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Titanium(IV)-Catalyzed Stereoselective Synthesis of Spirooxindole-1-pyrrolines

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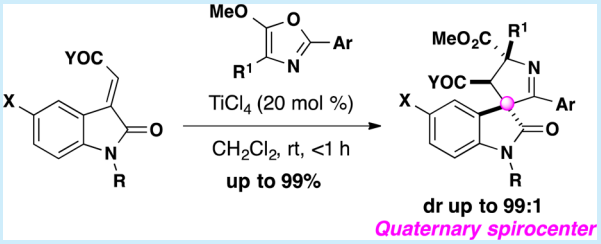
Supporting Information

ABSTRACT: A stereoselective cyclization between alkylidene oxindoles and 5-methoxyoxazoles has been developed using catalytic titanium(IV) chloride (as low as 5 mol %) to afford spiro[3,3′-oxindole-1-pyrrolines] in excellent yield (up to 99%) and diastereoselectivity (up to 99:1). Using a chiral scandium(III)−indapybox/BArF complex affords enantioenriched spirooxindole-1-pyrrolines where a ligand-induced reversal of diastereoselectivity is observed. This methodology is further demonstrated for the synthesis of pyrrolines from malonate alkylidene and coumarin derivatives.



Heterocyclic spirooxindoles are prevalent in natural products and exhibit important biological activity.[1] Although methods have been reported to access nitrogen-containing spirooxindole heterocycles, there are few one-step transformations that provide access to 3′-nitrogen-containing structures,[2] which are found in many bioactive molecules (Figure 1).[3]

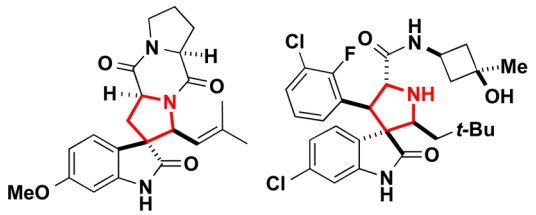
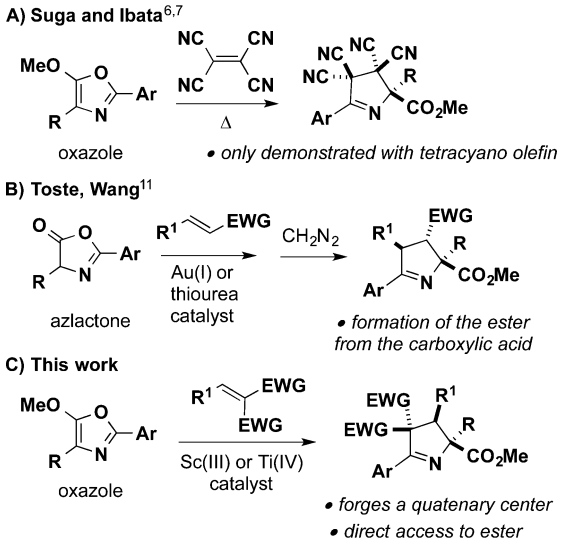


Figure 1. Representative biologically active spirooxindole natural products and druglike molecules.

Our laboratory has recently shown that 5-methoxy-2-aryloxazoles cyclize onto isatins to form spirooxindole oxazolines in excellent yields and high diastereoselectivity.[4,5] In an early pioneering example, Suga and Ibata demonstrated that 5-methoxy-2-aryloxazoles undergo a formal [3 + 2]-cycloaddition with tetracyanoethylene to give 1-pyrroline derivatives (Scheme 1A).[6,7] Despite these early reports, this transformation and its application to other α,β-unsaturated systems have been limited.[8−10] Alternatively, the Toste and Wang groups have shown that azlactones undergo a 1,3-dipolar cycloaddition with electron-deficient alkenes to form 1-pyrrolines using gold(I) and thiourea catalysis, respectively (Scheme 1B).[11] Here, we report a

Scheme 1. Oxazole and Azlactone Additions to Electron-Deficient Alkenes To Form 1-Pyrrolines



Lewis acid catalyzed method for the stereoselective synthesis of spiro[3,3′-oxindole-1-pyrrolines] upon addition of 5-methoxy-2-aryloxazoles to alkylidene oxindoles (Scheme 1C). We also demonstrate this methodology for the synthesis of pyrrolines derived from malonate alkylidenes and coumarins.

We recognized that Lewis acid activation of chelating *N*-acylalkylidene **1a** would provide a rigid platform for the formal [3 + 2] cycloaddition reaction to access spirooxindoles.[12] Employ-

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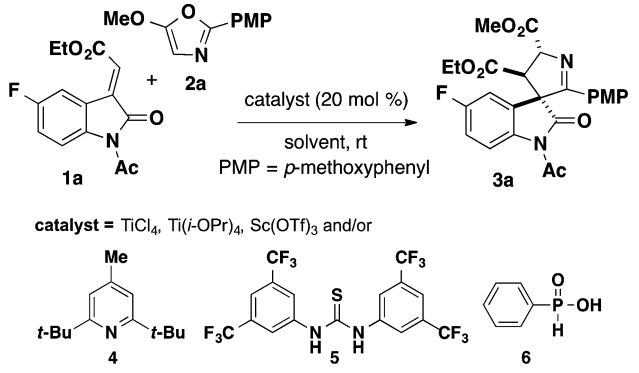
ing 20 mol % of titanium(IV) tetrachloride catalyzed the addition of 5-methoxy-2-(4-methoxyphenyl)oxazole (**2a**) to afford spiro-1-pyrroline **3a** in 90% yield with 91:9 diastereoselectivity (Table 1, entry 2). Comparing dichloromethane and toluene demonstrated that using dichloromethane is optimal; using toluene resulted in a significant decrease in reactivity (Table 1, entry 2 vs 3). Using 5 mol % of catalyst loading maintained the high yield and diastereoselectivity with only a minimal increase in reaction time, even on gram scale (Table 1, entries 4 and 5). A control experiment performed with the addition 2,6-di-*tert*-butyl-4-methylpyridine (**4**) as a proton scavenger supports Lewis acid activation of oxindole **1a** (Table 1, entry 6), but the reduced reaction rate suggests that protic acid may enhance catalyst turnover. In comparison, titanium(IV) isopropoxide was ineffective in catalyzing the reaction, and significant deacylation was observed (Table 1, entry 7). Scandium(III) triflate also afforded **3a** with excellent yield and diastereoselectivity (Table 1, entry 8). The relative stereochemistry of **3a** was unambiguously determined by X-ray crystallographic analysis.

Table 1. Optimization for Addition of 5-Methoxyoxazole 2a to Alkylidene Oxindole 1a[a]



entry	catalyst	solvent	time	dr[b]	% yield[c]
1	none	CH_2Cl_2	5 d		0
2	$TiCl_4$	CH_2Cl_2	10 min	91:9	90
3	$TiCl_4$	$PhCH_3$	3 d	88:12	50[d]
4[e]	$TiCl_4$	CH_2Cl_2	45 min	91:9	99
5[e,f]	$TiCl_4$	CH_2Cl_2	45 min	90:10	87
6[g]	$TiCl_4$ + **4**	CH_2Cl_2	48 h	90:10	98[d]
7[h]	$Ti(Oi\text{-}Pr)_4$	CH_2Cl_2	24 h		0
8[e]	$Sc(OTf)_3$	CH_2Cl_2	5 h	90:10	99[d]
9	**5**	CH_2Cl_2	5 d		0
10	**6**	CH_2Cl_2	5 d		0
11	K-10	CH_2Cl_2	7 d	50:50	<25[d]

[a]Reactions performed with 1.5 equiv of alkylidene under argon. [b]Diastereomeric ratio determined using ^{1}H NMR analysis of unpurified reaction mixture and reported as major plus sum of minor isomers. Diastereomers are inseparable by column chromatography. [c]Isolated yield. [d]Conversion determined using ^{1}H NMR spectroscopy. [e]Run with 5 mol % of catalyst. [f]Run on 2.7 mmol scale. [g]Run with 10 mol % of **4**. [h]Significant deacylation observed.

Brønsted acid catalysts such as 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea (**5**) and phenylphosphinic acid (**6**) failed to promote reactivity (Table 1, entries 9 and 10).[13] We also investigated the use of montmorillonite K-10, which was recently shown by our group to be an effective heterogeneous catalyst for the addition of crotylsilanes to iminoxindoles;[14,15] however, K-10 provided poor catalytic activity and diastereoselectivity for this transformation (Table 1, entry 11).

With efficient conditions in hand, we proceeded to investigate the scope of oxazole additions to α,β-unsaturated alkylidene oxindoles (Figure 2). Ester-substituted alkylidenes work with a variety of 2-aryl-substituted oxazoles including 2-phenyl- and 2-(4-bromophenyl)oxazoles **3b** and **3c**. Reactions with the *N*-Cbz-protected and ketone-substituted alkylidenes both proceed with excellent diastereoselectivity and yield (**3d** and **3e**). A chelating group on nitrogen is essential for selectivity; as expected, the *N*-methyl-substituted alkylidene proceeds with low selectivity (**3f**). Substitution at the 4-position of the oxazole (4-methyloxazole) provides access to methyl-substituted spiro-1-pyrroline **3g**, containing two stereogenic quaternary centers, with high diastereoselectivity.[16] In the case of the 4-isopropyloxazole (not shown) the isomers proved difficult to separate by column chromatography.[17] The acyl group can be readily removed to reveal the free NH oxindole **7** using conditions with base and hydrogen peroxide.[18]

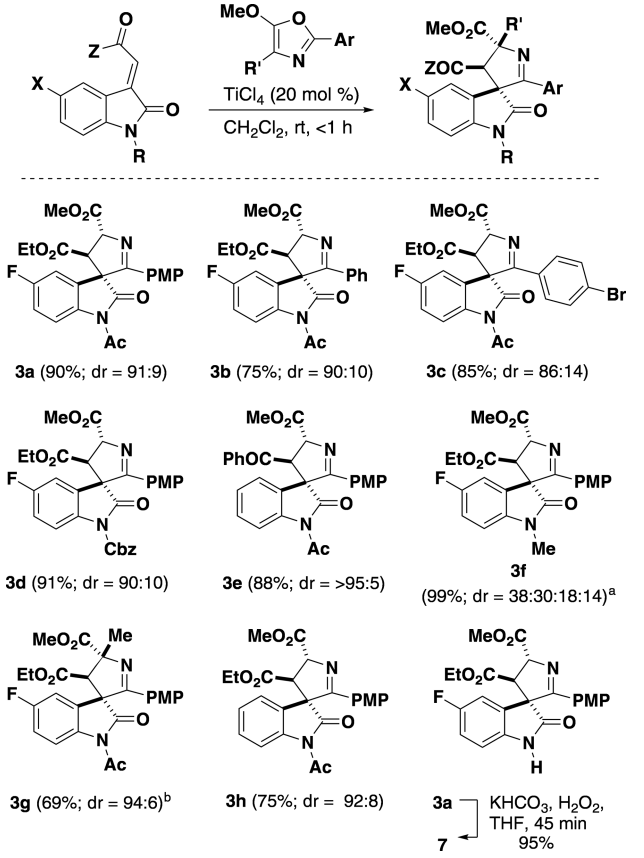


Figure 2. Scope of spirooxindole-1-pyrrolines. Reactions run with 20 mol % of $TiCl_4$ and 1.5 equiv of alkylidene under argon. Diastereomeric ratio determined using ^{1}H NMR analysis of the unpurified reaction mixture and reported as major vs sum of minor isomers. (a) Conversion determined using ^{1}H NMR spectroscopy. (b) Diastereoselectivity based on purified material.

We also demonstrated this methodology for the cyclization of malonate[19] **8** and coumarin[20,10] **10** electrophiles to access densely functionalized pyrrolines **9** and **11** (Scheme 2). The synthesis of pyrroline **9** proceeded with high yield; however, 1 equiv of $TiCl_4$ was required and an erosion of diastereoselectivity was observed for this substrate (Scheme 2, eq 1).[21] The synthesis of 1-pyrroline **11** proceeds in high yield and good diastereoselectivity (80:20) (Scheme 2, eq 2). The relative stereo-

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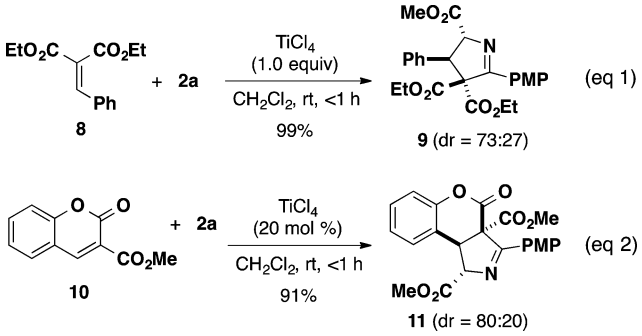
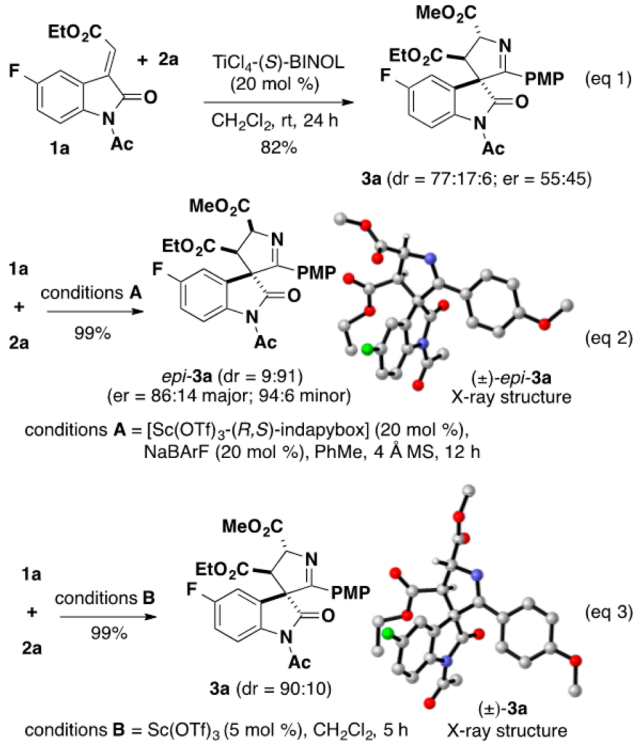
Scheme 2. Cyclization with Malonate and Coumarin Electrophiles



chemistry of pyrroline **11** was unambiguously determined by X-ray crystallographic analysis.

We examined several conditions for an asymmetric synthesis of spirooxindole-1-pyrrolines (Scheme 3, eqs 1 and 2). Initial

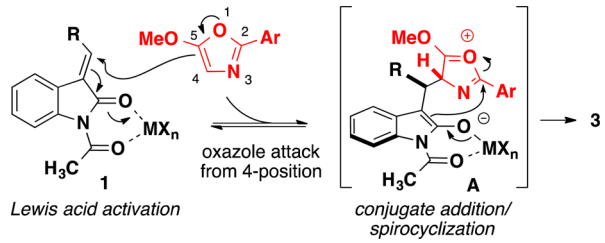
Scheme 3. Synthesis of Enantioenriched Pyrroline *epi*-3a and Ligand-Induced Reversal of Diastereoselectivity



attempts to induce asymmetry using a chiral Ti(IV)−(*S*)-BINOL complex resulted in reduced diastereoselectivity and no enantioselectivity (Scheme 3, eq 1).[22] Using Lewis acidic metals (e.g., Mg, Zn, and Cu) in combination with (*S*)-Ph-bisoxazoline provided low yields and no enantioselectivity. Next, we investigated several chiral Sc(III) complexes for the reaction of 5-methoxy-2-aryloxazoles with α,β-unsaturated alkylidene oxindoles. We have recently shown that Sc(III)−indapybox complexes effectively catalyze nucleophilic addition and annulation reactions with high levels of enantioselectivity.[23−25] We were pleased to determine that using $Sc(OTf)_3$, (*R*,*S*)-indapybox, and NaBArF in toluene afforded pyrroline product in high yield with 86:14 er (conditions A) (Scheme 3, eq 2). The use of sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BArF) to promote formation of a cationic scandium complex proved to be essential for enhancing the reaction rate in the presence of ligand. It was notable that these conditions afford a reversal in the diastereoinduction to afford pyrroline *epi*-**3a** (dr = 91:9) with the 4,5-*syn* isomer as the major product. The relative stereochemistry of *epi*-**3a** was determined by X-ray crystallographic analysis.[26] The reversal in diastereoselectivity is directly attributed to the addition of the ligand because the Sc-catalyzed reaction in the absence of ligand (conditions B) (Scheme 3, eq 3) still affords **3a** with high 4,5-*anti* diastereoselectivity.

A proposed mechanism for the formation of **3** (in the absence of a chiral ligand) is shown in Scheme 4. Lewis acid activation of

Scheme 4. Proposed Mechanism for Lewis Acid Catalyzed Formation of 3a



alkylidene **1** followed by oxazole conjugate addition would give rise to enolate-bound oxocarbenium intermediate **A**. Subsequent cyclization and oxazole ring opening affords spirocycle **3**.[27,28]

In conclusion, we have developed methodology for the synthesis of a new class of spirocyclic oxindole 1-pyrrolines upon cyclization of 5-alkoxy-2-aryloxazoles to alkylidene oxindoles. This strategy forges a quaternary spirocenter with excellent levels of stereocontrol. Using a chiral scandium(III)−indapybox/BArF complex provides efficient access to enantioenriched spiro-1-pyrrolines, and the addition of the ligand reverses the diastereoselection relative to conditions performed without the ligand for either the $Sc(OTf)_3$ or $TiCl_4$ catalyst. Furthermore, we demonstrate that this methodology can be extended to other α,β-unsaturated systems such as malonate alkylidenes and coumarins. Efforts to optimize the enantioselectivity and control diastereoselectivity are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data for all new compounds, including X-ray crystal structures for **3a**, *epi*-**3a**, and **11**. 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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BD/69258/2010. Julia Jennings (UCD) is acknowledged for technical assistance.

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(16) Using the 5-methoxy-2-(4-methoxyphenyl)-4-methyloxazole provided a complex mixture of regio- and diastereomers; however, the major product was readily separable by column chromatography.

(17) Disubstituted alkylidene oxindoles such as diethyl 2-(1-acetyl-2-oxoindolin-3-ylidene)malonate) and 2-(1-acetyl-2-oxoindolin-3-ylidene)malononitrile were determined to be unreactive. Both (*E*)-2-(1-acetyl-2-oxoindolin-3-ylidene)acetonitrile and (*E*)-1-acetyl-3-benzylideneindolin-2-one proceed with little or no selectivity.

(18) See the Supporting Information for standard deprotection conditions.

(19) For examples of Lewis acid activated π-nucleophile additions to alkylidene maolonates, see: (a) Liu, Y.; Shang, D.; Zhou, X.; Liu, X.; Feng, X. *Chem.—Eur. J.* **2009**, *15*, 2055−2058. (b) Wu, J.; Wang, D.; Wu, F.; Wan, B. *J. Org. Chem.* **2013**, *78*, 5611−5617.

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(21) The reaction was sluggish using 20 mol % of $TiCl_4$, and the oxazole is prone to decomposition upon extended exposure to Lewis acids.

(22) For examples of asymmetric Lewis acid−BINOL-derived catalysts for the addition of oxazoles to carbonyl compounds, see: (a) Suga, H.; Ikai, K.; Ibata, T. *J. Org. Chem.* **1999**, *64*, 7040−7047. (b) Suga, H.; Shi, X.; Ibata, T. *J. Org. Chem.* **1993**, *58*, 7397−7405.

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(26) The absolute stereochemistry of the major enantiomer for *epi*-**3a** was assigned by analogy based on the selectivity observed for the addition of allylsilanes to alkylidenes (see ref 25) to be 3*S*,4′*R*,5′*S*. CCDC 1006412−1006414 contain the supplementary crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(27) An alternative mechanism involving a Diels−Alder adduct followed by ring opening could also be operable (see ref 7).

(28) See the Supporting Information for a proposed rationale to explain the ligand-induced reversal of diastereoselectivity.