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Catalytic Stereoselective Synthesis of Diverse Oxindoles and Spirooxindoles from Isatins

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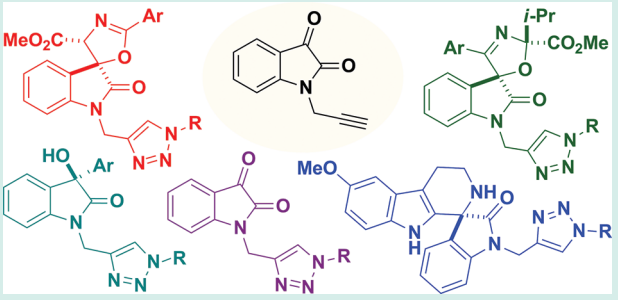
Supporting Information

ABSTRACT: A strategy for the efficient two-step synthesis of triazole derivatives of oxindoles and spirooxindoles is presented. Using a common set of *N*-propargylated isatins, a series of mechanistically distinct stereoselective reactions with different combinations of nucleophiles and catalysts provide access to diverse hydroxy-oxindoles, spiroindolones, and spirocyclic oxazoline structures. The resulting *N*-propargylated oxindoles are then converted to triazoles using copper-catalyzed azide−alkyne cycloaddition (CuAAC) reactions. Overall, this strategy affords a 64-member pilot-scale library of diverse oxindoles and spirooxindoles.



KEYWORDS: *heterocycles, isatins, oxindoles, spirooxindoles, spiroindolones, oxazolines, triazoles*

INTRODUCTION

Complex functionalized molecules are important compounds of interest for biological probes and as new molecules for pharmaceutical lead discovery. Oxindole and spirooxindole scaffolds have generated considerable synthetic interest due to their occurrence in diverse natural products and notable biological activity.[1,2] In a recent discovery, spiroindolone NITD609 demonstrated nanomolar activity as a therapeutic agent that kills the blood stage of *Plasmodium falciparum* and has single-dose efficacy in a rodent malaria model (Figure 1).[3] Various hydroxy-oxindoles scaffolds also demonstrate important biological activity, such as Convolutamydine A, a natural product with potent activity against leukemia cells.[4] Substituted isatin (indole-2,3-diones) scaffolds have also shown promising examples of biological activity. For example, isatin **1** is a potent inhibitor of SARS CoV 3C-like proteases.[5] Initially driven by efficient synthetic methods, the 1,2,3-triazole has now emerged as a heterocycle of biological interest in drug discovery and medicinal chemistry programs.[6,7] For example, triazole **2** shows activity against tuberculosis strain H37RV.[6b] The significant biological activities observed for oxindoles and triazoles emphasizes the need to develop efficient synthetic strategies to access these scaffolds and increase structural diversity for drug discovery and medicinal chemistry programs.

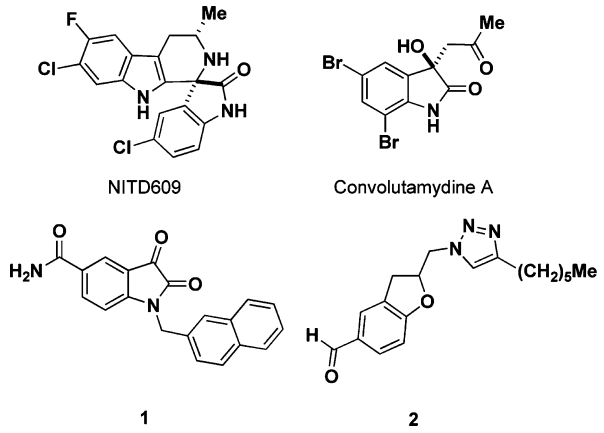


Figure 1. Biologically active oxindoles and triazoles.

Previous work from our laboratory has demonstrated several methods of catalytic activation of the isatin dicarbonyl for efficient and selective nucleophilic additions and spirocyclizations at the 3-position.[8] The strategy we envisioned utilizes a common set of *N*-propargylated isatins **3** to access diverse oxindole scaffolds through a series of mechanistically distinct nucleophilic addition pathways. Each resulting oxindole scaffold contains an alkyne group that provides further opportunities for structural diversification with triazole heterocycles using the copper-catalyzed azide−alkyne cycloaddition (CuAAC) reaction. We also envisioned that the *N*-propargylated isatins **3** would be directly utilized in the CuAAC reaction as a fifth scaffold because triazole-containing isatins have not previously been reported or evaluated for biological activity. Here we describe the realization of this strategy for rapid access (two synthetic steps) to a pilot-scale library of diverse triazole-containing hydroxy-oxindoles **4**−**6**, spiroindolones **7**, isatin-triazoles **8**, and spirooxazolines **9** and **10** emanating from a common set of propargylated isatins **3** (Scheme 1). Overall, our two-step strategy affords a library of 64 oxindole and

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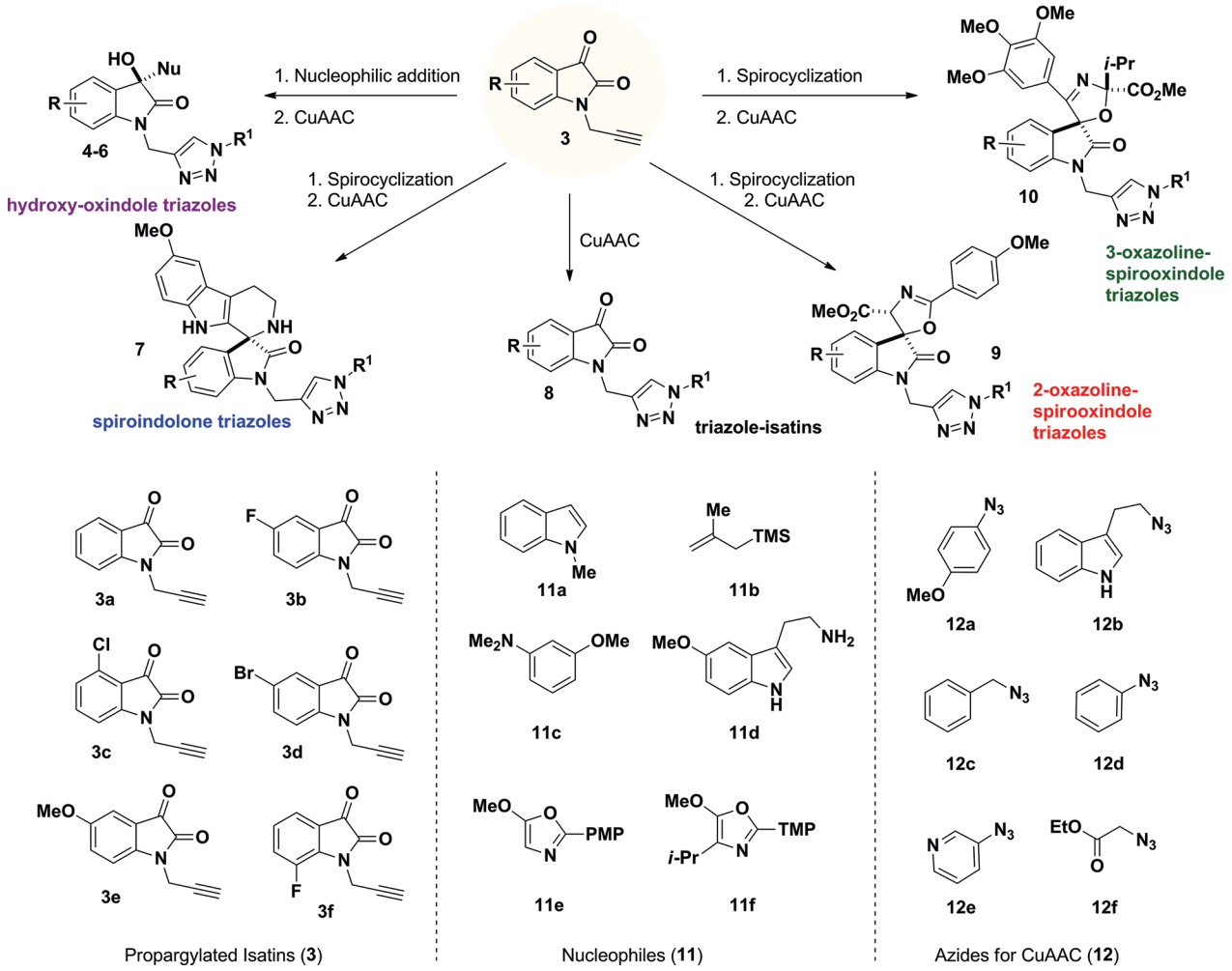
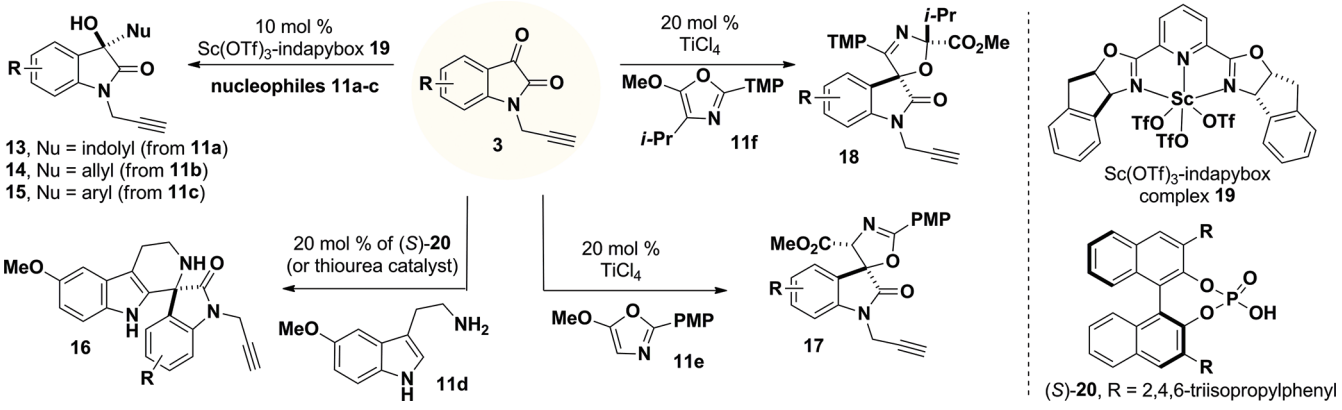
Scheme 1. Outline of Synthetic Strategy towards Substituted Triazole-Containing Oxindoles



Scheme 2. Nucleophilic Addition Reactions to Access Oxindoles and Spirooxindoles



spirooxindole compounds, including 15 core scaffolds and 49 triazole derivatives. The efficient stereoselective syntheses of complex heterocycles combining both oxindole and triazole motifs have not been described previously. On the basis of the breadth of biological activity known for isatins, oxindoles and spirooxindoles, these densely functionalized heterocycles should serve as important biological probes for chemical biology.

RESULTS AND DISCUSSION

A key feature in this strategy is the regio-, diastereo- and enantioselective synthesis of the oxindole and spirooxindole scaffolds (Scheme 2). On the basis of the nucleophile component (**11**) utilized (Scheme 1), four oxindole scaffolds were selected for this library: hydroxy-oxindoles **13**−**15** are prepared enantioselectively using a chiral Lewis acid catalyst (**19**);[8b] spiroindolones **16** are prepared enantioselectively using a chiral Brönsted acid catalyst (**20**);[8c] and the 2-oxazoline and

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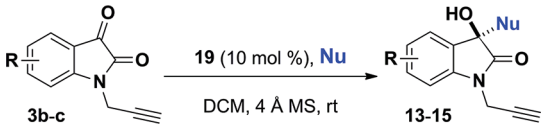
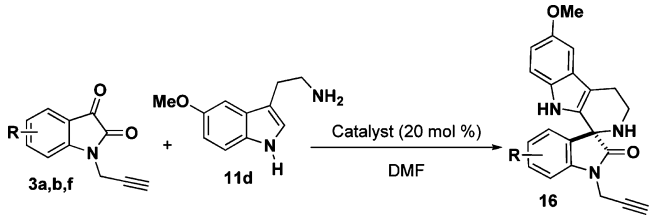
Table 1. Enantioselective Synthesis of Substituted Hydroxy−Oxindole Scaffolds



entry	R	isatin	nucleophile	product	yield[a]	%ee[b]
1[c]	5-F	**3b**	**11a**	**13b**	97	98
2[d]	5-F	**3b**	**11b**	**14b**	79	87
3	5-F	**3b**	**11c**	**15b**	97	96
4[c]	4-Cl	**3c**	**11a**	**13c**	78	86
5[d]	4-Cl	**3c**	**11b**	**14c**	90	94
6	4-Cl	**3c**	**11c**	**15c**	97	99

[a]Isolated yields. [b]Determined using HPLC analysis with chiral stationary phase. [c]Reaction performed at −20 °C. [d]Reaction was performed using 3.0 equiv of TMSCl and 0.1 equiv of $NaSbF_6$ in MeCN.

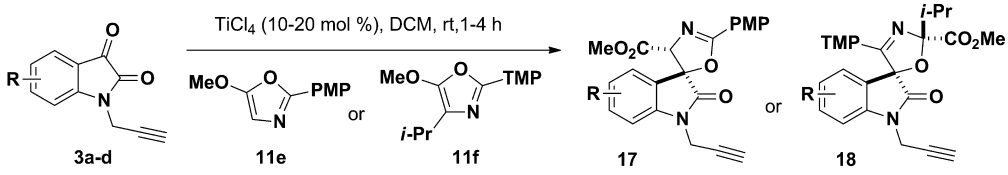
Table 2. Enantioselective Synthesis of Spiroindolone Scaffolds



entry	R	isatin	product	catalyst	yield (%)[a]	%ee[b]
1	H	**3a**	**16a**	$Sc(OTf)_3$	89[c]	
2	**5-F**	**3b**	**16b**	**20**	86	84
3	**7-F**	**3f**	**16f**	thiourea[d]	92[c]	

[a]Isolated yield. [b]Determined using HPLC analysis with chiral stationary phase. [c]Reaction was performed in DCM solvent. [d]Thiourea = 1,3-bis(3,5-bis(trifluoromethyl)-phenyl)thiourea.

Table 3. Regio- and Stereoselective Spirocyclization to Afford 2- and 3-Spirooxazoline Scaffolds



PMP = *p*-methoxyphenyl
TMP = 3,4,5-trimethoxyphenyl

entry	R	isatin	oxazole	product	yield (%)[a]	dr[b]
1	5-F	**3b**	**11e**	**17b**	55[c]	90:10
2	4-Cl	**3c**	**11e**	**17c**	74	99:1
3	H	**3a**	**11f**	**18a**	77[c]	90:10
4	5-F	**3b**	**11f**	**18b**	87	93:7
5	4-Cl	**3c**	**11f**	**18c**	51[c]	95:5
6	5-Br	**3d**	**11f**	**18d**	95	99:1

[a]Isolated yield of major diastereomer. [b]Determined by analysis of ^1H NMR spectroscopy of crude reaction mixture. [c]Yields sacrificed for purity due to the presence of byproduct which proved to be difficult to separate by column chromatography (conversion ≥80% by TLC).

3-oxazoline spirocycles **17** and **18** are each prepared diastereo- and regioselectively using a titanium(IV) Lewis acid catalyst (Scheme 2).[8a] For some scaffolds, isatins (**3**) are selected on the basis substitution patterns that ensure high selectivity.

First, a series of 3-substituted-3-hydroxy-oxindole scaffolds **13**−**15** were accessed using scandium(III)-catalyzed enantioselective additions with representative π-nucleophiles: *N*-methylindole (**11a**), 2-methallylsilane (**11b**), and *N*,*N*-dimethyl-*m*-anisidine (**11c**).[8b] Scandium(III) complexes formed with the 2,6-bis[(3*aS*,8*aR*)-3a,8a-dihydro-8H-indeno-[1,2-d]oxazolin-2yl]pyridine ligand (e.g., **19**) are known to be effective chiral Lewis acid catalysts with good chelating potential.[9] As outlined in Table 1, isatins **3b**−**c** were utilized to afford hydroxy oxindoles **13**−**15** with high yields (78−97%) and enantioselectivity (85−99% *ee*). All reactions were performed at room temperature, with the exception of entries 1 and 4, which were performed at −20 °C because of the high reactivity of the nucleophile. In the case of the methallylsilane (**11b**, entries 2 and 5), the reaction is run in acetonitrile with TMSCl and $NaSbF_6$ as additives to increase the efficiency of

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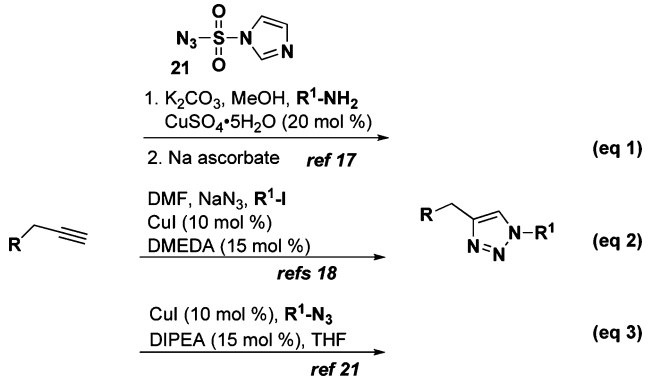
the reaction and promote in situ deprotection of any resulting OTMS product so that the hydroxy-oxindole products **13**−**15** are obtained exclusively.[10,11]

Using an asymmetric Pictet−Spengler-type spirocyclization reaction,[12] three spiroindolone scaffolds were prepared upon acid-catalyzed spirocyclization of 5-methoxytryptamine (**11d**) with isatins (Table 2).[8c,13] We have previously shown that this reaction is efficiently catalyzed using Lewis acidic metal salts, thioureas, or BINOL-derived chiral phosphoric acids. The 5-fluorospiroindolone **16b** was prepared using a BINOL-derived phosphoric acid catalyst to demonstrate the enantioselective synthesis and evaluate the retention of enantiomeric excess in the CuAAC reaction. Using (*S*)-3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (**20**) as the catalyst, fluorospiroindolone **16b** was attained in excellent yield (86%) and high enantioselectivity (84% ee) (Table 2, entry 2).[11] Using either $Sc(OTf)_3$ or 1,3-bis(3,5-bis(trifluoromethyl)-phenyl)thiourea provides an efficient (and less expensive) catalyst for the preparation of racemic spiroindolones (Table 2, entries 1 and 3). Isatins **3b** and **3f** were selected due to the therapeutic relevance of fluorinated molecules as well as the efficient performance of these isatins in the Pictet−Spengler reaction.[3b,14]

A series of spirooxindole oxazoline scaffolds were prepared using the titanium(IV)-catalyzed regio- and diastereoselective addition and spirocyclization of 5-methoxyoxazoles to isatins.[8a,15] Substitution at the 4-position of the oxazole controls the regiochemistry, with the 4-isopropyloxazole (**11f**) giving rise to the 3-oxazoline scaffold **18** and the 4-H oxazole (**11e**) leading to the 2-oxazoline scaffold **17**.[8a,11,16] In general, the oxazole addition to propargyl isatins **3a**−**d** proceeded with high regio- and diastereoselectivity (>99% rr, up to 99% dr) and in high yields (up to 95%); however, in two cases (**17b** and **18c**) the isolated yield was low because of the presence of byproduct that proved to be difficult to separate by column chromatography. All reactions proceed with high diastereoselectivity, but the 4-chloroisatin **3c** is particularly effective for dictating high diastereoselectivity in the formation of 2-oxazolines, such as **17c**.

Triazole Synthesis. This collection of diverse oxindole and spirooxindole scaffolds contains a common feature through the *N*-propargyl group of each scaffold, which can be further diversified using azide−alkyne cycloaddition chemistry. We set out to compare several variations of CuAAC reactions for this collection of *N*-propargylated oxindoles. We began by exploring one-pot reaction conditions that utilize in situ generated azides, prepared from the corresponding amine using the shelf-stable diazotransfer reagent 1H-imidazole-1-sulfonyl azide (**21**) (Scheme 3, eq 1).[17] Unfortunately, this method did not work for these oxindole substrates due to side reactions and decomposition of starting material under the diazo transfer conditions. Several solvent combinations (THF, MeOH/THF, DCM), copper reagents, and conditions (i.e., Cu(I) vs Cu(II) reduction by sodium ascorbate in situ) were explored, but only minimal triazole formation was observed for the one-pot procedure. Next, we investigated a route utilizing in situ generated aryl azides prepared from commercially available aryl iodides with sodium azide in the presence of copper iodide (Scheme 3, eq 2).[18] This method was also considered to be attractive because it provides access to diverse aryl triazoles, including amino-substituted triazoles that are not available when preparing azides from amines. This method has previously only been reported for less-functionalized substrates,

Scheme 3. Methods Compared for the Synthesis of Triazoles with Propargylated Isatins



but here the conditions generally afforded low yields (33−40%) for the more complex oxindole substrates. Low yields are attributed to the formation of undesired polymeric-side products.

Ultimately, we utilized a method applicable for the synthesis of both alkyl- and aryl-substituted triazoles using purified azides that were prepared in one-step from the corresponding amine and diazotransfer reagent **21** (Table 4).[19] Azides **12a**-**f** were selected to include indolyl, pyridyl, ester, and phenyl derivatives in order to provide a variation in molecular weights, hydrogen bonding donor and acceptor properties, and capabilities for π-interactions. Azides **12a**−**e** were each prepared from the amine using diazotransfer reagent **21**, and azide **12f** was prepared by direct displacement of a chloride with sodium azide.[20] After purification and isolation, azides **12a**−**f** were then allowed to react directly with the *N*-propargyl-oxindoles or spirooxindoles in the presence of catalytic Cu(I) iodide (10 mol %) and di-*iso*propylethylamine (15 mol %) in THF to afford triazoles **4**−**10**.[21] A representative combination of *N*-propargyl-oxindole scaffolds and azide components were evaluated to ascertain the scope of compounds accessible using this strategy (Scheme 1). Overall, these reactions proceeded with high yields (>70%) for 36 of 45 triazoles prepared, and only 8 of the 45 reactions afforded less than 66% yield (Table 4). These low yields are attributed to lower conversion and unreacted starting material for the given reaction time. Of practical consideration, the CuAAC reactions of isatins (entries 20−27) proceeded with excellent yields and were particularly clean and easy to purify. Examples of representative final oxindole and spirooxindole products are shown in Figure 2.

Because hydroxy-oxindoles **13**−**15** were prepared as enantiomerically enriched compounds using asymmetric catalysis, it is especially important to demonstrate that the enantiomeric excess of these compounds was maintained during the CuAAC reaction since these compounds are known to form stabilized carbocations under metal- and acid-catalyzed conditions.[22] The enantiomerically enriched N-propargylated 3-hydroxy-oxindoles were subjected to the CuAAC conditions with azides **12a**−**c** (Table 4, entries 1−14). The enantiomeric excess of the triazole-containing 3-hydroxy-3-indolyl-oxindole **4ba** was confirmed by HPLC analysis using chiral stationary phase by comparison to the triazoles produced by racemic synthesis.[23] Due to the similarity of hydroxy-oxindoles **13**−**15**, the retention of enantiomeric excess for **4ba** was used as a model for retention of enantioselectivity for all triazole products. Enantiomerically

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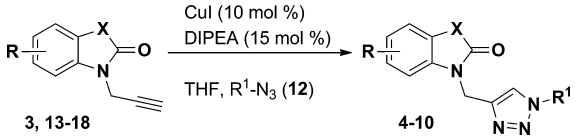
Table 4. Synthesis of Triazole-Functionalized Isatins, Oxindoles, and Spirooxindoles



entry	R	isatin/oxindole	azide (R^1)	product[a]	yield (%)[b]
1	5-F	**13b**	**12a**	**4ba**	78
2	5-F	**13b**	**12b**	**4bb**	80
3	5-F	**13b**	**12c**	**4bc**	99
4	5-F	**14b**	**12a**	**5ba**	64
5	5-F	**14b**	**12b**	**5bb**	71
6	5-F	**15b**	**12a**	**6ba**	56
7	5-F	**15b**	**12b**	**6bb**	99
8	4-Cl	**13c**	**12a**	**4ca**	40
9	4-Cl	**13c**	**12b**	**4cb**	70
10	4-Cl	**14c**	**12a**	**5ca**	94
11	4-Cl	**14c**	**12b**	**5cb**	58
12	4-Cl	**15c**	**12a**	**6ca**	91
13	4-Cl	**15c**	**12b**	**6cb**	94
14	4-Cl	**15c**	**12c**	**6cc**	58
15	H	**16a**	**12c**	**7ac**	95
16	H	**16a**	**12f**	**7af**	95
17	5-F	**16b**	**12b**	**7bb**	62
18	5-F	**16b**	**12c**	**7bc**	97
19	7-F	**16f**	**12a**	**7fa**	70
20	H	**3a**	**12d**	**8ad**	69
21	H	**3a**	**12a**	**8aa**	99
22	H	**3a**	**12e**	**8ae**	95
23	4-Cl	**3c**	**12a**	**8ca**	55
24	4-Cl	**3c**	**12f**	**8cf**	99
25	4-Cl	**3c**	**12c**	**8cc**	97
26	5-Br	**3d**	**12a**	**8da**	74
27	5-OMe	**3e**	**12a**	**8ea**	99
28	5-F	**17b**	**12b**	**9bb**	74
29	4-Cl	**17c**	**12a**	**9ca**	88
30	4-Cl	**17c**	**12b**	**9cb**	94
31	4-Cl	**17c**	**12c**	**9cc**	88
32	4-Cl	**17c**	**12f**	**9cf**	87
33	4-Cl	**17c**	**12d**	**9cd**	99
34	H	**18a**	**12a**	**10aa**	92
35	H	**18a**	**12b**	**10ab**	76
36	H	**18a**	**12f**	**10af**	70
37	H	**18a**	**12d**	**10ad**	90
38	5-F	**18b**	**12a**	**10ba**	80
39	5-F	**18b**	**12b**	**10bb**	74
40	5-F	**18b**	**12c**	**10bc**	70
41	5-F	**18b**	**12e**	**10be**	94
42	5-F	**18b**	**12d**	**10bd**	74
43	4-Cl	**18c**	**12b**	**10cb**	66
44	4-Cl	**18c**	**12d**	**10cd**	93
45	5-Br	**18d**	**12a**	**10da**	99

[a]All reactions performed with CuI (10 mol %) and DIPEA (15 mol %) in THF from 12 to 24 h. [b]Isolated yield.

enriched spiroindolone **16b** was used to demonstrate that the enantiomeric excess for this class of spirooxindoles is retained under CuAAC reaction conditions (entry 17).

The spirocyclic oxazolines **17** and **18** afforded spirocyclic triazoles **9** and **10** in excellent yields (Table 4, entries 28−45); however, the reversed order of the reaction sequence was also investigated. For spirooxazoline-triazole **9**, the titanium(IV)-catalyzed addition and spirocyclization of 5-methoxyoxazole **11e** can also be performed using a triazole-containing isatin (derived from azide **12a**) in 71% yield and maintaining high diastereoselectivity (97:3 dr). However, the success of the spirocyclization is dependent on the nature of the triazole substrate (see Supporting Information). Although the reaction proceeded successfully with the isatin triazole derived from *p*-methoxy phenyl azide **12a**, the use of an isatin triazole derived from azide **12b** did not undergo spirocyclization, presumably

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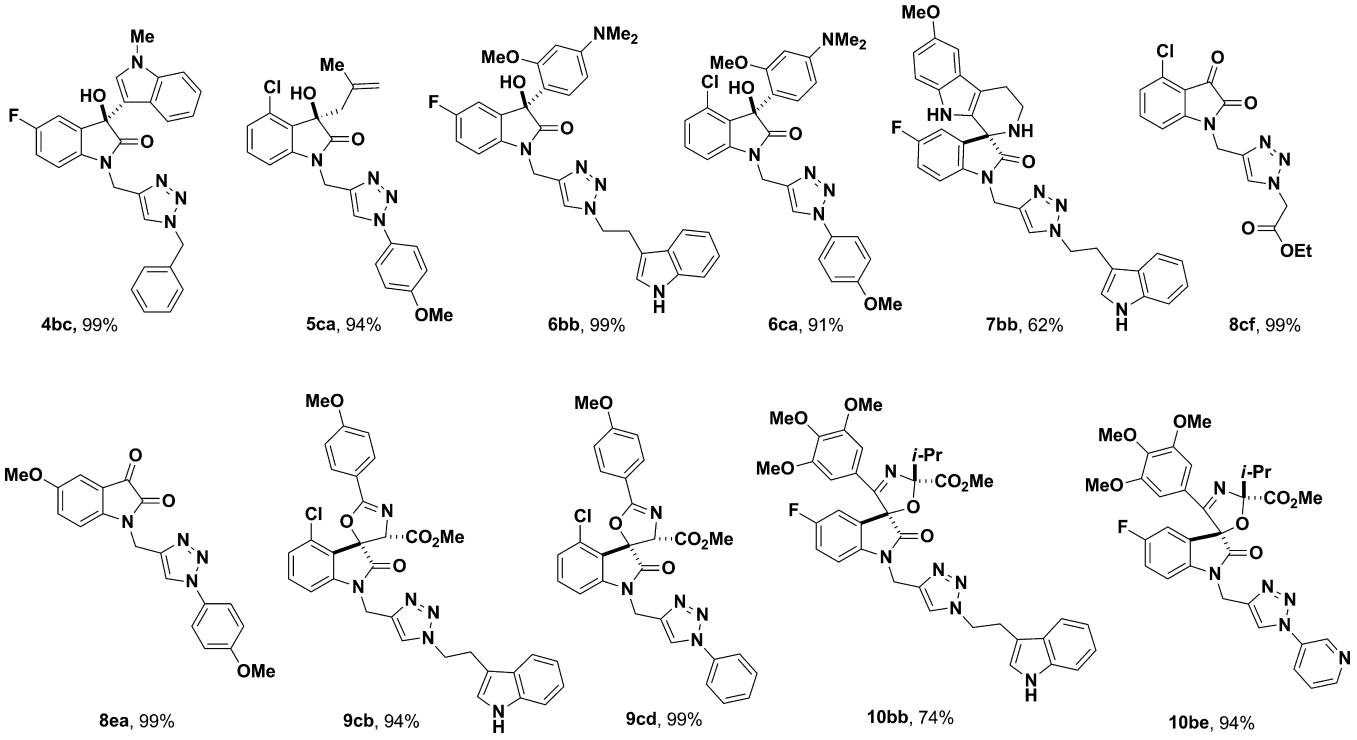
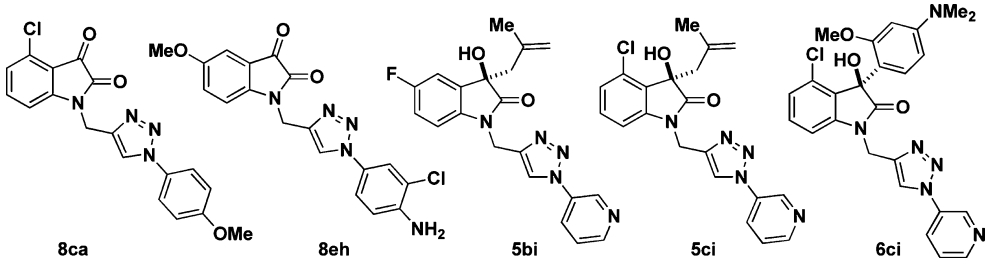


Figure 2. Representative final oxindole and spirooxindole products.

Table 5. Synthesis of Triazole-Functionalized Oxindoles and Isatins from Aryl-iodides



entry	R^1	isatin/oxindole	Ar–N_3[a]	product	yield (%)[b]
1[c]	4-Cl	**3c**	**12g**	**8ca**	23
2[c]	5-OMe	**3e**	**12h**	**8eh**	35
3[d]	5-F	**14b**	**12i**	**5bi**	28
4[d]	4-Cl	**14c**	**12i**	**5ci**	40
5[d]	4-Cl	**15c**	**12i**	**6ci**	19

[a]Azide generated in situ from the corresponding aryl-iodide. [b]Isolated yield. [c]Reactions performed using CuI (10 mol %), and DMEDA (15 mol %) according to Scheme 3, eq 3. [d]Reaction performed with 1 equiv of $CuSO_4 \cdot 5H_2O$, and 1.1 equiv of sodium ascorbate.

due to interactions between the indole ring and the titanium catalyst.

Although our earlier investigations had shown that the one-pot reaction using aryl iodides proceeded with low yield, we briefly explored this approach to incorporate additional triazole diversity (Table 5). For example, this one-pot method allows the synthesis of triazole isatin **8eh** containing an amino group, which cannot be accessed with the previous route described above (Table 4). This CuAAC strategy uses 10 mol % of CuI and 15 mol % of DMEDA with one equivalent of aryl-iodide and one equivalent of the alkyne in DMF.[18] Triazoles **8ca** and **8eh** were obtained when isatins **3c**,**e** were subjected to the reaction with aryl-iodides; however, low yields were observed (Table 5, entries 1–2). Similarly, with hydroxy-oxindoles **14** and **15**, the reaction was sluggish with catalytic amounts of copper, also affording low yields of the triazole products. When the amount of copper was increased to stoichiometric amounts, several unidentified side-products were formed and the increase in yield was negligible. In order to reduce the amount of side products and increase yields, conditions were modified to use a stoichiometric amount of copper(II) reagent with sodium ascorbate to generate the catalytic Cu(I) species in situ. Even with these optimized conditions, the yield of pyridinyl triazoles remained low (Table 5, entries 3–5). This result is in contrast to the reaction of pyridyl azide **12e**, which was successfully utilized and afforded triazole products with excellent yields (Table 4, entries 22 and 41). However, this method can provide additional interesting compounds for biological screening.

An analysis of the molecular properties and shape for this collection of oxindole compounds indicates desirable properties

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and diversity for high-throughput screening and the discovery of pharmaceutical leads or biological probes. Molecular properties for all compounds were calculated (see Supporting Information) and a summary of the average values are provided in Table 6. The majority of compounds and average values are within accepted ranges for the development of lead compounds.[24] The nucleophile and azide building blocks selected here afford a collection of compounds with molecular weights ranging from 259 to 721, and calculated partition coefficients (cLogP) values with a range of 0.56 to 5.38, based on the XLogP method of Wang.[25] The molecular weights span a range that includes molecular weights appropriate for lead-like molecules, as well as access to higher molecular weight compounds, which could prove useful as biological probes for the disruption of protein−protein interactions.[26] In order to visualize the molecular shape diversity, we generated a scatter plot based on the principal moments of inertia (PMI) ratios (Figure 3), a method developed by Sauer and Schwarz.[27] This method classifies the molecular shape into three categories: rod (acetylene), disk (benzene), or spherical (adamantane). Since several conformations of a compound are capable of binding to a biological target, a collection of 3D-conformations ≤3 kcal/mol from the minimum energy conformer are represented. This shape analysis also includes the structures of the known biologically active compounds in Figure 1 for comparison.

Table 6. Average values of Molecular Properties

property	oxindole cores (n = 15)	isatin triazoles (n = 9)	oxindole triazoles (n = 40)
MW	399	353	551
XLogP[a]	3	2	3
TPSA[b]	67	81	109
rotatable bonds	4	4	8
HBA	3	4	5
HBD	1	0	1
no. of rings	2	3	4

[a]XLogP is used for the calculated partition coefficients (cLogP) values based on the method of Wang, see ref 25. [b]Topological Polar Surface Area (TPSA) based on the method of Ertl, see ref 28.

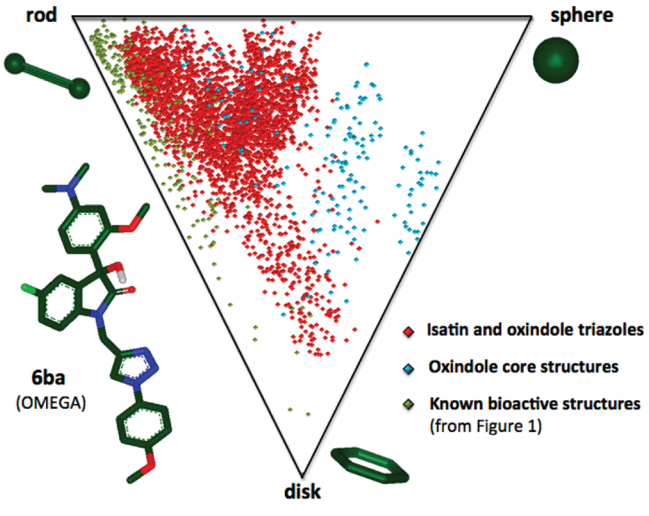

Figure 3. Scatter plot with principal moments of inertia (PMI) ratios plotted to compare the molecular shape diversity of oxindole core structures (blue), triazole-containing isatins and oxindoles (red), and known biologically active compounds from Figure 1 (green). For each compound, PMI ratios were calculated for all minimum energy conformers ≤3 kcal/mol from the global minimum.

In conclusion, we have developed an efficient enantio- and diastereoselective synthetic strategy to access a diverse 64-compound pilot-scale library including 15 oxindole scaffolds and 49 triazole containing-oxindoles and isatins. We demonstrate that enantiomeric excess resulting from the catalytic asymmetric synthesis of oxindoles and spirooxindoles is retained upon further functionalization with the CuAAC reaction, thus providing efficient methods to prepare libraries of enantiomerically enriched spirocyclic compounds. The nucleophile and azide building blocks selected here afford a collection of compounds with diversity that is appropriate for high-throughput screening and the discovery of pharmaceutical leads or biological probes. All of the compounds in this report have been submitted to the *NIH Molecular Libraries Small Molecule Repository* for biological screening.

■ ASSOCIATED CONTENT

Supporting Information

Complete characterization data for 27 compounds, including HPLC data for enantioenriched compounds; ^{1}H NMR spectra and mass spectrometry data available for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

A.K.F. conceived the strategy and experiments; J.P.M., J.J.B., G.E.A., and A.S. designed and performed the experiments; A.K.F. and J.P.M. cowrote the manuscript; J.P.M. and J.J.B. cowrote the Supporting Information.

Notes

The authors declare no competing financial interest.

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