc'd for $[M+H]^+$ 323.1390, found 323.1390.

172: 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

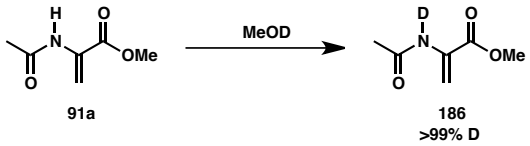
172: enantioenriched, 92% ee



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

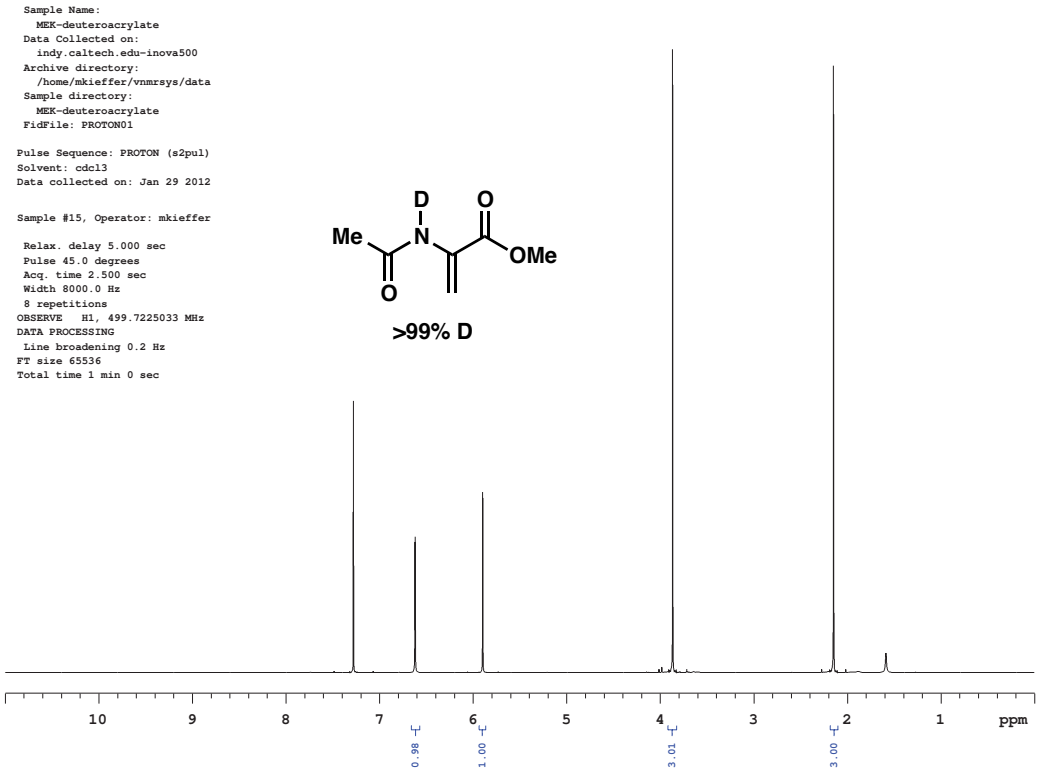
3.4.9 Deuterium Labeling Studies

Preparation of *N*-deuteroacrylate (186).

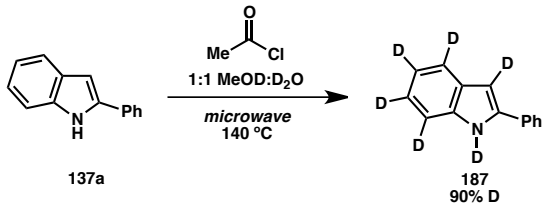


91a 186
>99% D

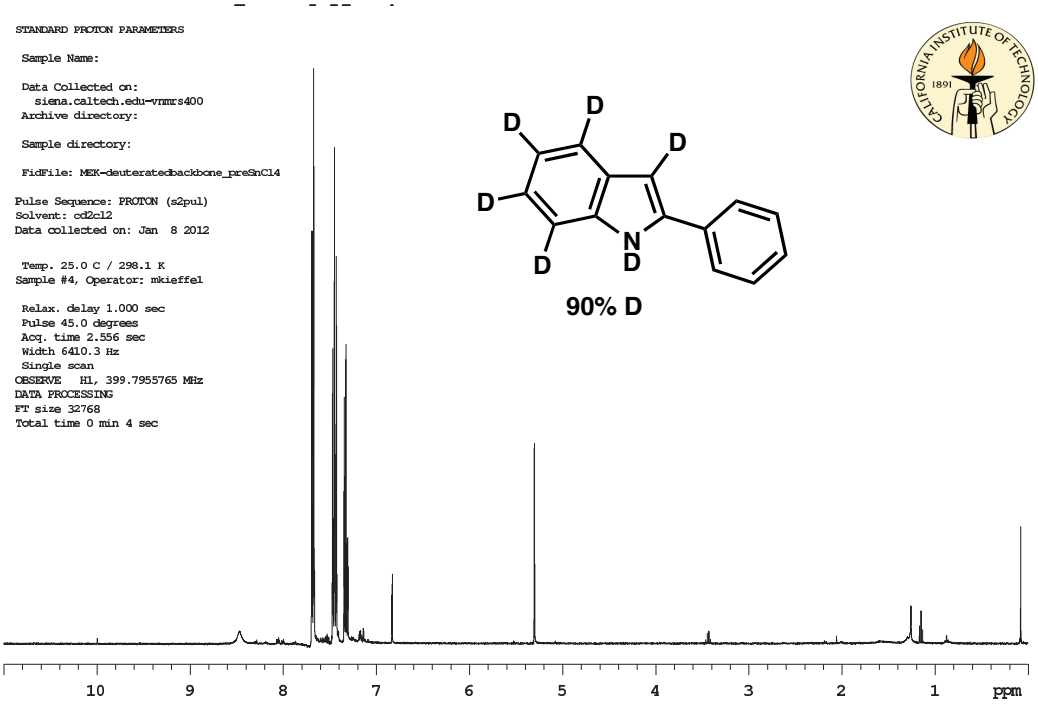
Acrylate **91a** was dissolved in MeOD (1 mL) under nitrogen. After stirring for 1 minute, the solution was concentrated under high vacuum. This procedure was repeated three times to give >99% deuterium incorporation.



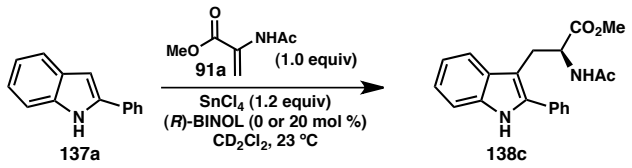
Preparation of per-deutero-2-phenylindole (187).



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 (**187**) with 90% deuterium incorporation.

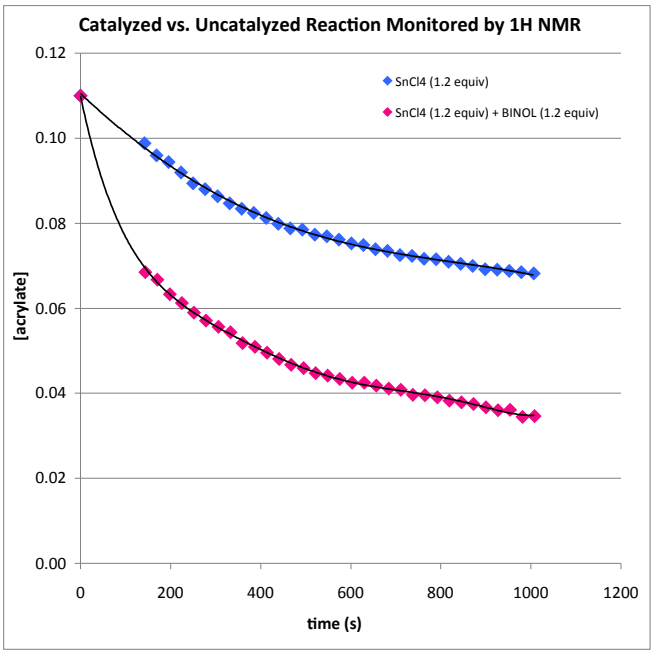


3.4.10 ^{1}H NMR Kinetics Experiment for $SnCl_4$ and (R)-BINOL (102a)•$SnCl_4$ Promoted Reaction of 137a and 91a.



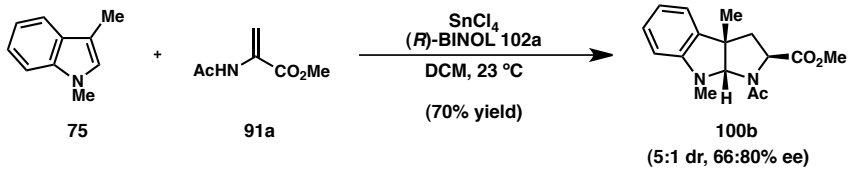
An oven-dried vial was charged with 2-phenylindole (**137a**, 19.0 mg, 0.10 mmol, 1.00 equiv), methyl 2-acetamidoacrylate (**91a**, 14.0 mg, 0.10 mmol, 1.00 equiv), (*R*)-BINOL if necessary (6.0 mg, 0.02 mmol, 0.20 equiv) and 1,4-diethylbenzene (4.7 μL, 0.03 mmol, 0.30 equiv) as the internal standard. 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.

Kinetics Plot



3.4.11 Comparison of Conditions for Pyrroloindoline Formation.

Table 3.2.6**, entry 1:**

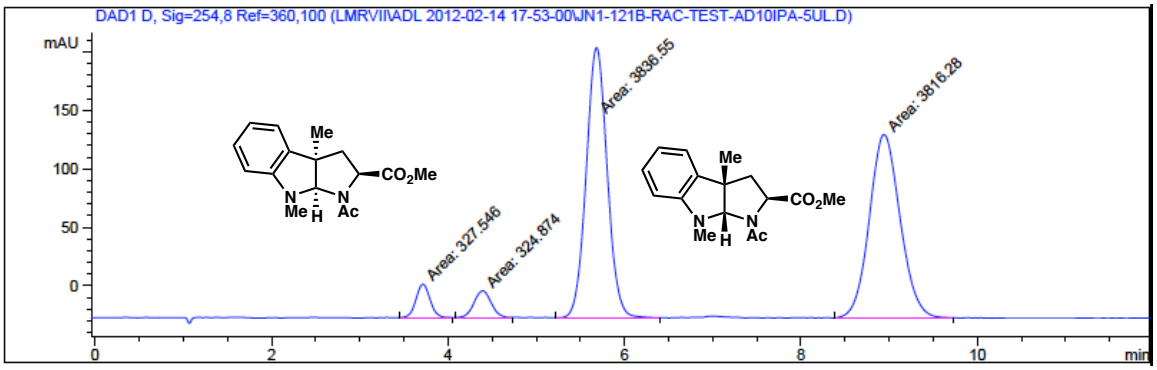


75 91a 100b

(5:1 dr, 66:80% ee)

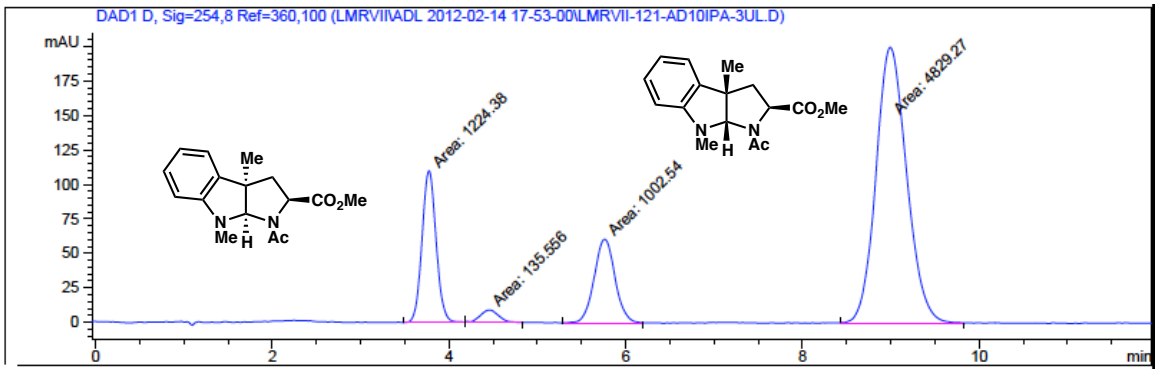
To a flame-dried 10 mL flask was added 1,3-dimethylindole (**75**, 29.0 mg, 0.20 mmol, 1.00 equiv), acrylate **91a** (28.6 mg, 0.20 mmol, 1.00 equiv), and (*R*)-BINOL (**102a**, 11.4 mg, 0.04 mmol, 0.20 equiv). The flask was charged with DCM (1.5 mL), followed by addition of $SnCl_4$ (1 M in DCM, 240 μL, 0.24 mmol, 1.20 equiv) and the reaction mixture was stirred at room temperature for 4 hours, then quenched by diluting with MeCN (1 mL) and 1 M HCl (5 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (15 mL). The aqueous layer was back extracted with EtOAc (10 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The product **100b** was formed in a 5:1 ratio of diastereomers favoring the *exo* diastereomer (determined by ^1H NMR analysis of the crude reaction mixture) and purified by silica gel chromatography (0:100 to 100:0 EtOAc:hexanes) to yield 40.1 mg (70% yield) of the combined diastereomers as a yellow oil. The enantiomeric excess of the *exo* diastereomer was determined to be 66% by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in CO_2, λ = 254 nm): t_R(major) = 9.0 min, t_R(minor) = 5.8 min. The enantiomeric excess of the *endo* diastereomer was determined to be 80% by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in CO_2, λ = 254 nm): t_R(major) = 3.8 min, t_R(minor) = 4.5 min. Spectral data are in agreement with the literature.[46]

100b (Table 3.2.6, **entries 1-2**): racemic



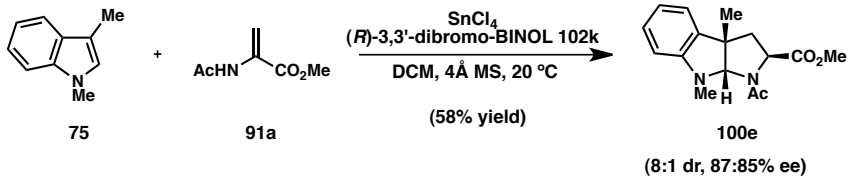
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.716	MM	0.1887	327.54623	28.92616	3.9438
2	4.393	MM	0.2327	324.87354	23.26702	3.9117
3	5.684	MM	0.2766	3836.55249	231.14015	46.1943
4	8.941	MM	0.4056	3816.27661	156.80905	45.9502

100b (Table 3.2.6, **entry 1**): enantioenriched, *exo*: 65% ee, *endo*: 80% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.774	MM	0.1852	1224.37573	110.17274	17.0248
2	4.454	MM	0.2457	135.55609	9.19677	1.8849
3	5.762	MM	0.2749	1002.53888	60.78873	13.9402
4	8.994	MM	0.4027	4829.26514	199.89325	67.1502

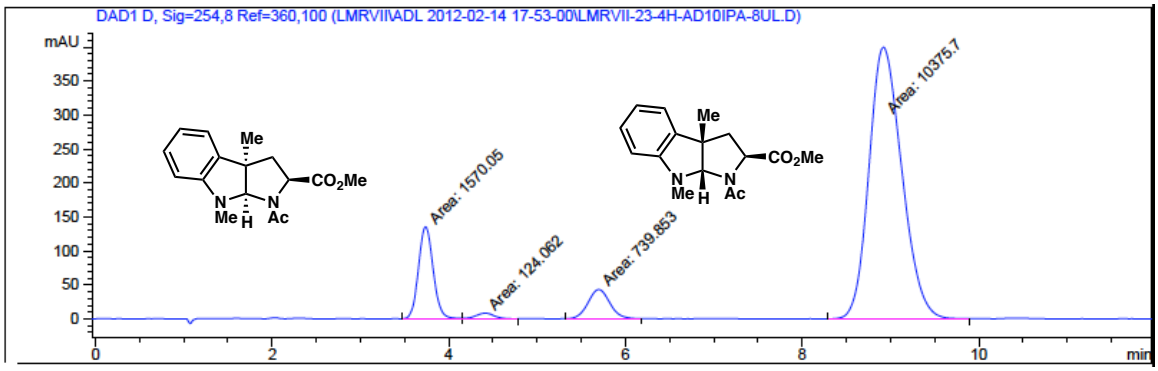
Table 3.2.6**, entry 2:**



An oven-dried vial was charged with 1,3-dimethylindole (**75**, 29.0 mg, 0.20 mmol, 1.00 equiv), acrylate **91a** (34.3 mg, 0.24 mmol, 1.20 equiv), and (*R*)-3,3'-dibromo-BINOL (**102k**, 17.8 mg, 0.04 mmol, 0.20 equiv) and pumped into a glove box. To the vial was added flame-dried powdered 4Å molecular sieves (200 wt % relative to **75**). The vial was charged with DCM (1.5 mL) and $SnCl_4$ (1 M in DCM, 200 μL, 0.20 mmol, 1.00 equiv) was added. The reaction was stirred at 20 °C for 4 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 (3 x 5 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (15 mL). The aqueous was back extracted with EtOAc (10 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The product **100b** was formed in a 8:1 ratio of diastereomers favoring the *exo* diastereomer (determined by ^1H NMR analysis of the crude reaction mixture) and purified by silica gel chromatography (0:100 to 100:0 EtOAc:hexanes) to yield 33.5 mg (58% yield) of the combined diastereomers as a yellow oil. The enantiomeric excess of the *exo* diastereomer was determined to be 87% by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in CO_2, λ = 254 nm): t_R(major) = 8.9 min, t_R(minor) = 5.7 min. The enantiomeric excess of the *endo* diastereomer was determined to be 85% by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in CO_2, λ = 254 nm):

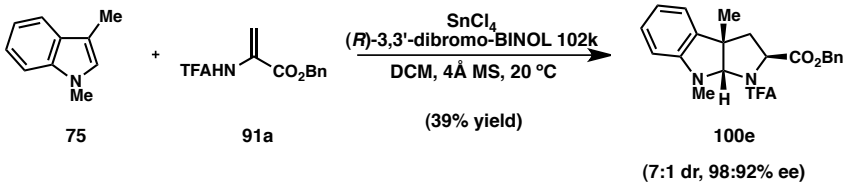
t_R(major) = 3.7 min, t_R(minor) = 4.4 min. Spectral data are in agreement with the literature.[46]

100b (Table 3.2.6, **entry 2**): enantioenriched, *exo*: 87% ee, *endo*: 85% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.737	MM	0.1930	1570.05005	135.56972	12.2568
2	4.408	MM	0.2459	124.06150	8.40710	0.9685
3	5.698	MM	0.2863	739.85333	43.07298	5.7757
4	8.919	MM	0.4323	1.03757e4	400.02573	80.9990

Table 3.2.6**, entry 4:**[§]

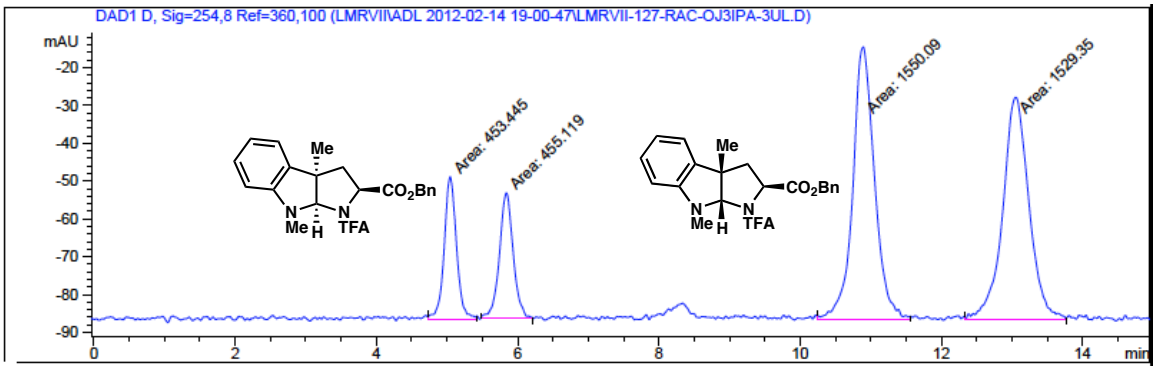


An oven-dried vial was charged with 1,3-dimethylindole (**75**, 29.0 mg, 0.20 mmol, 1.00 equiv), acrylate **91d** (65.5 mg, 0.24 mmol, 1.20 equiv), and (*R*)-3,3'-dibromo-BINOL (**102k**, 17.8 mg, 0.04 mmol, 0.20 equiv) and pumped into a glove box. To the vial was added flame-dried powdered 4Å molecular sieves (200 wt % relative to **75**). The vial was charged with DCM (1.5 mL) and $SnCl_4$ (1 M in DCM, 200 μL, 0.20 mmol, 1.00 equiv) was added. The reaction was stirred at 20 °C for 4 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 (3 x 5 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (15 mL). The aqueous was back extracted with EtOAc (10 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The product **100e** was formed in a 7:1 ratio of diastereomers favoring the *exo* diastereomer (determined by ^{1}H NMR analysis of the crude reaction mixture) and purified by silica gel chromatography (0:100 to 10:90 EtOAc:hexanes) to yield 32.7 mg (39% yield) of the combined diastereomers as a yellow oil. The enantiomeric excess of the *exo* diastereomer was determined to be 98% by chiral SFC analysis (OJ-H, 2.5 mL/min, 3% IPA in CO_2, λ = 254 nm): t_R(major) = 12.5 min, t_R(minor) = 10.9 min. The enantiomeric excess of the *endo* diastereomer was determined to be 92% by chiral SFC analysis (OJ-H, 2.5 mL/min, 3% IPA in CO_2, λ = 254 nm):

[§] For information on Table 3.2.6, entry 3, see ref. 45.

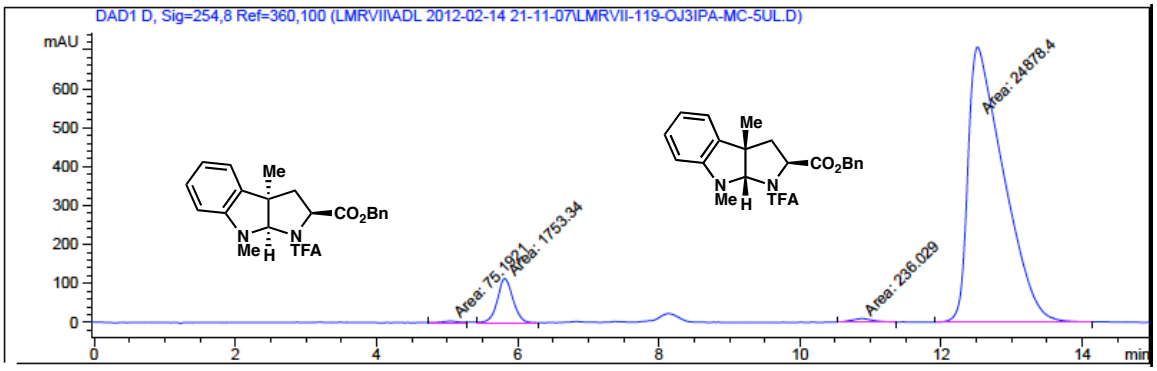
t_R(major) = 5.8 min, t_R(minor) = 5.0 min. Spectral data are in agreement with the literature.[46]

100e (Table 3.2.6, **entry 4**): racemic



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.046	MM	0.2006	453.44531	37.66904	11.3702
2	5.841	MM	0.2280	455.11948	33.27365	11.4122
3	10.895	MM	0.3583	1550.08838	72.09877	38.8688
4	13.054	MM	0.4330	1529.35278	58.87241	38.3488

100e (Table 3.2.6, **entry 4**): enantioenriched, *exo*: 98% ee, *endo*: 92% ee



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.047	MM	0.2718	75.19215	4.61071	0.2791
2	5.818	MM	0.2566	1753.34155	113.89976	6.5076
3	10.862	MM	0.3831	236.02933	10.26737	0.8760
4	12.514	MM	0.5861	2.48784e4	707.50366	92.3373

3.5 NOTES AND REFERENCES

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