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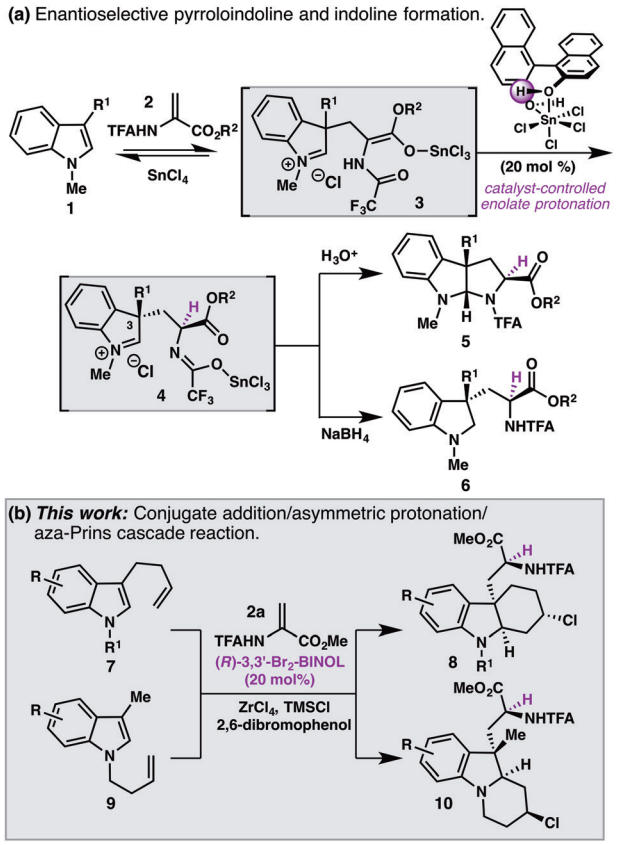
Synthesis of Enantioenriched Indolines by a Conjugate Addition/Asymmetric Protonation/Aza-Prins Cascade Reaction

*Blake E. Daniels[+], Jane Ni[+], and Sarah E. Reisman**

Abstract: *A conjugate addition/asymmetric protonation/aza-Prins cascade reaction has been developed for the enantioselective synthesis of fused polycyclic indolines. A catalyst system generated from $ZrCl_4$ and 3,3′-dibromo-BINOL enables the synthesis of a range of polycyclic indolines in good yields and with high enantioselectivity. A key finding is the use of TMSCl and 2,6-dibromophenol as a stoichiometric source of HCl to facilitate catalyst turnover. This transformation is the first in which a $ZrCl_4$·BINOL complex serves as a chiral Lewis-acid-assisted Brønsted acid.*

Cascade reactions, in which a single substrate undergoes a series of chemical transformations, provide rapid access to molecular complexity.[1] Many beautiful examples of cascade reactions have emerged from total synthesis endeavors, both in the context of biomimetic and de novo synthetic strategies.[2] More recently, attention has turned to developing cascade reactions involving asymmetric catalysis, which can convert simple, achiral starting materials into complex products with control over both the absolute and relative stereochemistry.[3] These transformations powerfully merge the attributes of asymmetric catalysis and cascade reactions for the synthesis of stereochemically rich small molecules.

In 2010, we reported a new method to prepare enantioenriched pyrroloindolines (**5**) from C3-substituted indoles (**1**) and 2-amidoacrylates (**2**) using $SnCl_4$ and catalytic (*R*)-BINOL (**L1**; Scheme 1 a).[4,5] Mechanistic investigations suggest that this reaction proceeds by a reversible conjugate addition of **1** to **2**, followed by a highly selective, catalyst-controlled protonation of the enolate **3**, in which a $SnCl_4$·**L1** complex serves as a chiral Lewis-acid-assisted Brønsted acid (LBA).[6] Subsequent studies in our group determined that the persistent indolinium ion **4** can be trapped with hydride to provide direct access to the corresponding indoline **6**.[7] Recognizing that iminium ions such as **4** can serve as electrophiles for C–C bond formation, we sought to develop an enantioselective cascade reaction that would terminate with an aza-Prins cyclization.[8,9] Herein we report the successful realization of this concept, and it has resulted in a direct synthesis of complex polycyclic indolines in a single step from simple indole derivatives (Scheme 1 b).



Scheme 1. Tandem conjugate addition/asymmetric protonation reactions of indoles. BINOL = 2,2′-dihydroxy-1,1′-binaphthyl, TFA = trifluoroacetyl, TMS = trimethylsilyl.

We began our studies with 3-(but-3-en-1-yl)-1-methylindole (**7a**), a substrate in which the pendant alkene is poised to undergo intramolecular attack to form a six-membered ring (Table 1). Exposure of a mixture of **7a** and the amidoacrylate **2a** to $SnCl_4$ (1.2 equiv) and (*R*)-BINOL (**L1**, 20 mol %)—the standard reaction conditions developed for the previously reported pyrroloindoline formation[4]—provided the hexahydrocarbazoles **8a** and **8a′** in low yield but with promising levels of diastereo- and enantioselection (entry 1). Presumably **8** arises from a conjugate addition/asymmetric protonation/aza-Prins cyclization cascade, with chloride trapping of the resulting carbocation. A screen of additional Lewis acids revealed that $ZrCl_4$ provides a slightly higher yield of **8**, although the major diastereomer (**8a**) was produced with a lower *ee* value. Notably, $Zr(OtBu)_4$ and

[*] B. E. Daniels,[+] J. Ni,[+] Prof. S. E. Reisman
The Warren and Katharine Schlinger Laboratory of Chemistry and Chemical Engineering, Division of Chemistry and Chemical-Engineering, California Institute of Technology
Pasadena, CA 91125 (USA)
E-mail: reisman@caltech.edu
Homepage: http://reismangroup.caltech.edu
[+] These authors contributed equally to this work.

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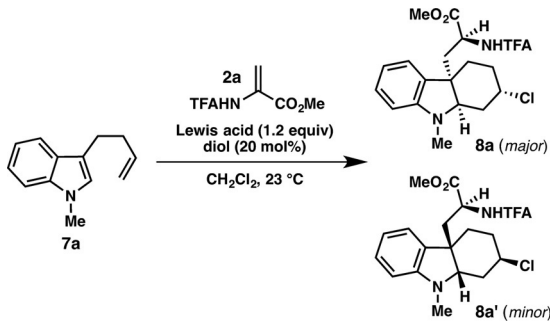
Table 1: Reaction optimization: Lewis acid and chiral diol screen.[a]



Entry	Lewis acid	Diol	**8** Yield [%][b]	d.r.	**8a** *ee* [%][c]
1	$SnCl_4$	(*R*)-BINOL (**L1**)	19	10:1	88
2	$TiCl_4$	(*R*)-BINOL	27	6:1	0
3	$SbCl_5$	(*R*)-BINOL	0	–	–
4	$ZrCl_4$	(*R*)-BINOL	30	9:1	40
5	$Zr(OtBu)_4$	(*R*)-BINOL	0	–	–
6	$ZrCl_4$	(*R*)-6,6′-dibromo-BINOL (**L2**)	38	9:1	30
7	$ZrCl_4$	(*R*)-3,3′-dibromo-BINOL (**L3**)	40	7:1	76
8	$ZrCl_4$	(*S*)-VANOL (**L4**)	33	6:1	74
9	$ZrCl_4$	(4*R*, 5*R*)-Ph-TADDOL (**L5**)	37	>10:1	66

[a] Reactions conducted with 0.20 mmol **7a** and 0.24 mmol **2a**.
[b] Combined yield of the two isolated diastereomers. [c] The *ee* value of the major diastereomer was determined by SFC using a chiral stationary phase. TADDOL = α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol, VANOL = 3,3′-diphenyl-2,2′-bi-1-naphthol.

related metal alkoxides failed to catalyze the reaction.[10] A further survey of alternate chiral diols in combination with $ZrCl_4$ determined that (*R*)-3,3′-dibromo-BINOL (**L3**) delivers the hexahydrocarbazole **8** in 40% yield and 7:1 d.r.; **8a** was formed with 76% *ee* (entry 7).

We hypothesized that the modest yields of **8** might result from poor catalyst turnover because of incorporation of chloride into the product. As illustrated by the simplified catalytic cycle in Figure 1 (conjugate addition step is not shown), upon protonation of the Zr-enolate **12** with $ZrCl_4$·**L3**, the indolinium ion **13** and complex **11** are formed. To regenerate the active catalyst, $ZrCl_4$·**L3**, an equivalent of HCl must be added to **11**. Since chloride from the catalyst is captured in the aza-Prins step, we suspected that this might inhibit the regeneration of $ZrCl_4$·**L3**. Guided by the pioneering studies of Yamamoto and co-workers on the chiral LBA-catalyzed protonation of silyl enol ethers,[6a,b] we hypothesized that the combination of a silyl chloride and achiral phenol could serve as our stoichiometric source of HCl. To maintain high enantio- and diastereoselectivity in the reaction, it would be necessary to identify a phenol that would not promote a nonselective, background protonation of the enolate.

To test this hypothesis, a variety of phenols and silyl chlorides were investigated for their ability to improve the yield and selectivity of the reaction. The addition of simple, achiral phenols, in the absence of silyl chloride, improved the yields in some cases, but did not increase the enantioselectivity of the transformation (Table 2, entry 3). However, we

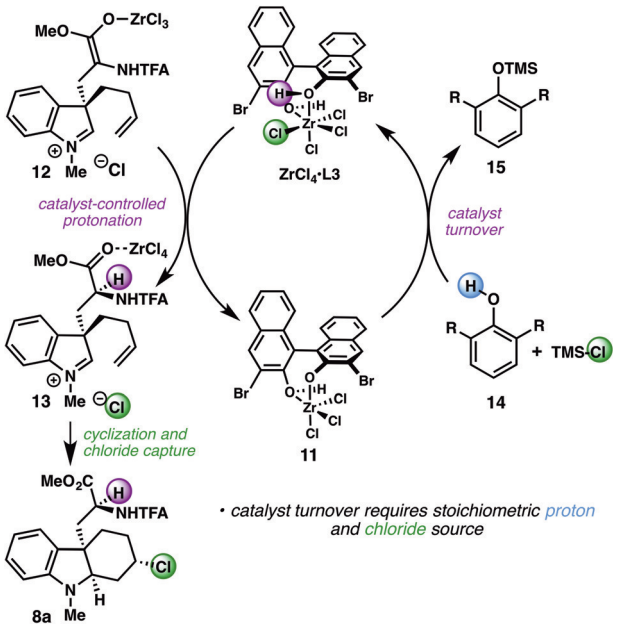
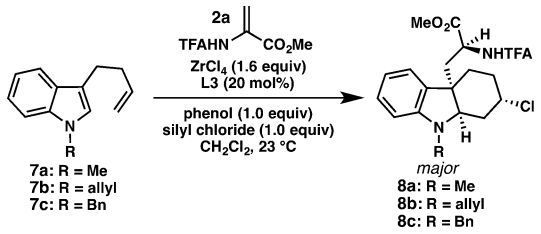


Figure 1. Proposed catalytic cycle (conjugate addition is omitted for simplicity).

Table 2: Reaction optimization: achiral phenol and silyl chloride screen.[a]



Entry	R	Phenol	Silyl chloride	Yield [%][b]	**8** *ee* [%][c]
1	Me	–	–	30	40
2	Me	phenol	–	33	35
3	Me	2,6-dimethylphenol	–	66	19
4	Me	2,6-dimethylphenol	TMSCl	72	50
5	Me	2,6-dimethylphenol	TBSCl	68	44
6	Me	2,6-dichloro-4-methylphenol	TMSCl	84	87
7	Me	2,6-dibromophenol	TMSCl	56	86
8	Allyl	2,6-dichloro-4-methylphenol	TMSCl	75	86
9	Allyl	2,6-dibromophenol	TMSCl	70	90
10	Bn	2,6-dichloro-4-methylphenol	TMSCl	74	85
11	Bn	2,6-dibromophenol	TMSCl	82[d]	86

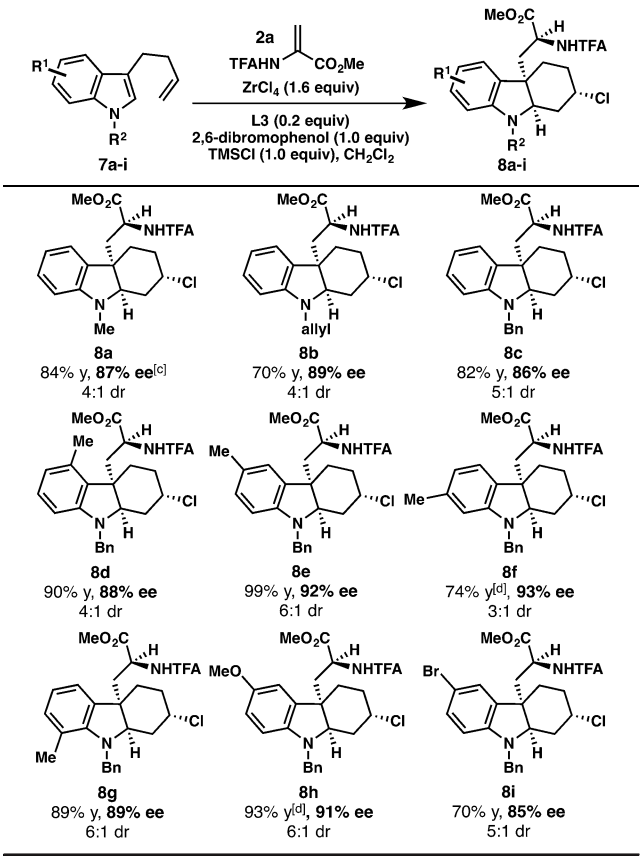
[a] Reactions conducted with 0.20 mmol **7a** and 0.24 mmol **2a**.
[b] Combined yield of two isolated diastereomers. [c] The *ee* value of major diastereomer was determined by SFC using chiral stationary phase. [d] Product formed as 5:1 mixture of **8c**/**8c′**.

were pleased to find that the combination of 2,6-disubstituted phenols and TMSCl improved both the yield and enantioselectivity of the reaction (entry 4). In general, 2,6-dihalogen-

ated phenols provided the highest combination of yield and selectivity. For the N-methyl substrate **7a**, the most synthetically useful results were obtained with 2,6-dichloro-4-methylphenol, which provided **8a** in 84% yield and 87% *ee* (entry 6). However, for substrates with slightly larger protecting groups on the indole nitrogen atom, superior results were obtained with 2,6-dibromophenol (entries 8–11). For example, with the N-benzyl substrate **7c**, the hexahydrocarbazole **8c** is obtained in 82% yield, 5:1 d.r., and 86% *ee* (major diastereomer) when 2,6-dibromophenol is used as the stoichiometric proton source (entry 11). To the best of our knowledge, this is the first example of a chiral diol·$ZrCl_4$ complex acting as a chiral Lewis-acid-assisted Brønsted acid catalyst for a highly enantioselective reaction.[10]

A series of 3-(but-3-en-1-yl)indoles were prepared and evaluated in the conjugate addition/asymmetric protonation/aza-Prins cascade reaction (Table 3). This transformation tolerates a range of indole substitutions, including substituents at C4, C5, C6, and C7. Although the reaction is compatible with halogenated indoles (e.g., **8i**), substrates bearing more electron-withdrawing functional groups are less reactive, thus providing products in lower yield.[11]

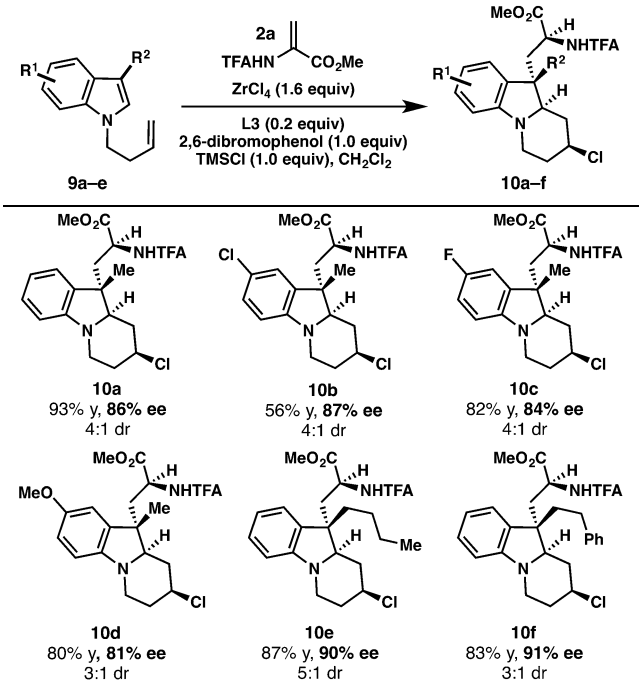
Table 3: Substrate scope of 3-(but-3-en-1-yl)-indoles.[a,b]



[a] Reactions conducted with 0.20 mmol **7** and 0.24 mmol **2a**. [b] Combined yield of the two isolated diastereomers. The d.r. value was determined by integration of the α-amino ester peaks in the ^{1}H NMR spectrum of the unpurified reaction mixture. The *ee* value of the major diastereomer is reported, and was determined by SFC using a chiral stationary phase. [c] 2,6-dichloro-4-methylphenol was used instead of 2,6-dibromophenol. [d] 1.1 equiv of $ZrCl_4$ was used.

Substrates in which the pendant alkene is linked through the indole nitrogen atom also undergo the cascade reaction (Table 4). Notably, a substrate bearing a tethered aryl nucleophile at C3 undergoes cyclization exclusively by the alkene, and no product resulting from attack of the arene at the iminium ion can be detected.

Table 4: Substrate scope of 1-(but-3-en-1-yl)-indoles.[a,b]



[a] Reactions conducted with 0.20 mmol **9** and 0.24 mmol **2a**. [b] Combined yield of the two isolated diastereomers. The d.r. value was determined by integration of the α-amino ester peaks in the ^{1}H NMR spectrum of the unpurified reaction mixture. The *ee* value of the major diastereomer is reported, and was determined by SFC using chiral stationary phase.

The stereochemical assignments of **8c** and **10b** were confirmed by single-crystal X-ray diffraction.[12] Treatment of diastereomerically pure **8c** with DBU in CD_2Cl_2 at room temperature results in equilibration to a 1.9:1 mixture of the diastereomers **8c** and *ent*-**8c′** (Figure 2a). Analysis by SFC using a chiral stationary phase confirmed that *ent*-**8c′**, resulting from epimerization, is the enantiomer of the minor diastereomer produced directly in the conjugate addition/asymmetric protonation/aza-Prins cyclization. This finding is consistent with the catalyst-controlled protonation mechanism proposed in Figure 1.

To probe the reversibility of the initial conjugate addition step, the deuterium-labelled acrylate [D](*Z*)-**2a** was prepared (Figure 2b). The reaction between **7c** and [D](*Z*)-**2a** was conducted under standard reaction conditions, and stopped after 30 minutes. The recovered acrylate was a 1:1 mixture of *Z* and *E* isomers. A control experiment determined that [D](*Z*)-**2a** does not isomerize in the absence of indole under otherwise identical reaction conditions. These findings support a mechanism involving a reversible conjugate addition,

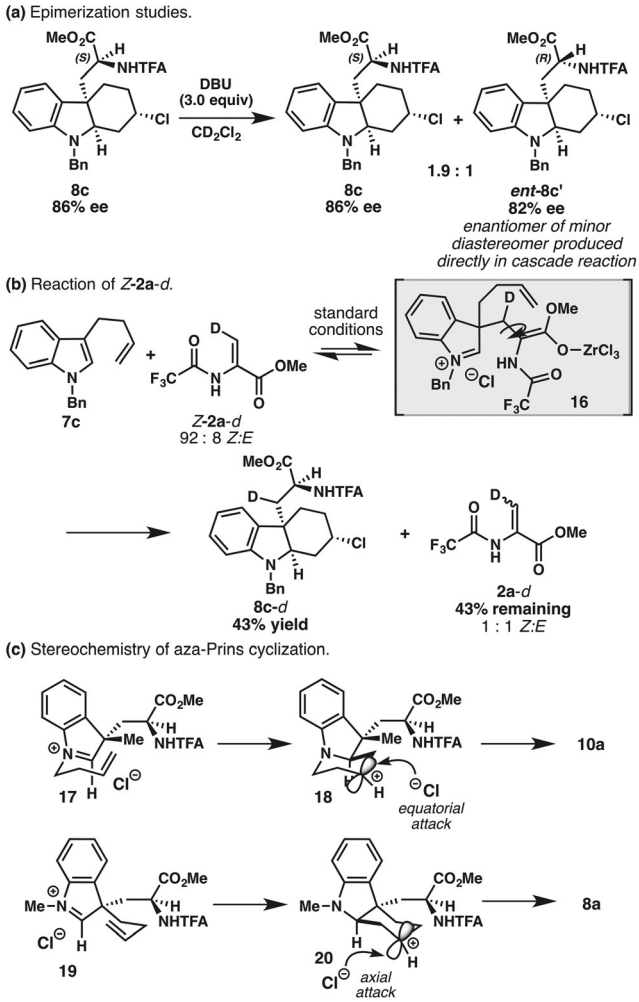


Figure 2. Mechanistic investigations of the conjugate addition/asymmetric protonation/aza-Prins cyclization. Standard reaction conditions: **7c** (1.0 equiv), [D](*Z*)-**2a** (1.0 equiv), (*R*)-3,3′-dibromo-BINOL (20 mol %), $ZrCl_4$ (1.6 equiv), 2,6-dibromophenol (1.0 equiv), TMSCl (1.0 equiv), CH_2Cl_2, 23 °C. DBU = 1,8-diazabicyclo[5-4-0]undec-7-ene.

which enables the isomerization of [D](*Z*)-**2a** by rotation around the C–C bond of the intermediate **16**.

It is also interesting to note the divergence in the stereochemical outcome of the aza-Prins cyclizations of the C3- and N-linked substrates (**8** and **10**, respectively). For the polycyclic indoline **10**, the configuration at the chlorine-bearing carbon atom results from equatorial trapping of the carbocation **18** (Figure 2c), and is consistent with a process that is driven by orbital alignment.[13,14] In contrast, the configuration at the chlorine-bearing carbon atom of **8** results from cyclization through an anti-periplanar arrangement between the alkene and iminium ion (**19**), followed by axial trapping of **20** by chloride. This diastereoselection is opposite to that observed by Hanessian and co-workers in their studies of aza-Prins reactions of structurally similar N-acyloxy iminium ions.[14] However, Rychnovsky and co-workers have reported that TMSBr-mediated oxonia-Prins reactions of α-bromoethers result in axial trapping.[15] In the present case, the origin of the axial-selective trapping is unclear.[16]

In conclusion, a conjugate addition/asymmetric protonation/aza-Prins cyclization reaction to prepare enantioenriched indolines has been developed. This reaction provides direct access to functionalized heterocyclic products in a single step from simple indole derivatives, and is the first example of a transformation in which a $ZrCl_4$·BINOL complex serves as a chiral LBA. This transformation demonstrates the utility of asymmetric cascade catalysis for rapidly generating molecules of complexity.

Experimental Section

General procedure for the conjugate addition/asymmetric protonation/Prins cyclization cascade: To a flame-dried flask were added indole (0.20 mmol, 1.00 equiv), acrylate (0.24 mmol, 1.20 equiv), (*R*)-3,3′-dibromo-BINOL (0.04 mmol, 0.20 equiv), and 2,6-dibromophenol (0.20 mmol, 1.00 equiv) under an N_2 atmosphere. The flask was charged with CH_2Cl_2 (1.5 mL), followed by addition of TMSCl (0.2 mmol, 1.00 equiv) and $ZrCl_4$ (0.32 mmol, 1.60 equiv unless specifically indicated). The mixture was stirred at room temperature for 24 h. The reaction was quenched by diluting with 1 mL MeCN and 1 mL 1M HCl, followed by addition of 5 mL H_2O. The aqueous layer was extracted with ethyl acetate (3 × 5 mL) and the combined organic layers were washed with saturated $NaHCO_{3(aq)}$ (10 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 crude residue was purified by silica gel chromatography.

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[16] It is possible that in the cyclization of **8**, the chloride trapping is directed by the pendant amide through coordination to zirconium. However, this requires a transition structure with an unusually large ring size.

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