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Titanium-Catalyzed Stereoselective Synthesis of Spirooxindole Oxazolines

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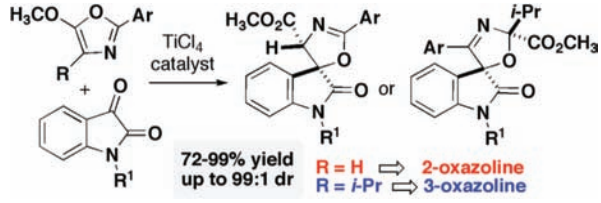
ABSTRACT



A regio- and stereoselective cyclization between isatins and 5-methoxyoxazoles has been developed using catalytic titanium(IV) chloride (10 or 20 mol %) to afford spiro[3,3′-oxindoleoxazolines] in excellent yield (up to 99%) and diastereoselectivity (dr >99:1). Substitution at the 4-position of the oxazole controls nucleophilic attack to provide either the 2-oxazoline or 3-oxazoline spirocycle with excellent (>99:1) regiocontrol.

The efficient and selective construction of complex heterocycles is a continuing challenge for synthetic chemistry. Spirocyclic oxindoles in particular have emerged as attractive synthetic targets because of their prevalence in numerous natural products and important biological activity.[1,2] Furthermore, the three-dimensional shape of spirooxindoles is an attractive target to complement the flat heterocyclic compounds encountered in many drug discovery programs. The synthetic challenge of the spiro motif continues to encourage the development of creative methods to access these important structures. Recent synthetic methods to access spirocyclic oxindoles include formal cycloaddition,[3] organocascade,[4] Prins cyclization,[5] and other cyclization reactions.[6] Each of the aforementioned methods results in a different class of spirocycle that may show promise as biologically active compounds. Here we report a titanium(IV)-catalyzed method for the selective synthesis of a new class of spiro[3,3′oxindoleoxazolines] upon addition of 5-methoxy-2-aryloxazoles[7] to isatins.

We initiated our investigations for the nucleophilic addition and cyclization of oxazoles by screening various Lewis acids for activation of chelating isatin **1a** (Table 1). Initial screening for spirocyclization was performed at 50 mol % of Lewis

(1) For recent reviews, see: (a) Badillo, J. J.; Hanhan, N. V.; Franz, A. K. *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 758. (b) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003. (c) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748.

(2) For recent examples, see: (a) Yong, S. R.; Ung, A. T.; Pyne, S. G.; Skelton, B. W.; White, A. H. *Tetrahedron* **2007**, *63*, 5579. (b) Yeung, B. K. S.; Zou, B.; Rottmann, M.; Lakshminarayana, S. B.; Ang, S. H.; Leong, S. Y.; Tan, J.; Wong, J.; Keller-Maerki, S.; Fischli, C.; Goh, A.; Schmitt, E. K.; Krastel, P.; Francotte, E.; Kuhen, K.; Plouffe, D.; Henson, K.; Wagner, T.; Winzeler, E. A.; Petersen, F.; Brun, R.; Dartois, V.; Diagana, T. T.; Keller, T. H. *J. Med. Chem.* **2010**, *53*, 5155. (c) Vintonyak, V.; Warburg, K.; Kruse, H.; Grimme, S.; Hübel, K.; Rauh, D.; Waldmann, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5902.

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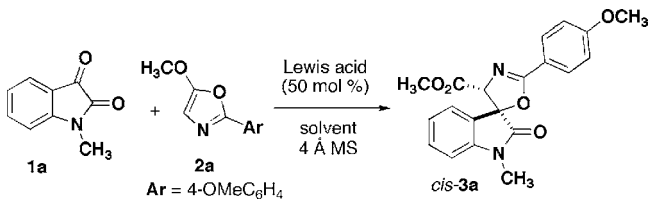
Table 1. Optimization of Spirocyclization of 5-Methoxyoxazole with *N*-Methylisatin[a]



entry	Lewis acid	solvent	temp (°C)	time (h)	dr[b]	yield (%)[c]
1	$Sc(OTf)_3$	DCM	rt	24	58:42	39
2	$ScCl_3$	DCM	rt	48	53:47	53
3	$InCl_3$	DCM	rt	24	52:48	92
4	$SnCl_4$	DCM	rt	1	73:27	99
5	$SnCl_4$	DCM	rt	24	74:26	80[d]
6	$SnCl_4$	MeCN	rt	4	72:28	86
7	$SnCl_4$	THF	rt	48	57:43	17
8	$SnCl_4$	CH_3Ph	rt	4	66:34	99
9	$SnCl_4$	DCM	−20	4	75:25	99
10	$SnCl_4$	DCM	−40	48	79:21	99
11	$SnCl_4$/DTMP	DCM	rt	4	63:37	96
12	$SnCl_2$	DCM	rt	24	54:46	88
13	$SnCl_2$	MeCN	rt	72	66:33	15
14	$TiCl_4$	DCM	rt	4	92:8	45[d,e]
15	$TiCl_4$	DCM	rt	1	94:6	83[d,f]
16	$TiCl_4$	MeCN	rt	1	82:18	<10[d−f]

[a] All reactions performed at 0.12 M with 1.5 equiv of isatin under argon. [b] *cis:trans* ratio determined by analysis of unpurified reaction mixture using ^{1}H NMR spectroscopy. [c] Isolated yield. [d] Using 20 mol % of Lewis acid. [e] Significant oxazole decomposition was observed. [f] Reaction performed without 4 Å molecular sieves.

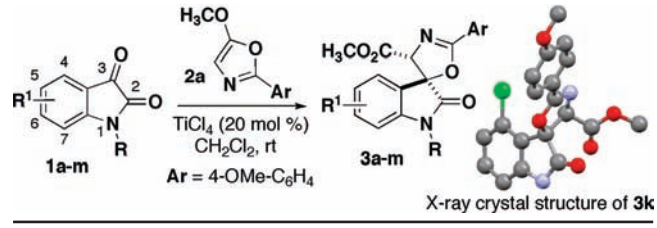
acid. Previously in our group, scandium(III) and indium(III) triflates have been shown to catalyze the nucleophilic addition of heteroaromatics to isatins.[8] In this reaction, scandium(III) triflate afforded spirocycle **3a** in 39% yield as a 58:42 inseparable mixture of *cis*- and *trans*-isomers (entry 1), as determined by ^{1}H NMR analysis of the unpurified reaction mixture. Although scandium(III) and indium(III) chlorides afforded **3a** in moderate to excellent yield (entries 2, 3), the diastereoselectivity observed was still negligible.

Additional Lewis acids were investigated to improve diastereoselectivity for the *cis*-oxazoline product. Tin(IV) chloride showed exceptional reactivity (99% yield in <1 h), with an improved diastereomeric ratio of 73:27 (entry 4) in favor of the *cis*-oxazoline product.[9] The effect of solvent and temperature were examined for the tin(IV)-promoted reactions in order to improve the diastereoselectivity (entries 6−10). Changing the solvent from dichloromethane (DCM) to acetonitrile gave comparable reactivity and diastereoselectivity (entry 6), whereas THF resulted in a dramatically decreased yield with no improvement in diastereoselectivity (entry 7). Reducing the reaction temperature required longer reaction times and still provided no selectivity improvement (entries 9, 10). A control experiment was performed with 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) to confirm that the reaction is indeed catalyzed by a Lewis acid mechanism and not by HCl potentially generated during the reaction (entry 11). Furthermore, Brönsted acids such as triflic and phosphinic acid did not catalyze spirocycle formation. Tin(II) chloride was also investigated and showed no improvement in diastereoselectivity (entry 12).

Evaluation of titanium(IV) chloride showed excellent promise, providing spirocycle *cis*-**3a** with excellent 92:8 diastereoselectivity. However, poor yields were observed as a result of significant decomposition of the oxazole starting material (entry 14). Upon further optimization it was determined that removing molecular sieves increased the rate of the reaction and also prevented oxazole decomposition, with no effect on the diastereoselectivity (entry 15). The structure of the major diastereomer was confirmed to be the *cis*-oxazoline by X-ray analysis. Notably, both $SnCl_4$- and $TiCl_4$-promoted reactions proceed efficiently at 20 mol % (entries 5, 15). Additional Lewis acids such as $In(OTf)_3$, $Zn(OTf)_2$, $ZnBr_2$, $CuCl_2$, $Cu(OTf)_2$, MgF_2, and $BF_3{\cdot}OEt_2$ showed no reaction or poor conversion (<20%). Overall, titanium(IV) chloride was identified as the optimal catalyst on the basis of conversion and diastereoselectivity.

Using the optimal conditions with titanium(IV) chloride (without molecular sieves), the scope of the isatin electrophile was examined (Table 2). The titanium(IV) chloride catalyst

Table 2. Scope of Isatins for 2-Oxazoline Spirocycles[a]



entry	R	R^1	product	time (h)	dr[b]	% yield[c]
1	CH_3	H	**3a**	1	94:6[d]	83
2	PMB	H	**3b**	3	91:9	82
3	Ph	H	**3c**	1.5	91:9	88
4	Bn	H	**3d**	3	91:9	83
5	PMB	5-Br	**3e**	1	91:9	72
6	CH_3	5-Br	**3f**	1	93:7	85
7	CH_2CCH	5-F	**3g**	1	90:10	55
8	CH_3	5-OCH_3	**3h**	3	86:14	65
9	CH_3	5-Cl	**3i**	1	92:8	85
10	CH_3	4-Cl	**3j**	15	99:1	99
11	H	4-Cl	**3k**	23	99:1	81
12	H	H	**3l**	23	83:17	81
13	H	Br	**3m**	19	81:9	77

[a] Reactions performed with 1.5 equiv of isatin under argon. [b] Determined by ^{1}H NMR analysis of unpurified reaction mixture. Diasteromers are inseparable by column chromatography. [c] Isolated yield. [d] Diasteroselectivity for purified product.

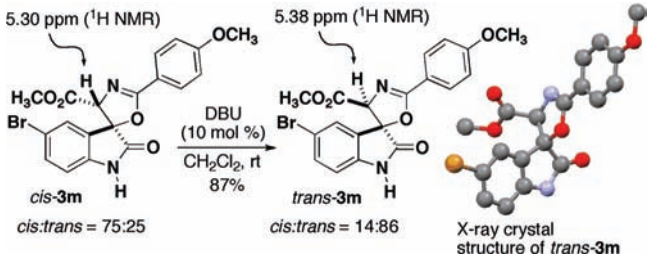
(8) Hanhan, N. V.; Sahin, A. H.; Chang, T. W.; Fettinger, J. C.; Franz, A. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 744.

(9) For reports of aldehyde cyclizations, diastereoselectivity is dependent on selection of metal, with *cis*-selectivity observed for Sn(IV) and *trans*-selectivity observed for Ti(IV) and Al(III) Lewis acids, see reference: Suga, H.; Hirotsu, Y; Fujieda, H.; Ibata, T. *Tetrahedron Lett.* **1991**, *32*, 6911. The *trans*-oxazoline is proposed to result from epimerization of the initial *cis*-adduct under the reaction conditions. Also see ref 7 for additional details.

continued to provide excellent diastereoselectivity with *N*-alkylated isatins (entries 1−10), including the synthetically useful *N*-protected *p*-methoxybenzyl (PMB) isatins. The *N*-propargyl spirooxazolines can also be accessed in good yield and diastereoselectivity, and are expected to be useful for further diversification and incorporation of heterocycles with alkyne cycloaddition reactions.[10] Slightly reduced diastereoselectivity (86:14) was observed with the 5-methoxy electron donating substituent on isatin (entry 8). Notably, 4-chloroisatin provided excellent 99:1 diastereoselectivity for both the NH and *N*-methyl derivatives (entries 9, 10). Unprotected NH isatins could be successfully utilized with high yield and up to 99:1 diastereoselectivity (entries 11−13).

The major product has been assigned to be the *cis*-oxazoline, which is the kinetic product. Epimerization studies demonstrate that the *cis*-oxazoline can be converted to the *trans*-oxazoline upon treatment with catalytic 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 1).[11] X-ray

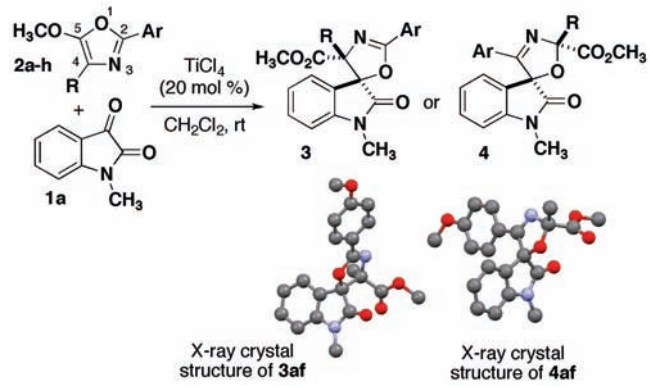
Scheme 1. Epimerization with DBU



crystal structure analysis of the epimerized product (*trans*-**3m**) confirmed the trans stereochemistry. Computational analysis revealed that *trans*-**3m** has a ground-state energy that is 1.11 kcal/mol lower relative to the *cis*-isomer.[12] This supports our observation that the *cis*-product is the kinetic product. Thus, the reduced diastereoselectivity observed for other Lewis acids in Table 1 is likely due to conditions that allow epimerization to occur upon complexation of the Lewis acid to the oxazoline ring or ester substituent.[9]

When the oxazole scope was investigated, it was observed that the substitution at the 4-position of the oxazole controls the regioselectivity of the reaction, thus providing selective access to either 2- or 3-oxazoline spirocycles (e.g., **3** or **4**, Table 3).[13] Varying the electronic and steric effects of the aryl ring on oxazole **2a** still provided good, albeit reduced, diastereoselectivity and did not influence the regioselectivity (entries 1−5). Interestingly, with a more electron-withdrawing aryl group (*p*-Br), a 3-hydroxy-2-oxindole ring-opened product was also isolated in 8% yield.[11] The (2-methoxyphenyl)oxazole **2e** proceeds with poor conversion where the

Table 3. Scope of Oxazole and Regiocontrol of Oxazoline



entry	R	Ar	product	time (h)	yield (%)[a]	dr[b] of **3**	dr[b] of **4**
1	H	4-OCH_3	**3a**	1	83	94:6	
2	H	H	**3ab**	24	88[c]	81:19	
3	H	TMP[d]	**3ac**	9	75	88:12	
4	H	4-Br	**3ad**	14	57[e]	86:14	
5	H	2-OCH_3	**3ae**	24	no rxn		
6	CH_3	4-OCH_3	**3af/4af**[f]	4	99	84:16	55:45
7[g]	CH_3	4-OCH_3	**3af/4af**[g]	20	99	83:17	54:46
8	*i*-Pr	4-OCH_3	**4ag**	1	84		89:11
9	*i*-Pr	TMP	**4ah**	1	91		92:8

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis of unpurified reaction mixture. [c] ^{1}H NMR spectra includes 12% of the amide decomposition byproduct. [d] TMP = 3,4,5-trimethoxyphenyl. [e] A 3-hydroxy ring-opened product was also isolated in 8% yield; Yield is lower in order to ensure separation. [f] Regioselectivity (**3af**:**4af**) is 49:51 with $TiCl_4$. [g] Performed with 20 mol % $SnCl_4$; regioselectivity is 87:13 (**3af**:**4af**).

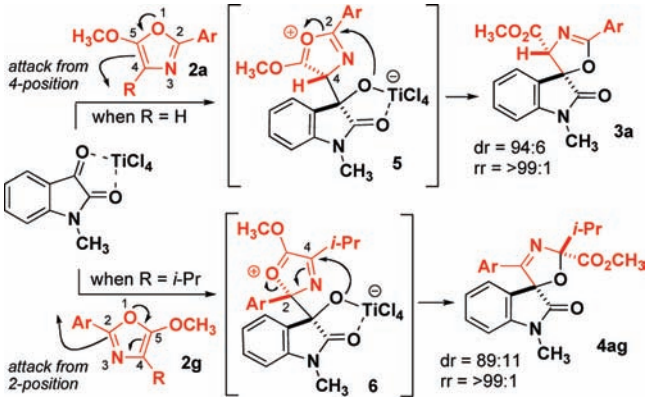
attenuated reactivity is attributed to the steric hindrance and disruption of conjugation between the aryl and oxazole rings.

Smaller substituents at the 4-position of the oxazole (i.e., H and CH_3), favor formation of the 2-oxazoline (**3**) (Table 3, entries 1−4, 7). However, when 4-(isopropyl)oxazoles were investigated, exclusive formation of the *cis*-adduct of regioisomer **4** was observed in high yield (91%) and excellent 92:8 diastereoselectivity (entries 8, 9). The 4-methyloxazole provides an intermediary case where the regioselectivity is dependent on both the substituent and the selection of Lewis acid. With titanium(IV) chloride, a 49:51 mixture of regioisomers was obtained, while tin(IV) chloride provided an improved 87:13 regioselectivity for 2-oxazoline **3** with similar diastereoselectivity. The structures and relative stereochemistry for both regioisomers have been confirmed by X-ray crystal structure analysis.

The proposed mechanism is initiated by titanium(IV) activation of the isatin dicarbonyl to accelerate nucleophilic attack by the oxazole, proceeding in a stepwise mechanism through zwitterionic intermediate **5** or **6** (Scheme 2).[7,13] This intermediate cyclizes through an intramolecular acyl transfer to afford the *cis*-oxazoline selectively.[14] The Lewis acid may also accelerate the cyclization by coordination to the imino-nitrogen. When the 4-substituent on the oxazole is a hydrogen (or methyl) group, the reaction likely proceeds with initial bond formation at the 4-position of the oxazole through

(10) Meldal, M.; Tornoe, C. W. *Chem. Rev.* **2008**, *108*, 2952.
(11) See Supporting Information for complete experimental details.
(12) The calculated ground-state energy difference is based on the B3LYP/6-31+G(d) model of crystal structures for *trans*-**3m** and modified *cis*-**3af**.
(13) (a) Suga, H.; Shi, X.; Ibata, T. *Chem. Lett.* **1994**, 1673. (b) Suga, H.; Shi, X.; Ibata, T.; Kakehi, A. *Heterocycles* **2001**, *55*, 1711.

Scheme 2. Mechanism and Regiochemical Reversal



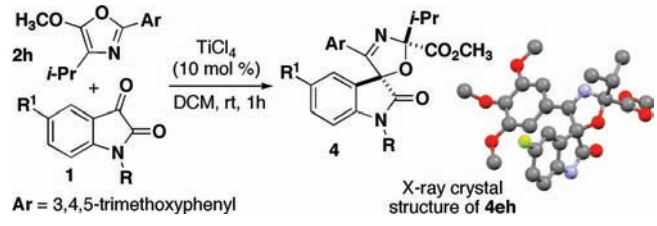
intermediate **5**. However, steric interactions with the 4-isopropyl group inhibit the attack from the 4-position and divert the initial bond-formation to the 2-position of the oxazole, proceeding through intermediate **6**. Increasing the size of the alkoxy group at the 5-position showed no effect on the diastereo- or regioselectivity.

The scope of isatins for the synthesis of 3-oxazoline spirocycles **4** was examined. In addition to providing a dramatic reversal of regioselectivity, the 4-(isopropyl)oxazoles maintain excellent diastereoselectivity and generally appear to be more reactive proceeding with 10 mol % catalyst loading (Table 4). Although diastereoselectivity is somewhat diminished for cyclization with the NH isatins, the isomers are separable and products can be isolated as single diastereomers.

In conclusion, we have developed a method for the synthesis of a new class of spirocyclic oxindole oxazolines by the addition of 5-alkoxy-2-aryloxazoles to isatins. Utilizing the substitution at the 4-position of the oxazole, we are able to access either the 2- or 3-oxazoline spirocycles with excellent regiocontrol. Biological evaluation and efforts to make the reaction enantioselective are ongoing.

(14) In an alternate mechanistic pathway, it is envisioned that intermediate **5** may first undergo ring opening to form a nitrilium ion, followed by cyclization to give the observed product.

Table 4. Scope of 3-Oxazoline Spirocycles[a]



entry	R	R^1	product	dr[b]	yield of major isomer (%)[c]
1	CH_3	H	**4ah**	92:8	91
2	CH_3	Br	**4bh**	93:7	90
3	PMB	Br	**4ch**	98:2	90
4	CH_3	Cl	**4dh**	91:9	88
5	H	F	**4eh**	85:15	82
6	H	H	**4fh**	78:22	72

[a] All reactions performed with 1.5 equiv of oxazole under argon. [b] Determined by analysis of unpurified reaction mixture using ^{1}H NMR spectroscopy. [c] Isolated yield; Diastereomers are separable and isolated yield is reported for major isomer.

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Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds, including X-ray crystal structures for **3k**, *trans*-**3m**, **3af**, **4af**, and **4eh**. This material is available free of charge via the Internet at http://pubs.acs.org.

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