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Synthesis of Spirooxindoles via the *tert*-Amino Effect

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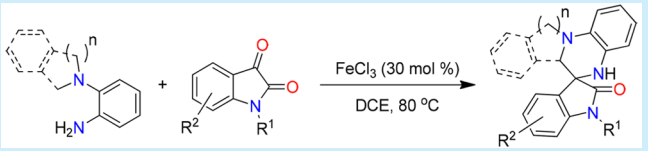
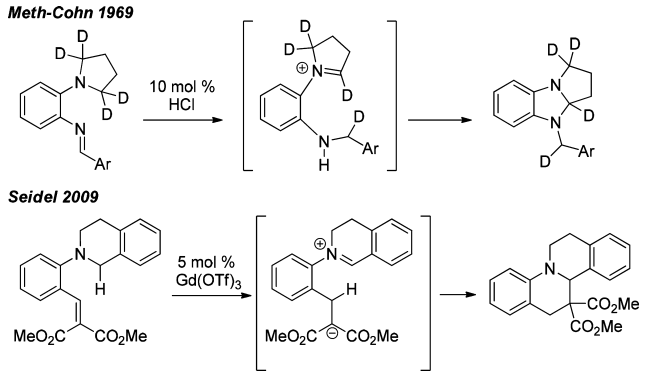
Supporting Information

ABSTRACT: A new method is developed for the synthesis of spirooxindoles from amines and isatins via C−H functionalization. The reaction leverages the *tert*-amino effect to form an enolate−iminium intermediate via [1,5]-hydride shift followed by cyclization. Interestingly the hydride migrates to the N atom of a C═N, which is atypical for hydride additions to imines.



Synthesis of biologically active compounds through functionalization of relatively unreactive C−H bonds is an area of intense interest. For example, C(sp^3)−H bond activation has attracted considerable attention because of its potential to rapidly generate molecular complexity and expedite the synthesis of natural products and drug intermediates.[1] Likewise, the *tert*-amino effect provides an interesting mechanism for complexity generation via C−H functionalization.[2,3] These reactions commonly proceed by an internal redox isomerization involving a hydride migration from the α-carbon of amines (Scheme 1). For example, Seidel[2c] and others have

Scheme 1. *tert*-Amino Effect: Hydride Migrations



shown the [1,5]-hydride shift from amines to alkenes that are activated by a Lewis acid, followed by cyclization.[2j−q] Similarly, hydride shifts can occur from amines to the carbon atom of appropriately activated imines.[2d−i,3] Herein we report a related synthesis that proceeds via formal hydride shift to the nitrogen atom of an imine, giving rise to spirooxindoles.

Spirooxindoles are of significant interest due to their presence in bioactive natural products such as the spirotryprostatins, horsfiline, gelsemine, gelseverine, rhynchophylline, and elacomine (Figure 1).[4] We hypothesized that unique

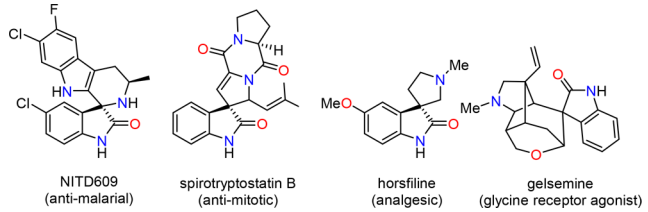
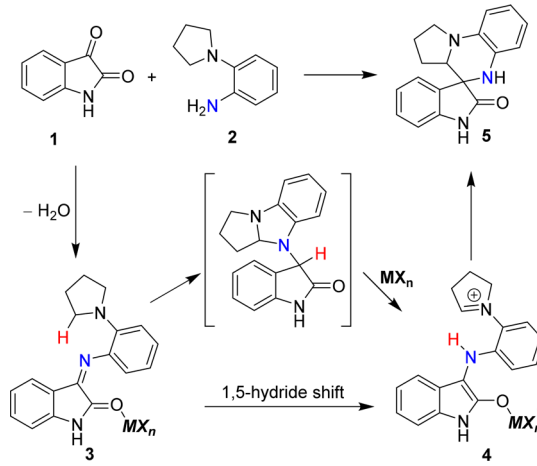


Figure 1. Biologically active spirooxindoles.

spirooxindoles could be accessed via exploiting the *tert*-amino effect in cyclocondensations with α-dicarbonyl compounds (Scheme 2). In such a case, condensation of a diamine with the α-dicarbonyl compound should generate an imine that is predisposed for [1,5]-hydride migration to nitrogen.[5] Cycliza-

Scheme 2. Hypothetical Mechanisms for Cyclocondensation



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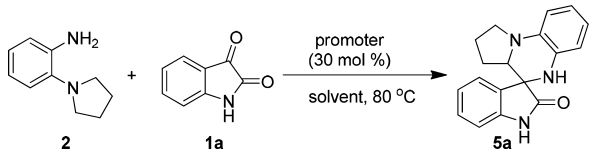
tion of the resulting enolate by reaction with the iminium electrophile would form spirooxindoles. Indeed, a thorough search of the literature revealed one example of this overall transformation, although a yield was not reported.[3]

While hydride migration to the carbon of imines is preferred under conditions where the imine has its standard polarization, it was expected that Lewis acids could activate the α-imino amide **3** and stabilize the intermediate enolate, which would facilitate hydride shift to nitrogen.[2r,5] Intermediate **4** may also be accessible through hydride shift to carbon followed by rearrangement.[3b,6] In either case, subsequent cyclization would give rise to potentially valuable spirooxindoles **5**.[7] A screen of potential catalysts showed that the reaction of diamine **2** with isatin and a catalytic amount of $MgCl_2$ furnished a 2:1 ratio of diastereomeric spirooxindoles in 15% yield after reaction for 20 h in dichloroethane at 80 °C (Table 1). Screening a variety of

Table 1. Optimization of Spirooxindole Formation[a]



2 **1a** **5a**

entry	promoter	solvent (0.5 M)	time (h)	dr[b]	yield (%)[c]
1	$MgCl_2$	DCE	20	2.0:1	15
2	$Gd(OTf)_3$	DCE	5	1.0:1	15
3	$AuCl_3$	DCE	2	4.3:1	20
4	$Cu(OTf)_2$	DCE	2	1.6:1	25
5	$In(OTf)_3$	DCE	3	1.3:1	30
6	$Zn(OTf)_2$	DCE	4	2.5:1	31
7	$Sc(OTf)_3$	DCE	21	1.7:1	36
8	TfOH	DCE	2	2.7:1	37
9[d]	$FeCl_3$	DCE	21	1.0:1	45
10[d]	**$FeCl_3$**	**DCE**	**2.5**	**2.0:1**	**68**
11	–	DCE	24	–	–
12	$FeCl_3$	toluene	24	–	–
13	$FeCl_3$	THF	2	1.5:1	48
14	$FeCl_3$	DMSO	2	1.3:1	50
15	$FeCl_3$	$CHCl_3$	2	2.6:1	50
16	$FeCl_3$	EtOH	2	1.1:1	54
17[e]	$FeCl_3$	DCE	2	2.1:1	58
18[f]	$FeCl_3$	DCE	2	1.6:1	30

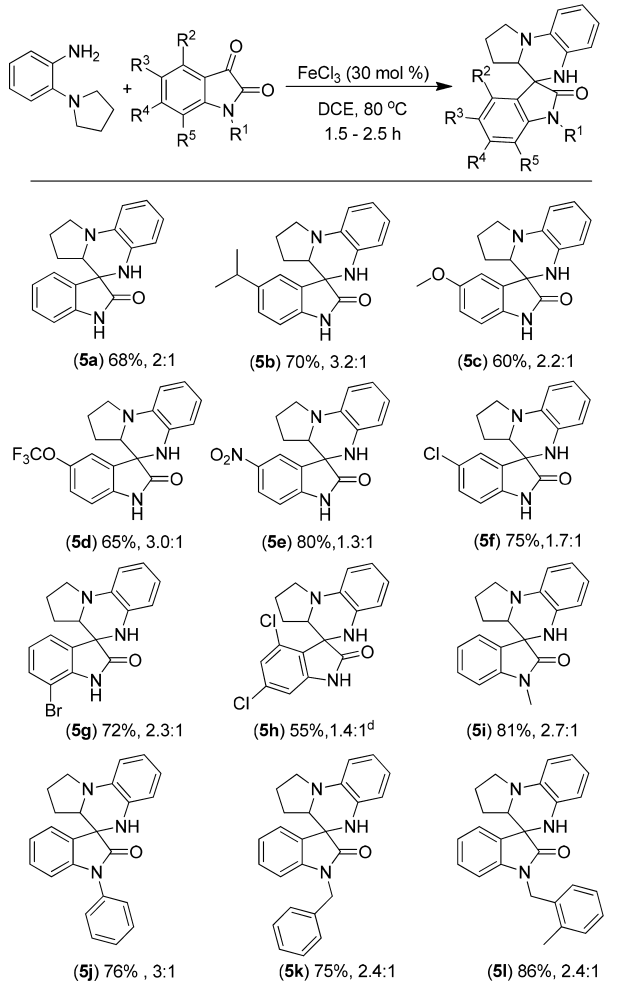
[a]Reactions of *o*-pyrrolidinyl aniline (0.5 mmol), isatin (0.5 mmol), and promoter (0.15 mmol) in 1 mL of solvent. [b]Determined by ^1H NMR of the crude reaction mixture. [c]Isolated yield [d]0.6 mmol of *o*-pyrrolidinyl aniline was used. [e]1.0 mmol of *o*-pyrrolidinyl aniline was used. [f]1.0 mmol of isatin was used.

other Lewis acids showed that, while $AuCl_3$ provided the highest diastereoselectivity for spirocyclization (entry 3, Table 1), $FeCl_3$ produced the product in highest overall yield. Interestingly, the $FeCl_3$-promoted reaction gives higher yields at shorter reaction times, and decomposition has been observed at longer reaction times (entries 9 and 10, Table 1). Importantly, no product formation was observed in the absence of promoter in DCE solvent after 24 h (entry 11). Finally, a screen of other solvents revealed that the reaction proceeds well in THF, DMSO, and EtOH, but failed in toluene. However, none of the solvents evaluated produced higher yields of **5a** than were achieved in DCE, nor did they provide substantially higher diastereoselectivity in the cyclization. Unfortunately, we were unable to definitively observe equilibration of diastereomers since they were inseparable; thus, it is not clear whether the observed diastereoselectivities arise from a kinetic or thermodynamic selectivity or a combination of both.

Importantly, attempts to increase the yield of redox cyclization by increasing the quantity of isatin from 1 to 2 equiv led to much lower yields (entry 18). The decrease in yield may be explained by preferential binding of the catalyst to isatin instead of intermediate **3**, slowing the activation. Thus, the best conditions for the spirocyclization involve reaction of isatin with 1.2 equiv of amine at 80 °C in DCE with 30 mol % of $FeCl_3$ as a promoter.

With the optimized reaction conditions in hand, we further explored the substrate scope of this reaction using diamine **2** and functionalized isatins (Scheme 3). A series of isatins

Scheme 3. Spirooxindole Formation Using Different Isatins[a,b,c]



[a]*o*-Pyrrolidinyl aniline (0.6 mmol), isatin (0.5 mmol) and $FeCl_3$ (0.15 mmol) in 1 mL of DCE. [b]Determined by ^1H NMR of the crude reaction mixture. [c]Isolated yield. [d]1 mmol of *o*-pyrrolidinyl aniline was used; 18 h reaction time.

containing different functional groups were treated with amine and 30 mol % of $FeCl_3$ at 80 °C in DCE to furnish spirooxindoles with moderate to good yields as shown in Scheme 3.

Isatins that are substituted at the 5-position with either electron-donating (*i*-Pr, OMe) or electron-withdrawing (OCF_3,

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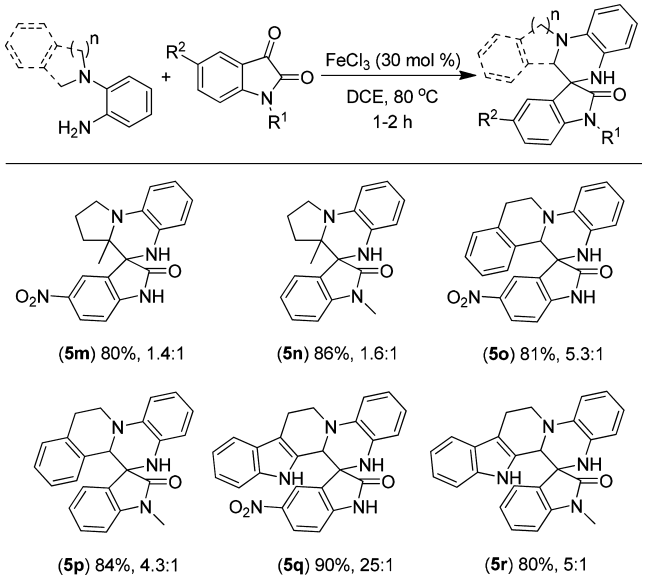
NO_2, Cl) groups were compatible with the cyclization conditions, providing yields ranging from 60% to 80% (Scheme 3). Moreover, halogen substitution at the 7- (**5g**) or 4,6-positions (**5h**) led to spirooxindoles in 72% and 55% yield, respectively. Importantly, related halogenated spirooxindoles have proven useful as antimalarial agents[4f] and as intermediates in the parallel synthesis and screening of cross-coupled derivatives.[4b] While unprotected isatins with free N−H groups were effective substrates for the reaction, the isatin nitrogen can also be alkylated with methyl (**5i**), aromatic (**5j**), or benzyl groups (**5k**, **5l**). In fact, the *N*-substituted isatins gave somewhat higher yields than the analogous unprotected isatin.

Next, the ability of various substituted *ortho*-amino anilines to form spirooxindoles was evaluated (Scheme 4). For example,

Scheme 4. Spirooxindole Formation from Different Amines[a,b,c]



[a]Reactions were carried out in a mixture of amine (0.6 mmol), isatin (0.5 mmol) and $FeCl_3$ (0.15 mmol) in 1 mL of DCE. [b]dr determined by ^{1}H NMR of the crude reaction mixture. [c]Yield refers to column purified product.

the reaction of a 2-methylpyrrolidinyl aniline derivative smoothly reacted with *N*-methylisatin and 5-nitroisatin to furnish **5m** and **5n** in 80% and 86% yields, respectively. Notably, the reaction was completely selective for formation of the more substituted C−C bond. This is a consequence of the better hydride donor ability of the secondary amine center, which results in the formation of a stabilized, methyl-substituted cation intermediate (**4**, Scheme 2).[2,8] Similarly, the reaction of a tetrahydroisoquinoline-derived aniline with 5-nitroisatin furnished the product **5o** in 81% yield as a single regioisomer (Scheme 4). Again, this is due to the better hydride donor ability of a benzylic C−H bond over a primary C−H bond.[2,8] Interestingly, spirooxindole formation using a 1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-substituted aniline with 5-nitroisatin furnished the product **5q** in 90% yield and with high diastereoselectivity (25:1); a 5-unsubstituted isatin also provided a good yield of product **5r**, but with lower diastereoselectivity (5:1). Nonetheless, it appears that *ortho*-aminoanilines that bear sterically extended amines such as isoquinoline or carboline result in higher diastereoselectivities.

To conclude, we have developed a method for the synthesis of spirooxindoles through intermolecular reaction between diamines and isatins. This cyclocondensation process leverages the inherent reducing power of a tertiary amine donor and is facilitated by a Lewis acid promoter ($FeCl_3$). Ultimately, the formal hydride migration from carbon to nitrogen provides rapid access to biologically and medicinally relevant spirooxindoles.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and complete compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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