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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

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

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

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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-diisopropoxynitrobenzene 1bb under argon. Diastereomeric ratio determined using 1H NMR spectroscopy. **F**Run with 5 mol % of catalyst. **G**Run on 2.7 mmol scale. **H**Run with 10 mol % of 4. **I**Significant deacylation observed.

| entry | catalyst | solvent | time  | dr | % yield |
|-------|----------|---------|-------|----|---------|
| 1     | none     | CH₂Cl₂  | 5 d   | 0  | 0       |
| 2     | TiCl₄    | CH₂Cl₂  | 10 min| 91:9| 90      |
| 3     | TiCl₄    | PhCH₂   | 3 d   | 88:12| 50⁶    |
| 4    | TiCl₄    | CH₂Cl₂  | 45 min| 91:9| 99      |
| 5    | TiCl₄    | CH₂Cl₂  | 45 min| 90:10| 87      |
| 6    | TiCl₄ + 4| CH₂Cl₂  | 48 h   | 90:10| 99⁴    |
| 7    | Ti(O-Bu)₃| CH₂Cl₂  | 24 h   | 0   | 0       |
| 8    | Sc(OTf)₃| CH₂Cl₂  | 5 h    | 90:10| 99     |
| 9    | 5        | CH₂Cl₂  | 5 d    | 0  | 0       |
| 10   | 6        | CH₂Cl₂  | 5 d    | 0  | 0       |
| 11   | K-10     | CH₂Cl₂  | 7 d    | 50:50| <25    |

**Reactions performed with 1.5 equiv of alkylidene under argon.**
**Diastereomeric ratio determined using 1H NMR analysis of unpurified reaction mixture and reported as major plus sum of minor isomers. Diastereomers are inseparable by column chromatography.**
**Isolated yield.**
**Conversion determined using 1H NMR spectroscopy.**
**Run with 5 mol % of catalyst.**
**Run on 2.7 mmol scale.**
**Run with 10 mol % of 4.**

With efficient conditions in hand, we proceeded to investigate the scope of oxazole additions to αβ-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. In the case of the 4-isopropyl-oxazole (not shown) the isomers proved difficult to separate by column chromatography. The acyl group can be readily removed to reveal the free NH oxindole 7 using conditions with base and hydrogen peroxide.

We also demonstrated this methodology for the cyclization of malonate and coumarin 10 electrophiles to access densely functionalized pyrrolines 2a and 2b (Scheme 2). The synthesis of pyrroline 2a proceeded with high yield; however, 1 equiv of TiCl₄ was required and an erosion of diastereoselectivity was observed for this substrate (Scheme 2, eq 1). The synthesis of 1-pyrroline 2b proceeds in high yield and good diastereoselectivity (80:20) (Scheme 2, eq 2). The relative stereochemistry of 2a was unambiguously determined by X-ray crystallographic analysis.

![Figure 2. Scope of spirooxindole-1-pyrrolines. Reactions run with 20 mol % of TiCl₄ and 1.5 equiv of alkylidene under argon. Diastereomeric ratio determined using 1H NMR analysis of unpurified reaction mixture and reported as major vs sum of minor isomers. (a) Conversion determined using 1H NMR spectroscopy. (b) Diastereoselectivity based on purified material.](image-url)
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 attempts to induce asymmetry using a chiral Ti(IV)–(S)-BINOL complex resulted in reduced diastereoselectivity and no enantioselectivity (Scheme 3, eq 1). 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. 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 diastereinduction 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. 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 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. 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 TiCl4 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

* S 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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(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-alkylidene-3-ylidene)malonate were determined to be unreactive. Both (S)-2-(1-alkylidene-3-ylidene)malononitrile and (E)-1-alkylidene-3-ylideneindolin-2-one proceeded with little or no selectivity.

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

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