

Enantioselective Synthesis of Pyrroloindolines by a Formal [3 + 2] Cycloaddition Reaction

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Abstract: (*R*)-BINOL•SnCl₄ was found to catalyze a formal [3 + 2] cycloaddition reaction between C(3)-substituted indoles and 2-amidoacrylates to provide pyrroloindolines. A variety of pyrroloindolines were prepared with high enantioselectivity in one step from simple precursors. This methodology is expected to facilitate the total synthesis of pyrroloindoline alkaloids, an important class of biologically active natural products.

Pyrroloindoline alkaloids are an important class of natural products¹ that exhibit an impressive array of promising biological properties, including anticholinesterase,² anti-inflammatory,³ and anticancer activities.⁴ Owing to their medicinal relevance and structural complexity, pyrroloindoline alkaloids have served as a fertile area for the discovery and development of new chemical reactions.^{5,6} As part of a program targeting new methods for the total synthesis of alkaloid natural products, we sought to develop a convergent method to prepare enantioenriched pyrroloindolines.

From a design perspective, it was hypothesized that pyrroloindolines (**5**) could be assembled through the union of a C(3)-substituted indole (**1**) and a 2-amidoacrylate (**2**) in what would constitute a formal [3 + 2] cycloaddition reaction (Scheme 1). It was envisioned that the reaction would proceed through a stepwise mechanism in which a Lewis acid activates 2-amidoacrylate **2**, promoting conjugate addition by the indole to give iminium ion **4**. Subsequent intramolecular attack of the nucleophilic amide would provide pyrroloindoline **5**.

The proposed reaction would harness the intrinsic C(3)-nucleophilicity of the indole substrate and, in principle, could provide rapid access to a variety of pyrroloindolines from simple C(3)-substituted indole precursors.^{7,8} Although 2-amidoacrylates are typically poor electrophiles for conjugate addition reactions due to the electron-donating effects of the nitrogen lone pair, Piersanti and co-workers recently reported that EtAlCl₂ promotes the reaction of indole (**1**, R = R¹ = R² = H) and methyl 2-acetamidoacrylate

to provide the C(3)-Friedel–Crafts type product **3** (R = R² = H, R³ = R⁴ = Me, Scheme 1).⁹

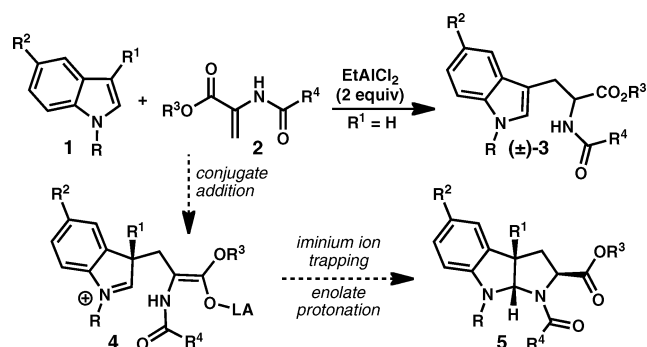
Table 1. Optimization Studies

entry	R ¹ , R ²	pdt	BINOL (equiv)	solvent	yield (%) ^a	d.r. ^b	ee (%) ^{c,d}
1	Me, Me (8)	7a	0.0	DCE	64	6:1	–
2	Me, Me (8)	7a	1.1 ^e	DCE	86	4:1	64/83
3	Me, Me (8)	7a	0.3	DCE	96	5:1	62/81
4	Me, Me (8)	7a	0.2	DCE	94	5:1	63/83
5	Me, Me (8)	7a	0.1	DCE	93	5:1	61/79
6	Me, Me (8)	7a	0.05	DCE	82	5:1	51/72
7	CF ₃ , Me (9)	7b	0.2	DCE	77	6:1	86/nd
8	Me, Bn (10)	7c	0.2	DCE	81	2:1	74/82
9	CF ₃ , Bn (11)	7d	0.2	DCE	81	3:1	91/90
10	CF₃, Bn (11)	7d	0.2	DCM	86	4:1	94/91
11	CF ₃ , Bn (11)	7d	0.2	CHCl ₃	58	3:1	88/89
12	CF ₃ , Bn (11)	7d	0.2	CCl ₄	0	–	–

^a Isolated yield of combined diastereomers. ^b Determined by ¹H NMR analysis of crude reaction mixture. ^c Determined by chiral stationary phase SFC. ^d ee of *exolendo* diastereomers. ^e 1.0 equiv of SnCl₄ was used. nd = not determined.

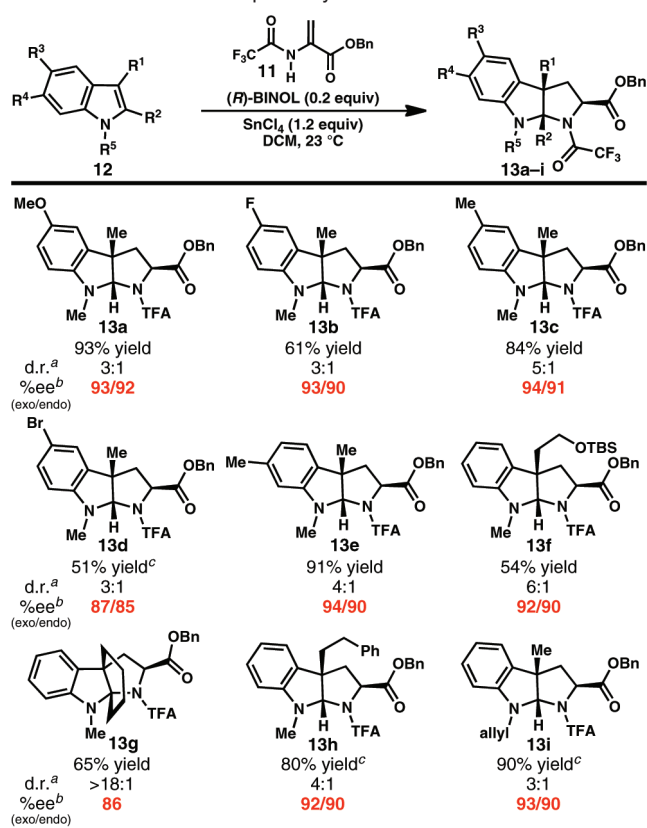
Preliminary experiments were conducted in which equimolar mixtures of commercially available methyl 2-acetamidoacrylate (**8**) and 1,3-dimethylindole (**6**) were exposed to various Lewis acids. We were pleased to find that strong Lewis acids such as EtAlCl₂, TiCl₄, and SnCl₄ provided isolable quantities of the desired pyrroloindoline **7a**, as well as varying amounts of the C(2)-Friedel–Crafts type product analogous to **3** (not shown). After a preliminary survey of reaction parameters, the use of SnCl₄ (1.2 equiv) in dichloroethane at room temperature was found to provide pyrroloindoline **7a** in 64% yield as a 6:1 mixture of *exo* and *endo* diastereomers (Table 1, entry 1; *exo* diastereomer is shown).

At this stage we wished to determine the feasibility of accessing enantioenriched pyrroloindolines using this formal [3 + 2] cycloaddition reaction. To this end, a screen of chiral diol additives anticipated to form chiral Lewis or Brønsted acid complexes with SnCl₄ was conducted.¹⁰ Of the conditions evaluated, it was found that utilization of a 1.1:1 mixture of (*R*)-BINOL and SnCl₄ provided pyrroloindoline **7a** in 86% yield as a 4:1 diastereomeric mixture favoring *exo*-**7a**, which was formed in 64% ee (Table 1, entry 2).^{11,12} Interestingly, the minor, *endo* diastereomer was formed in 83% ee. In follow-up studies, a side-by-side comparison of two reactions varying only by the presence or absence of (*R*)-BINOL

Scheme 1. Proposed Reaction To Prepare Pyrroloindolines

showed that it accelerates the rate of **7a** formation and increases the overall conversion.¹³

Scheme 2. Substrate Scope of Pyrroloindoline Formation



^a Determined by ¹H NMR analysis of mixture. ^b Determined by chiral stationary phase SFC or HPLC. ^c 1.6 equiv of SnCl₄ was employed.

Based on these observations, it was hypothesized that catalytic quantities of (*R*)-BINOL may still provide pyrroloindoline **7a** with good levels of enantioselectivity. Indeed, use of as low as 10 mol % (*R*)-BINOL furnished **7a** without significantly affecting the observed enantioselectivity (Table 1, entries 3–5). Whereas 10 mol % (*R*)-BINOL provided comparable selectivities for the formation of **7a**, 20 mol % (*R*)-BINOL imparted consistently higher enantioselectivities for more functionalized substrates (*vide infra*) and was therefore utilized in subsequent experiments. Control experiments confirmed that no reaction occurred in the absence of SnCl₄ and that 1.2 equiv SnCl₄ were required to drive the reaction to high conversions.¹⁴

In an effort to improve the enantioselectivity of the reaction, the amide and ester groups of the acrylate were modified.^{15,16} An increase in ee was observed when methyl 2-trifluoroacetamidoacrylate (**9**) was employed (Table 1, entry 7). A similar increase was observed using benzyl 2-acetamidoacrylate (**10**, entry 8). Gratifyingly, these effects proved to be additive: use of benzyl 2-trifluoroacetamidoacrylate (**11**) provided pyrroloindoline **7d** in 81% yield and 91% ee. Preliminary studies indicated that chlorinated solvents provided the best combination of yields and selectivities. A further screen identified methylene chloride as the solvent of choice. Under our optimized conditions, pyrroloindoline **7d** was isolated in 86% yield as a 4:1 mixture of *exo* and *endo* diastereomers, which are formed in 94% and 91% ee, respectively (entry 10).¹⁷

Having identified conditions to prepare **7d** in high yields and enantioselectivities, a survey of indole substrates was conducted. Substrates substituted at C(5) with electron-donating and electron-

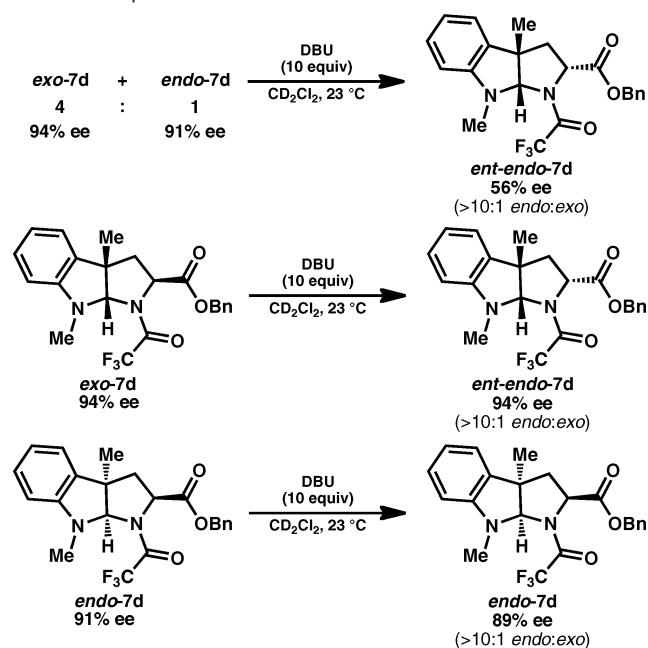
withdrawing substituents provided uniformly high ee's, although a moderate decrease in yield was observed with electron-poor substrates (Scheme 2, **13a–d**). 1,3,6-Trimethylindole reacts smoothly to give a 4:1 mixture of *exo*- and *endo*-**13e** in 91% yield (94% and 90% ee, respectively).

More functionalized substituents are also tolerated at C(3) of the indole substrate. Pyrroloindolines bearing *tert*-butyldimethylsiloxyethyl (**13f**) and phenylethyl (**13h**) substituents are prepared in moderate to good yield and high enantioselectivity (Scheme 2). Most notably, use of *N*-methyl-1,2,3,4-tetrahydrocarbazole provided a single diastereomer of pyrroloindoline **13g** in 65% yield and 86% ee. Using this reaction, the aza-propellane core of natural products such as vincorine¹⁸ and minfiensine¹⁹ was prepared in only two steps from commercially available 1,2,3,4-tetrahydrocarbazole.

Whereas the *exo* diastereomer predominates in the (*R*)-BINOL•SnCl₄-catalyzed formation of the pyrroloindolines shown in Scheme 2, it is known that the *endo* diastereomer of similar compounds is favored thermodynamically.^{20,21} Accordingly, treatment of a 4:1 mixture of *exo*-**7d** and *endo*-**7d** diastereomers (94% and 91% ee, respectively) with excess DBU in CD₂Cl₂ resulted in epimerization to give a greater than 10:1 *endo/exo* mixture of products after 72 h (Scheme 3). Interestingly, the *endo*-**7d** product was recovered in 56% ee, favoring the opposite enantiomer.²² In a subsequent experiment, exposure of diastereomerically pure *exo*-**7d** to DBU (10 equiv) provided *ent-endo*-**7d** in 94% ee. Exposure of diastereomerically pure *endo*-**7d** to the epimerization conditions returned *endo*-**7d** without significant erosion of enantiomeric excess. Taken together, these studies suggest that the initially formed *exo* and *endo* diastereomers of **7d** must be of opposite enantiomeric series. From a synthetic perspective, the diastereomers can be separated prior to subsequent functionalization to avoid erosion of optical activity through this epimerization mechanism.

At this time the mechanism of the reaction remains to be elucidated. As *exo*- and *endo*-**7d** have opposite configurations at C(3), analysis of the diastereomeric and enantiomeric ratios suggests that the first step of the reaction (conjugate addition) occurs with modest levels of catalyst control, whereas the enolate protonation step occurs with high levels of catalyst control.²³ In effect, the catalyst-controlled protonation step serves to resolve the mixture

Scheme 3. Epimerization Studies



of enantiomeric intermediates. Yamamoto and co-workers have demonstrated that BINOL•SnCl₄ behaves as a Lewis acid assisted Brønsted acid that promotes a number of enantioselective protonation reactions.^{11a–b} It is unusual, however, for high enantioselectivities to be observed when employing an excess of SnCl₄ relative to BINOL. The observation that at least 1 equiv of SnCl₄ is required for high conversions, coupled with the fact that use of strong Brønsted acids²⁴ in the absence of SnCl₄ fails to provide **7d**, may suggest that this reaction benefits from cooperative Lewis acid–Brønsted acid activation.

In conclusion, a convergent method to prepare enantioenriched pyrroloindolines is described. The optimal conditions employ (*R*)-BINOL as a catalyst in the presence of stoichiometric SnCl₄ and provide access to functionalized pyrroloindolines in uniformly high ee's. The application of this methodology to the total synthesis of pyrroloindoline natural products and studies aimed at understanding the mechanism of this new transformation are the focus of ongoing research in our laboratory.²⁵

Acknowledgment. We thank Dr. Scott Virgil for insightful discussions; Drs. Michael Day and Larry Henling for X-ray crystallographic structural determination; and Prof. Brian Stoltz and the Caltech Center for Catalysis and Chemical Synthesis for access to analytical equipment. HRMS and X-ray crystallographic data were obtained on instruments purchased through awards to the California Institute of Technology by the NSF CRIF program (CHE-0639094, CHE-0541745). NMR spectra were obtained on a spectrometer funded by the NIH (RR027690). Financial support from the California Institute of Technology and the Baxter Foundation is gratefully acknowledged.

Supporting Information Available: Experimental details, characterization data, and NMR spectral charts. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (15) Acrylates **9**, **10**, and **11** are prepared in one step from the commercially available materials. See Supporting Information for details.
- (16) A small screen of BINOL derivatives was also conducted, in which several 3,3'-difunctionalized-(*R*)-BINOL catalysts were found to provide diminished rates and selectivities.
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- (22) As determined by chiral stationary phase SFC. See Supporting Information for details.
- (23) A reversible, nonselective conjugate addition followed by a moderately diastereoselective cyclization cannot be ruled out at this time. Diastereomerically pure solutions of *endo-7d* or *exo-7d* do not equilibrate upon re-exposure to SnCl₄ (1.2 equiv) and (*R*)-BINOL (0.2 equiv) in CD₂Cl₂.
- (24) For example, use of HCl (1.2 equiv) or diphenylphosphate (1.2 equiv) failed to promote the formal [3 + 2] reaction.
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