

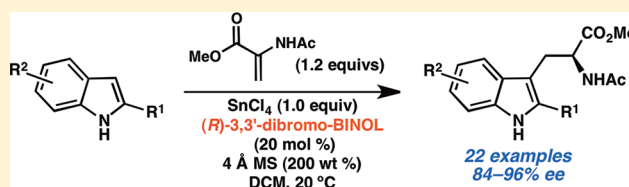
Enantioselective Synthesis of Tryptophan Derivatives by a Tandem Friedel–Crafts Conjugate Addition/Asymmetric Protonation Reaction

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S Supporting Information

ABSTRACT: The tandem Friedel–Crafts conjugate addition/asymmetric protonation reaction between 2-substituted indoles and methyl 2-acetamidoacrylate is reported. The reaction is catalyzed by (R)-3,3'-dibromo-BINOL in the presence of stoichiometric SnCl₄, and is the first example of a tandem conjugate addition/asymmetric protonation reaction using a BINOL·SnCl₄ complex as the catalyst. A range of indoles furnished synthetic tryptophan derivatives in good yields and high levels of enantioselectivity, even on a preparative scale. The convergent nature of this transformation should lend itself to the preparation of unnatural tryptophan derivatives for use in a broad array of synthetic and biological applications.



INTRODUCTION

Tryptophan and unnatural tryptophan derivatives are important building blocks for the total synthesis of natural products, as well as the development of new drugs,¹ biological probes,^{2,3} and chiral small molecule catalysts.⁴ For example, functionalized tryptophan derivatives have served as key intermediates in the syntheses of the bioactive natural products indolactam V⁵ and stephacidin A.⁶ Alternatively, unnatural tryptophan derivatives have been employed as probes for studying protein conformational dynamics by way of Förster resonance energy transfer (FRET) experiments,² as well as for elucidating cation– π binding interactions by linear free energy relationship studies.³ As a result, the development of new catalytic asymmetric methods to prepare enantioenriched unnatural tryptophans is an important area of chemical research.⁷

As part of our research program aimed at establishing new methods for the enantioselective synthesis of alkaloids, we are interested in developing convergent syntheses of tryptophans and cyclo-tryptophans (also known as pyrroloindolines) from simple indole starting materials. In 2010, we reported a new reaction for the preparation of enantioenriched pyrroloindolines (**3**) in which (R)-BINOL·SnCl₄ catalyzes a formal (3 + 2) cycloaddition reaction between 1,3-disubstituted indoles (**1**) and benzyl 2-trifluoroacetamidoacrylate (**2a**) (part a of Scheme 1).⁸ Good yields, moderate *exo:endo* diastereoselectivities, and high enantioselectivities were obtained for a variety of indole substrates (Table 1). The enantio- and diastereoselectivity of pyrroloindoline formation were found to be dependent on the identity of the acrylate; the highest ee values were observed using acrylate **2a**. Use of the commercially available methyl 2-acetamidoacrylate (**2c**) provided higher drs but attenuated ees. *N*-Alkyl substitution on the indole substrates gave higher yields

of the pyrroloindoline products relative to the *N*-protio-indoles (Table 1, entry 1 versus entry 10).

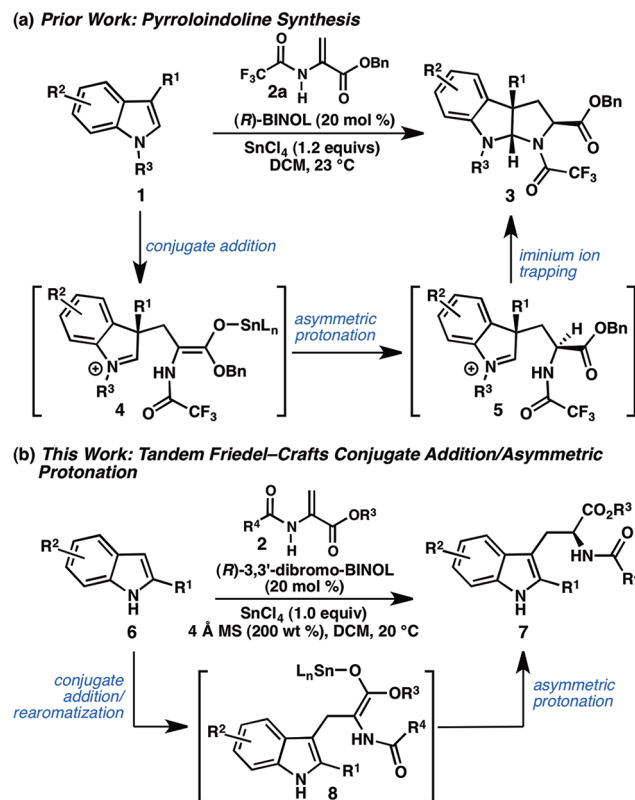
Unexpectedly, our studies revealed that the initially formed *exo* and *endo* diastereomers of **3** were generated in opposite enantiomeric series. These findings led us to propose that pyrroloindoline formation proceeds by a stepwise mechanism, in which an initial conjugate addition of indole **1** to **2a** is followed by a catalyst-controlled protonation to give **5** (part a of Scheme 1). Subsequent cyclization of the amide onto the iminium ion provides the pyrroloindoline product (**3**). We hypothesized that the (R)-BINOL·SnCl₄ complex (**9a**·SnCl₄, as seen in Figure 1) served as a chiral Lewis acid-assisted Brønsted acid (LBA)^{9,10} to effect an asymmetric protonation of the enolate intermediate. Whereas Yamamoto and co-workers initially developed (R)-BINOL·SnCl₄ as an LBA to effect enantioselective protonation of silyl enolates, these complexes had never previously been used in tandem conjugate addition/asymmetric protonation reactions.

Herein, we report our efforts to expand the scope of products accessible by (R)-BINOL·SnCl₄-catalyzed conjugate addition/asymmetric protonation processes. These studies have resulted in the direct, enantioselective synthesis of tryptophan derivatives by a tandem Friedel–Crafts conjugate addition/asymmetric protonation reaction (part b of Scheme 1).¹¹ The reactions require no preactivation of the indole substrates and provide convergent access to a range of substituted tryptophan derivatives in enantioenriched form. Friedel–Crafts conjugate addition reactions in which a new stereogenic center is set *solely* at the α -position of the conjugate acceptor through an enantioselective protonation event are rare,¹² and have only

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Scheme 1



recently been reported with indole nucleophiles.^{13–16} Genet and Darses have reported the synthesis of α -amino acids by a Rh-catalyzed conjugate addition of aryl trifluoroborate salts to 2-amidoacrylates with in situ asymmetric protonation;^{14d,h} however, there are no examples using indole-based nucleophiles to give tryptophan derivatives.

RESULTS AND DISCUSSION

Our studies commenced with efforts to promote the Friedel–Crafts conjugate addition/asymmetric protonation reaction between 2-phenylindole (6a) and benzyl 2-trifluoroacetamidoacrylate (2a) under the reaction conditions previously optimized for the enantioselective formal (3 + 2) cycloaddition reaction. Somewhat surprisingly, the desired reaction was sluggish under these conditions: after 2 h, trifluoroacetamido ester 7a was formed in low yield and poor enantiomeric excess (Table 2, entry 1). In an effort to improve the reactivity, a screen of additional 2-amidoacrylates was conducted. Gratifyingly, the use of commercially available methyl 2-acetamidoacrylate (2c) gave substantially improved results, providing acetamido ester 7c in 73% yield and 78% ee. As we observed in the enantioselective pyrroloindoline formation,⁸ SnCl₄ promotes the reaction between 6a and 2c in the absence of (R)-BINOL (9a) (entry 4); however, 9a produces a substantial acceleration in the rate of the SnCl₄-promoted reaction.¹⁷ No reaction is observed in the absence of SnCl₄ (entry 5).

We suspected that the reaction of adventitious water and SnCl₄ might generate HCl, which could erode the apparent ee of 7c by promoting a racemic background protonation reaction; thus, additives known to scavenge water or HCl were evaluated. Whereas insoluble inorganic bases such as K₂CO₃ showed no effect (entry 6), the use of soluble bases such as 2,6-lutidine completely inhibited the reaction (entry 7). On the other hand,

Table 1. Catalytic Asymmetric Synthesis of Pyrroloindolines

entry	ee (%) ^a (exo/endo) ^b	entry	ee (%) ^a (exo/endo) ^b
1)	86% yield dr = 4:1	6)	54% yield dr = 6:1
2)	93% yield dr = 3:1	7)	80% yield ^c dr = 4:1
3)	61% yield dr = 3:1	8)	65% yield dr = >18:1
4)	84% yield dr = 5:1	9)	90% yield ^c dr = 3:1
5)	91% yield dr = 4:1	10)	18% yield dr = 8:1

^aDetermined by chiral stationary phase SFC or HPLC. ^bDetermined by ¹H NMR analysis of mixture. ^c1.6 equivs SnCl₄ were employed.

the use of activated powdered 4 Å molecular sieves increased both the yield and selectivity of the reaction, furnishing acetamido ester 7c in 86% yield and 81% ee, while also improving the reproducibility (entry 8).

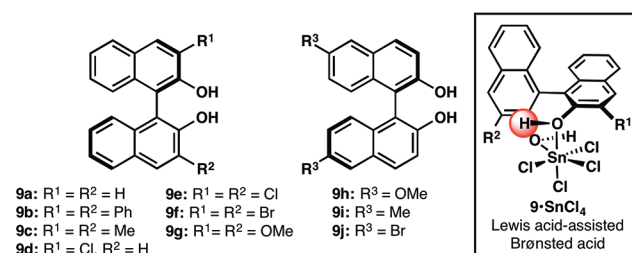


Figure 1. (R)-BINOL-derived catalysts.

Table 2. Optimization of Reaction Parameters^a

entry	R ³ , R ⁴	pdt	solvent	additive	yield (%) ^b	ee (%) ^c
1	Bn, CF ₃ (2a)	7a	DCM		12	35
2	Me, CF ₃ (2b)	7b	DCM		12	42
3	Me, Me (2c)	7c	DCM		73	78
4	Me, Me (2c)	7c	DCM	^d	13	
5	Me, Me (2c)	7c	DCM	^e	0	
6	Me, Me (2c)	7c	DCM	K ₂ CO ₃	73	78
7	Me, Me (2c)	7c	DCM	2,6-lutidine	0	
8	Me, Me (2c)	7c	DCM	4 Å MS	86	81
9	Me, Me (2c)	7c	DCE	4 Å MS	87	79
10	Me, Me (2c)	7c	CHCl ₃	4 Å MS	80	72

^aReactions conducted under inert atmosphere on 0.2 mmol scale for 2 h. ^bIsolated yield. ^cDetermined by chiral stationary phase SFC. ^dNo (R)-BINOL was employed. ^eNo SnCl₄ was employed.

At this stage, our efforts to further improve the enantioselectivity of this transformation turned to optimization of the catalyst structure. We were pleased to find that 3,3'-disubstitution with halides furnished improved selectivities and comparable yields (Table 3, entries 5 and 6).

Table 3. Catalyst Optimization^a

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

^aReactions conducted under inert atmosphere on 0.2 mmol scale for 2 h. ^bIsolated yield. ^cDetermined by chiral stationary phase SFC.

Interestingly, dimethoxy catalyst **9g** provided acetamido ester **7c** as a racemate in low yield (entry 7). It is proposed that the coordinating ability of the methoxy groups may permit alternative binding modes between SnCl₄ and **9g** resulting in mixtures of less reactive and less selective catalyst systems. To probe whether the electronic or steric properties of the 3,3'-substituents were responsible for modulating the selectivities of catalysts **9a–g**, several 6,6'-disubstituted BINOL derivatives

were also evaluated. However, no linear dependence between the BINOL electronics and the ee of **7c** was observed (Table 3, entries 1, 8–10). Of the catalysts evaluated, the commercially available (R)-3,3'-dibromo-BINOL catalyst **9f**¹⁸ gave optimal results, delivering acetamido ester **7c** in 76% yield and 93% ee (entry 6).¹⁹ Whereas 10 mol % **9f** provided comparable selectivity for the formation of **7c** (entry 13), use of 5 mol % **9f** resulted in diminished ee (entry 14). The decreased selectivity likely results from competition by the achiral SnCl₄-promoted background reaction at low catalyst loadings. Because 20 mol % catalyst imparted consistently higher enantioselectivities for more functionalized substrates (vide infra), this catalyst loading was utilized in subsequent experiments.

Having identified conditions to prepare acetamido ester **7c** in high yield and enantiomeric excess, a survey of indole substrates was conducted to evaluate the scope of the reaction (Table 4). In contrast to our observations in the formal (3 + 2) cycloaddition,⁸ methylation or allylation of the indole nitrogen provides tryptophans **7d** and **7e** in slightly lower yields and ee (entries 2 and 3).²⁰ Similarly, use of unsubstituted indole as the nucleophile provides *N*-α-acetyltryptophan methyl ester in 31% yield and 67% ee (not shown, Supporting Information).²¹ Alternatively, substitution of the 2-phenylindole backbone at the 4, 5, 6, and 7-positions is well tolerated (entries 4–7). Whereas substrates bearing either electron-donating or electron-withdrawing substituents furnish products with high enantioselectivity, the more electron-poor indoles are less reactive and provide lower yields of the acetamido ester products even with increased loadings of SnCl₄ (entries 9 and 10).

A range of substituents are tolerated at the 2-position of the indole, including both aryl and alkyl groups. 2-Arylindoles bearing substituents in either the *m*- or *p*-position of the arene are accommodated; on the other hand, *o*-substituted arenes are substantially less reactive (entries 12 and 16). For indoles containing 2-alkyl substituents, the ee improves in switching from a methyl group to the slightly larger *n*-butyl and *i*-propyl substituents (entries 18–20); however, both the yield and selectivity are diminished in the case of bulky *t*-butyl substitution (**7w**, entry 21). Notably, a phthalimide-protected amine functionality is also compatible, as demonstrated in **7x**

Table 4. Substrate Scope of the Tandem Friedel–Crafts Conjugate Addition/Asymmetric Protonation^a

<p>Me-C(=O)-NH-CH=C(OMe) 2c (1.2 equiv) SnCl₄ (1.0 equiv) 9f (20 mol %) 4 Å MS (200 wt %) DCM, 20 °C</p> <p>6 7c-x</p>	
entry	entry
1) <p>76% yield, 93% ee</p>	11) <p>86% yield, 94% ee</p>
2) R = Me (7d) 63% yield, 85% ee	12) <p>26% yield, 87% ee</p>
3) R = allyl (7e) 68% yield, 85% ee	
4) 4-Me (7f): 88% yield, 96% ee	13) <p>75% yield, 93% ee</p>
5) 5-Me (7g): 83% yield, 95% ee	
6) 6-Me (7h): 80% yield, 89% ee	14) <p>78% yield, 93% ee</p>
7) 7-Me (7i): 94% yield, 94% ee	15) <p>76% yield, 92% ee</p>
	16) <p>35% yield, 92% ee</p>
8) <p>85% yield, 91% ee</p>	17) <p>88% yield, 92% ee</p>
9) ^b <p>60% yield, 93% ee</p>	18) R = Me (7t): 61% yield, 85% ee
10) ^b <p>63% yield, 92% ee</p>	19) R = <i>n</i> -Bu (7u): 72% yield, 91% ee
	20) R = <i>i</i> -Pr (7v): 66% yield, 92% ee
	21) R = <i>t</i> -Bu (7w): 29% yield, 84% ee
	<p>80% yield, 90% ee</p>

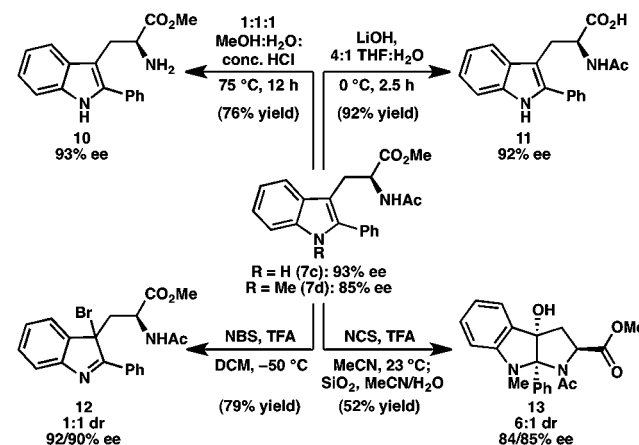
^aReactions conducted under inert atmosphere on 0.1 or 0.2 mmol scale for 2 h. Isolated yields are reported. Enantiomeric excess was determined by chiral stationary phase SFC. ^b1.6 equivs SnCl₄ were employed.

(entry 22). Attempts to further expand the scope of C2-substituents were unfruitful. For example, 2-iodoindole underwent decomposition under the reaction conditions, whereas 2-(trimethylsilyl)indole returned unreacted starting material.

Using 2-phenylindole (6a), this reaction has been conducted on a 5 mmol scale, providing acetamido ester 7c in 77% yield and 93% ee. Although our screening protocol was conducted in a glovebox, this preparative scale reaction could be run using standard Schlenk techniques. We have also demonstrated that the acetamide and methyl ester groups can be hydrolyzed under

orthogonal conditions. Heating 7c to 75 °C with HCl in aqueous methanol cleaves the acetamide group to deliver free amine 10 in 76% yield and 93% ee.²² Alternatively, exposure of 7c to aqueous LiOH in THF at 0 °C provides carboxylic acid 11 in 92% yield and 92% ee.²³

Scheme 2. Functionalization of Tryptophan 7c and 7d



Upon treatment with NBS and TFA, tryptophan 7c can be converted to bromo-dehydroindoline 12, which is formed as a 1:1 mixture of diastereomers. Interestingly, 12 does not undergo cyclization to the pyrroloindoline under the reaction conditions. However, exposure of *N*-methyl derivative 7d to NCS²⁴ and TFA in acetonitrile provides the corresponding chloro-pyrroloindoline, as detected by HRMS. Subsequent silica gel-promoted hydrolysis then delivers the more stable hydroxy-pyrroloindoline 13 in 52% yield and 6:1 dr, favoring the *endo* diastereomer.

Mechanistically, it seems likely based on Yamamoto's prior reports of catalytic asymmetric protonation of silyl enol ethers and silyl ketene acetals^{9b,c} that catalytically generated 9f·SnCl₄ is serving as a chiral LBA to protonate an intermediate Sn-enolate. Whether 9f·SnCl₄ is the species responsible for activating acrylate 2c toward conjugate addition by the indole is unclear. Although 9f·SnCl₄ is proposed to serve as the catalyst, stoichiometric tin is required due to binding of the acetamido ester product to tin resulting in product inhibition. Notably, no significant nonlinear effects are observed when using scalemic BINOL to catalyze the reaction (Chart 1).²⁵

Chart 1. Nonlinear Effects Study

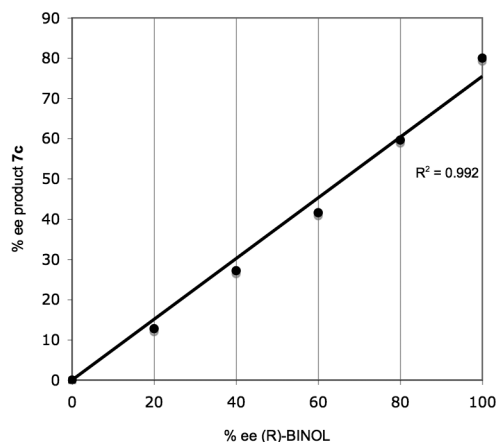
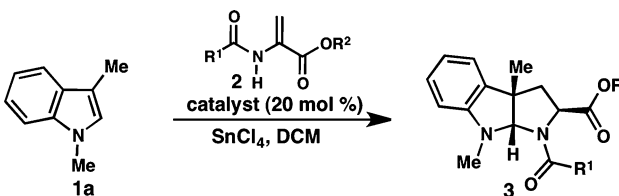


Table 5. Comparison of Conditions for Pyrroloindoline Formation



entry	conditions	R ¹ , R ²	pdt	yield ^a (%)	dr ^b	ee (%) ^c
1 ^d	9a	Me, Me (2c)	3k	70	5:1	66/80
2 ^e	9f, 4 Å MS	Me, Me (2c)	3k	58	8:1	87/85
3 ^d	9a	CF ₃ , Bn (2a)	3a	86	4:1	94/91
4 ^e	9f, 4 Å MS	CF ₃ , Bn (2a)	3a	39	7:1	98/92

^aIsolated yield. ^bDetermined by ¹H NMR analysis of mixture. ^cDetermined by chiral stationary phase SFC. ^dReaction run with 1.0 equiv acrylate, 1.2 equivs SnCl₄. ^eReaction run with 1.2 equivs acrylate, 1.0 equiv SnCl₄.

Given the proposed mechanistic similarities between the reactions to give pyrroloindoline 3 and tryptophan 7, we were interested in whether the conditions optimized for tryptophan formation would catalyze the formal (3 + 2) cycloaddition reaction with improved selectivity. Treatment of 1a and methyl 2-acetamidoacrylate (2c) with 1.0 equiv SnCl₄ and 20 mol % catalyst 9f in the presence of 4 Å MS furnished pyrroloindoline 3k in 58% yield as an 8:1 mixture of *exo* and *endo* diastereomers in 87 and 85% ee, respectively (Table 5, entry 2). Although these conditions provide pyrroloindoline 3k with improved dr and ee relative to the originally reported conditions (Table 5, entry 1), they are less enantioselective than when benzyl 2-trifluoromethylacetamidoacrylate (2a) is employed (entry 3). Finally, use of acrylate 2a with catalyst 9f and 4 Å MS provided pyrroloindoline 3a with high dr and exceptional ee; unfortunately 3a was isolated in unacceptably low yield. The lower reactivity of acrylate 2a is consistent with the reactivity trend observed for tryptophan formation (Table 2, entry 1). Taken together, these data highlight that an appropriate matching of the acrylate and catalyst is required to obtain 3 with both high yields and high enantioselectivity.

CONCLUSIONS

In conclusion, 9f:SnCl₄ catalyzes a tandem Friedel–Crafts conjugate addition/asymmetric protonation reaction between 2-substituted indoles (6) and methyl 2-acetamidoacrylate (2c). A range of indoles furnished synthetic tryptophan derivatives 7 in good yields and high levels of enantioselectivity, even on preparative scale. We have shown that such tryptophan derivatives can be orthogonally deprotected, or converted to more functionalized derivatives. This is the first example of a chiral diol:SnCl₄-catalyzed Friedel–Crafts conjugate addition reaction in which the new stereogenic centers are set solely at the α-position of the conjugate acceptor by an asymmetric protonation. The convergent nature of this transformation should lend itself to the preparation of unnatural tryptophan derivatives for use in a broad array of synthetic and biological applications. Further mechanistic studies and the development of related asymmetric protonation reactions are the subject of continued research in our laboratory.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Methylene chloride, ether, tetrahydrofuran, and dioxane were dried by passing through activated alumina columns. Dichloroethane and

chloroform were distilled over calcium hydride. Powdered 4 Å 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 AlCl₃. All other commercially obtained reagents were used as received unless specifically indicated. (R)-BINOL (9a), 2-phenylindole (6a) and 2-methylindole (6r) were purchased from Alfa Aesar, N-methyl-2-phenylindole (6b) was obtained from Sigma-Aldrich, and 1 M SnCl₄ in CH₂Cl₂ was purchased from Acros Organics. (R)-3,3'-diphenyl-BINOL (9b),²⁶ (R)-3,3'-dimethyl-BINOL (9c),²⁷ (R)-3,3'-dichloro-BINOL (9e),²⁸ (R)-3,3'-dibromo-BINOL (9f),¹⁸ (R)-3,3'-dimethoxy-BINOL (9g),¹⁸ (R)-6,6'-dimethyl-BINOL (9i),²⁹ and (R)-6,6'-dibromo-BINOL (9j)³⁰ were prepared according to literature procedures. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 precoated plates (0.25 mm). Silica gel column chromatography was performed either as described by Still et al.³¹ using silica gel (particle size 0.032–0.063) purchased from Silicycle or using prepackaged RediSepRf columns on a CombiSilica gel Rf system (Teledyne ISCO Inc.). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ¹H and ¹³C NMR spectra were recorded on a Varian Inova 500 (at 500 and 125 MHz, respectively) or a Varian Inova 600 (at 600 and 150 MHz, respectively) and are reported relative to internal chloroform (¹H, δ = 7.26, ¹³C, δ = 77.0) or internal acetonitrile (¹H, δ = 1.94, ¹³C, δ = 1.32). Data for ¹H 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 PerkinElmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm⁻¹). Analytical SFC was performed with a Mettler SFC supercritical CO₂ analytical chromatography system with Chiralcel AD-H, OD-H, AS-H, OB-H, and OJ-H columns (4.6 mm × 25 cm). HRMS were acquired using either an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode, or obtained from the Caltech Mass Spectral Facility.

General Procedure for the Synthesis of Tryptophan Derivatives. An oven-dried vial was charged with the indole (1.00 equiv), methyl 2-acetamidoacrylate (2c, 1.20 equivs), (R)-3,3'-dibromo-BINOL (9f, 0.20 equivs), and pumped into a glovebox. To the vial was added flame-dried powdered 4 Å molecular sieves (200 wt % relative to indole). The vial was charged with CH₂Cl₂ to an indole concentration of 0.12 M, and SnCl₄ (1.00 equiv as a 1 M solution in CH₂Cl₂) was added. The reaction was stirred at 20 °C for 2 h, after which time it was removed from the glovebox and quenched by dilution with 1 M HCl (5 mL) and CH₃CN (1 mL). The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic layers were washed with saturated aqueous NaHCO₃ (5 mL), dried (Na₂SO₄), filtered, and concentrated. The crude residue was purified by silica gel chromatography.

Preparative Scale Procedure for the Synthesis of Tryptophan 7c. To a flame-dried flask under nitrogen containing freshly activated powdered 4 Å molecular sieves (200 wt %) was added 2-phenylindole (**1a**, 1.00 g, 5.20 mmol, 1.00 equiv), methyl 2-acetamidoacrylate (**2c**, 890 mg, 6.20 mmol, 1.20 equivs), and (R)-3,3'-dibromo-BINOL (**9f**, 457 mg, 1.00 mmol, 0.20 equivs). The flask was charged with 40 mL DCM and SnCl₄ (1 M in DCM, 5.20 mL, 5.20 mmol, 1.00 equiv) was added. The reaction was stirred at room temperature for 2 h, then quenched by addition of 1 M HCl (50 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL) and the combined organic layers were washed with saturated aqueous NaHCO₃ (50 mL), dried (Na₂SO₄), 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 **7c** as a pale yellow foam. The enantiomeric excess was determined to be 93% by chiral SFC analysis (Chiracel AD-H, 2.5 mL/min, 30% IPA in CO₂, λ = 254 nm): t_R(major) = 5.7 min t_R(minor) = 6.9 min.

■ ASSOCIATED CONTENT

■ Supporting Information

Information regarding materials and methods, and NMR spectra of compounds from this study. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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