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# 3-Chlorooxindoles: Versatile Starting Materials for Asymmetric Organocatalytic Synthesis of Spirooxindoles

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**Abstract:** 3-Chlorooxoindoles have emerged as versatile precursors in the synthesis of spirocyclopropyl oxindoles. High enantio- and diastereoselectivity was attained under conditions of both iminium/enamine and H-bonding catalysis.

**Keywords:** asymmetric synthesis; organocatalysis; oxindoles; spiro compounds

Spirocyclic oxindole scaffolds in recent years have continued to draw attention as important and challenging structural motifs featuring in many natural and synthetic compounds.[1–3] The core structure can be found in many bioactive molecules exhibiting a diverse range of biological activities. For instance, spirooxindole **1** showed nanomolar activity as an HIV-1 non-nucleoside reverse transcriptase inhibitor,[4,5] whereas compounds of type **2** exhibited promising antitumor activity[6,7] and were also effective for the treatment of obesity and diabetes (Figure 1).[8] It is worth noting that the compounds in question were tested as racemates, making them highly desirable targets for asymmetric synthesis and subsequent biological evaluation in the enantiopure form. Recently, spiroindolone **3** showed good antimalarial activity at low nanomolar concentrations making this class of compounds potential drug candidates against malaria.[9]

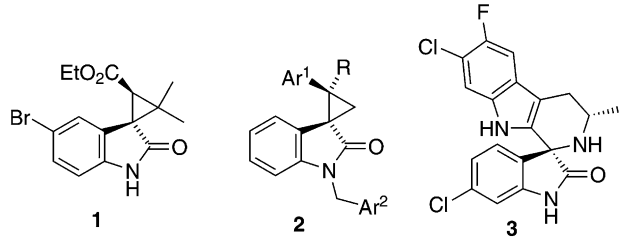



**Figure 1.** Bioactive spirooxindoles.

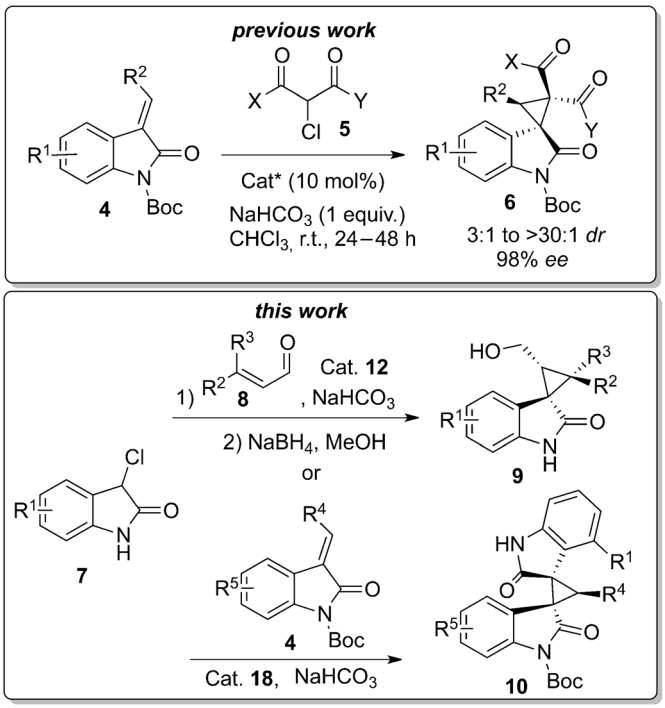
Generation of a chiral quaternary center at the 3-position of the oxindole ring remains a major challenge in the synthesis of spirooxindoles. Furthermore, it is often followed by sequential formation of arrays of other quaternary/tertiary centers, adding to the complexity of diastereo- and enantioselective synthesis. In general, the construction of even a single quaternary center is considered a challenge in asymmetric synthesis.[10]

Organocatalytic asymmetric cascades represent a promising strategy for the formation of spirooxindoles with efficient diastereo- and enantiocontrol, as the chirality generated in the first step of the sequence further influences the formation of the adjacent centers.

Currently, there are two main organocatalytic strategies for setting up a spiro stereocenter at the 3-position of the oxindole ring. The first one relies on Michael addition to exocyclic α,β-unsaturated oxindoles followed by spirocyclization.[11–15] Alternatively, the nucleophilicity of C-3 of oxindoles as enhanced by an electron-withdrawing group at this position, is exploited. The latter approach was recently employed by Melchiorre et al.[16] in a cascade addition of 3-hydroxyoxindoles to unsaturated aldehydes leading to spirolactones, and by us[17] using 3-chlorooxindoles. It is worth noting that 3-hydroxyoxindoles experienced a rather poor diastereocontrol resulting in nearly equimolar quantities of two diastereoisomers.[18]

The dual nucleophilic/electrophilic character of C-3 in 3-chlorooxindoles **7** provides an excellent opportunity for constructing an all-carbon quaternary center at this position by organocatalytic cascade reactions.




**Scheme 1.** Previous and present work.[19,20]

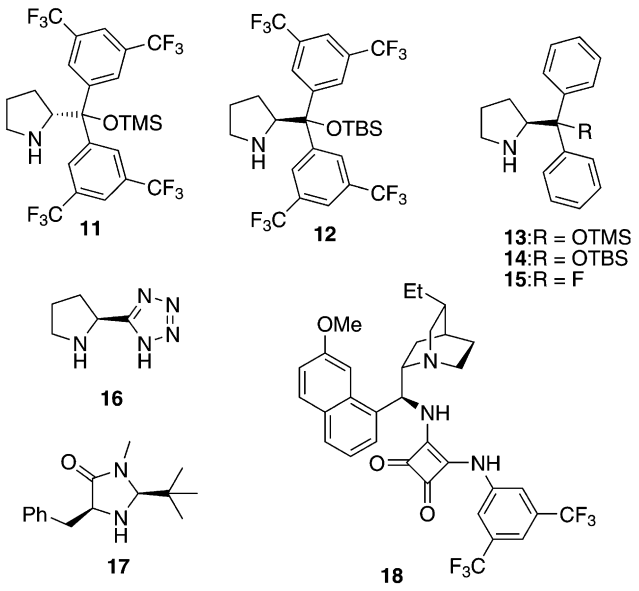



**Figure 2.** Chiral catalysts.

Thus, increased acidity of the C–H bond due to the presence of chlorine renders the 3-position more nucleophilic, while the chloride serves as a good leaving group for the subsequent cyclization step.

We recently also reported a novel domino reaction between methyleneindolinones **4** and 2-chloro-1,3-dicarbonyl compounds **5** leading to the highly stereoselective formation of spirooxindoles **6** under H-bond catalysis (Scheme 1).[20] In an effort to diversify the substitution pattern of the cyclopropane ring, 3-chlorooxindoles **7** were shown to lead to the formation of bis-spirooxindoles **10**.[17]

Herein, we present a new reaction of 3-chlorooxindoles **7** with α,β-unsaturated aldehydes **8** leading to the formation of spirooxindoles **9**, and also disclose an expanded substrate scope for the synthesis of bis-spirooxindoles **10**.

Motivated by the pronounced biological activity of the spirooxidole-containing compounds, in association with diversity oriented synthesis,[21] we set out to develop a general methodology to access the core spirocyclopropane motif[22,23] starting from 3-chlorooxindoles **7**. Two different strategies were envisioned: (i) aminocatalysis, for the reaction with α,β-unsaturated aldehydes **8** and (ii) H-bond catalysis, for the reaction with methyleneindolinones **4** (Scheme 1). The common feature of both strategies is the generation of two stereogenic centers in the initial Michael addition, followed by diastereoselective cyclization. During the course of the cascade, three stereogenic centers are formed and, therefore, a high level of stereocontrol has to be effected to ensure that the resulting products are formed with high enantio- and diastereoselectivities.

We have demonstrated earlier that 3-chlorooxindoles **7** can undergo a Michael addition to nitroolefines under H-bond catalysis.[17] Therefore, we envisioned that under conditions of aminocatalysis a similar reaction with α,β-unsaturated aldehydes **8** would give rise to spirooxindoles **9**.

Preliminary optimization experiments were carried out employing model substrates – 3-chlorooxindole **7a** and *para*-methoxycinnamaldehyde **8a** (Table 1).

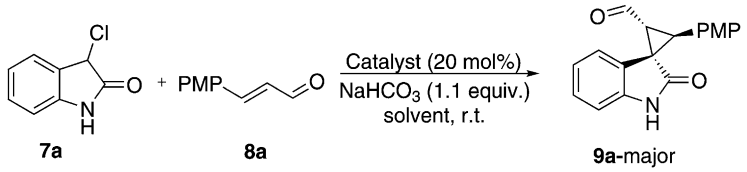
Catalyst screening revealed the catalyst **12** (Figure 2) to be the most selective and active for the reaction, resulting in a smooth conversion within three hours (Table 1, entry 2). The diastereoselectivity was further improved by changing the solvent from chloroform to toluene (Table 1, entry 9) and by reducing the concentration of oxindole **7a** (Table 1, entry 11). Both changes, lowering the temperature (Table 1, entry 8) and catalyst loading (Table 1, entry 10) had a detrimental effect on the reaction rate and diastereoselectivity.

The reaction product, aldehyde **9a**, turned out to be relatively unstable and prone to epimerization, thus complicating purification. Therefore, throughout the investigation, the products were *in situ* reduced to the corresponding alcohols with sodium borohydride.

With optimal conditions in hand (Table 1, entry 11), the reaction scope was examined next (Table 2). Gratifyingly, the diastereomeric ratios using 3-chlorooxindoles **7** were much higher than those observed for 3-hydroxyoxindoles. In the case of **7a**, using a two-fold excess of **8a** not only increased the reaction rate but also significantly improved the diastereoselectivity

**Table 1.** Optimization of reaction conditions.[a]

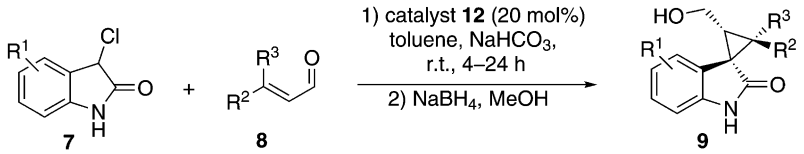



**7a** **8a** **9a**-major

| Entry | Catalyst | Solvent | Time [h] | Yield [%][b] | *dr*[c] | *ee* [%][d] |
|---|---|---|---|---|---|---|
| 1 | **11** | $CHCl_3$ | 3 | 95 | 3:1 | −97 |
| 2 | **12** | $CHCl_3$ | 3 | 89 | 4:1 | 98 |
| 3 | **13** | $CHCl_3$ | 16 | 55 | 1.3:1 | 79 |
| 4 | **14** | $CHCl_3$ | 16 | 61 | 1.2:1 | 95 |
| 5 | **15** | $CHCl_3$ | 16 | 99 | 1.5:1 | 95 |
| 6 | **16** | $CHCl_3$ | 3 | 95 | 2.7:1 | 8 |
| 7 | **17** | $CHCl_3$ | 24 | – | n.d. | n.d. |
| 8 | **11** | $CHCl_3$ | 15[e] | 95 | 2.6:1 | 94 |
| 9 | **12** | toluene | 3 | 95 | 7.1:1 | 98 |
| 10 | **12** | toluene | 5.5[f] | 95 | 5.3:1 | 97 |
| 11 | **12** | toluene | 9[g] | 95 | 9:1 | 98 |

[a] Unless stated otherwise, the reactions were carried out on a 0.1-mmol scale as a 0.2 M solution (in respect to **7a**) at room temperature with 1 equiv. of **7a**, 1.2 equiv. of **8a**, 1.1 equiv. of $NaHCO_3$ and 20 mol% catalyst loading. PMP = *p*-methoxyphenyl.
[b] Yield of isolated product.
[c] Determined from crude product by $^1$H NMR. Only two diastereoisomers were detected.
[d] Determined by chiral HPLC analysis.
[e] Reaction at 4 °C.
[f] 10 mol% of catalyst used.
[g] Reaction mixture 0.1 M.

**Table 2.** Cyclopropanation of α,β-unsaturated aldehydes **8a–h** with 3-chlorooxindoles **7a–c**.[a]

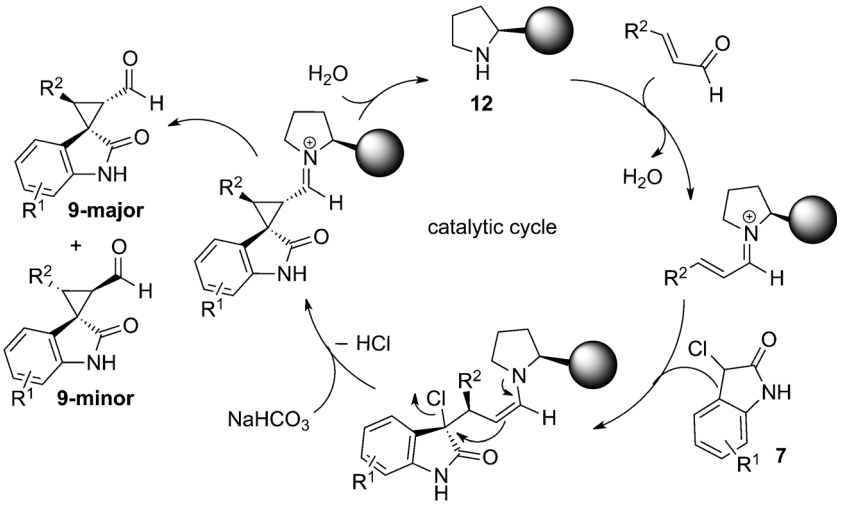



**7** **8** **9**

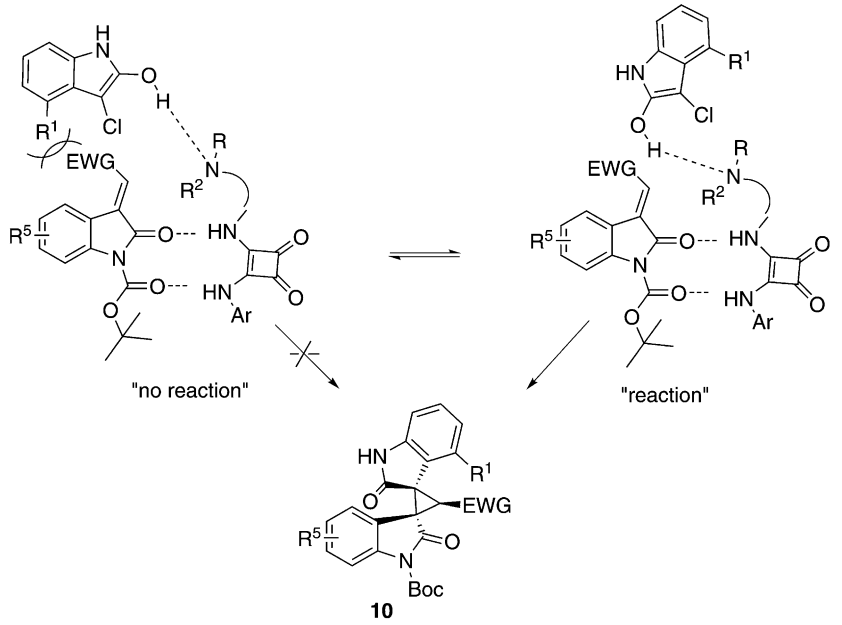
| **9** | **7** | **8** | $R^1$; $R^2$; $R^3$ | Yield [%][b] | dr[c,d] | *ee* [%][e] |
|---|---|---|---|---|---|---|
| **9aa** | **7a** | **8a** | H/4-MeO-$C_6H_4$/H | 71[f] | 19:1 (19:1) | >99 |
| **9ab** | **7a** | **8b** | H/Ph/H | 64 | 5:1 (10:1) | >99 |
| **9ac** | **7a** | **8c** | H/4-Br-$C_6H_4$/H | 44 | 5:1 (10:1) | 98 |
| **9ad** | **7a** | **8d** | H/4-$NO_2$-$C_6H_4$/H | 53 | 4:1 (7:1) | 98 |
| **9ba** | **7b** | **8a** | 4-Br/4-MeO-$C_6H_4$/H | 66[f] | 10:1 (14:1) | 98 |
| **9ca** | **7c** | **8a** | 5-Br/4-MeO-$C_6H_4$/H | 76[f] | 19:1 (20:1) | >99 |
| **9ae** | **7a** | **8e** | H/thiophen-2-yl/H | 60 | 5:1 (10:1) | 96 |
| **9af** | **7a** | **8f** | H/furan-2-yl/H | 69 | 19:1 (19:1) | 98 |
| **9ag** | **7a** | **8g** | H/Me/H | 62[g] | 2:1 (2:1) | 75/87 |
| **9ah** | **7a** | **8h** | H/Me/Me | 69[f] | 4:1 (4:1) | 36/89 |

[a] Unless stated otherwise, the reactions were carried out on a 0.2-mmol scale as a 0.1 M solution at room temperature with 1 equiv. of **7**, 1.2 equiv. of **8**, 1.1 equiv. of $NaHCO_3$ and 20 mol% catalyst loading.
[b] Yield of isolated product after reduction to an alcohol.
[c] Determined from crude product after reduction to an alcohol by $^1$H NMR.
[d] Diastereomeric ratio of isolated product in the brackets.
[e] Determined by chiral HPLC analysis from isolated product.
[f] Reaction with 2 equiv. of **8**.
[g] Reaction with 5 equiv. of **8**.




**Scheme 2.** Proposed catalytic cycle for the synthesis of spirooxindoles **9**.




**Scheme 3.** Proposed transition state for the synthesis of bis-spirooxindoles **10**.

(Table 1, entry 11 and Table 2, entry 1). Unfortunately, this trend did not prove to be general with other α,β-unsaturated aldehydes **8**. Therefore, to maximize the atom economy and the reaction selectivity, 1.2 equivalents of aldehyde **8** were used in most cases (Table 2, see footnotes).

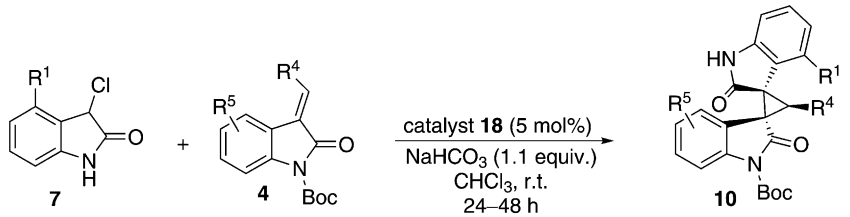
All cinnamic-type aldehydes **8a–d** yielded products with good diastereo- and high enantioselectivities. It is noteworthy that significant enrichments in diastereoselectivity could be effected during column chromatography, as the isomers were separable in most cases (Table 2).

When an aliphatic aldehyde, crotonaldehyde (**8g**), was subjected to the reaction conditions, the product was isolated with moderate diastereoselectivity but with good enantioselectivities for both isomers (Table 2, **9ag**). Most significantly, even prenal **8h** gave a smooth conversion to the desired product, although selectivity for the major isomer was moderate (Table 2, **9ah**). Substituents in the indole ring were well tolerated (Table 2, **9ba** and **9ca**), as well as heteroatoms in unsaturated aldehydes **8e** and **8f** yielding the products with high selectivities (Table 2, **9ae** and **9af**).

The reaction is believed to proceed over the cascade of initial Michael addition followed by cyclization (Scheme 2). That assumption was supported by the fact that in the case of spirooxindole **9ba** the un-

**Table 3.** Synthesis of bis-spirooxindoles.[a]




| 10 | 7 | 4 | $R^1$; $R^4$; $R^5$ | Yield [%][b] | *dr*[c] | *ee* [%][d] |
|---|---|---|---|---|---|---|
| **10aa** | **7a** | **4a** | H/COOMe/H | 99 | 1.4:1 | 96 |
| **10da** | **7d** | **4a** | Cl/COOMe/H | 96 | 14:1 | 95 |
| **10 db** | **7d** | **4b** | Cl/COOEt/H | 95 | 30:1 | 93 |
| **10bb** | **7b** | **4b** | Br/COOEt/H | 91 | 10:1 | 92 |
| **10eb** | **7e** | **4b** | Me/COOEt/H | 71[e] | 12:1 | 89 |
| **10dc** | **7d** | **4c** | Cl/COOEt/5-$NO_2$ | 95 | 12:1 | 84 |
| **10dd** | **7d** | **4d** | Cl/COOEt/7-F | 99 | 12:1 | 90 |
| **10de** | **7d** | **4e** | Cl/COOEt/5-$CF_3O$ | 81 | 12:1 | 90 |
| **10df** | **7d** | **4f** | Cl/CN/5-Br | 87 | 20:1 | 99 |
| **10dg** | **7d** | **4g** | Cl/4-$NO_2$-$C_6H_4CO$/5-Br | 71 | 20:1 | 83 |
| **10ed** | **7e** | **4d** | Me/COOEt/7-F | 75[e] | 20:1 | 86 |

[a] Unless stated otherwise, the reactions were carried out on a 0.1-mmol scale as a 0.2 M solution at room temperature with 1 equiv. of **7**, 1.2 equiv. of **4**, 1 equiv. of $NaHCO_3$ and 5 mol% catalyst loading.
[b] Yield of isolated product.
[c] Determined from crude product by $^1H$ NMR.
[d] Determined by chiral HPLC analysis.
[e] *Reaction conditions:* 1 equiv. of **7**, 1.2 equiv. of **4**, 2 equiv. of $NaHCO_3$ and 10 mol% of catalyst **18** at 60 °C.

cyclizised intermediate of the Michael addition was also isolated as a minor product (for details see the Supporting Information).

Next, we turned our attention to the cascade spirocyclization to furnish bis-spirooxindoles **10**. We envisioned that a similar domino reaction, involving Michael addition followed by an intramolecular nucleophilic substitution of chloride could be catalyzed by a bifunctional catalyst, incorporating both H-bond donor and acceptor groups. The use of a bifunctional catalyst did indeed allow for simultaneous activation of Michael donor **7** and acceptor **4** (Scheme 3). Based on our previous results[20] and preliminary screening, a number of *Cinchona* alkaloid-derived thioureas and squaramides were tested in the reaction. Squaramide **18** was found to be the most selective catalyst for this cascade (for details see the Supporting Information).

Under optimal reaction conditions, unsubstituted 3-chlorooxindole **7a** and methyleneindolinone **4a** provided the product in nearly quantitative yield and with high enantioselectivity, although the diastereoselectivity remained low (Table 3, **10aa**). However, a significant improvement in diastereoselectivity was observed when a substituent was introduced in the 4-position of the oxindole ring (Table 3, **10da**). Chlorine, bromine and methyl groups were well tolerated as $R^1$, although higher temperature and increased catalyst loading proved necessary in the latter instance for complete conversion. The electronic properties of the oxindole ring in **4** had little or no effect on the selectivity of the reaction.

The substrate scope was broadened by replacing the ester functionality with nitrile or ketone. Both re-

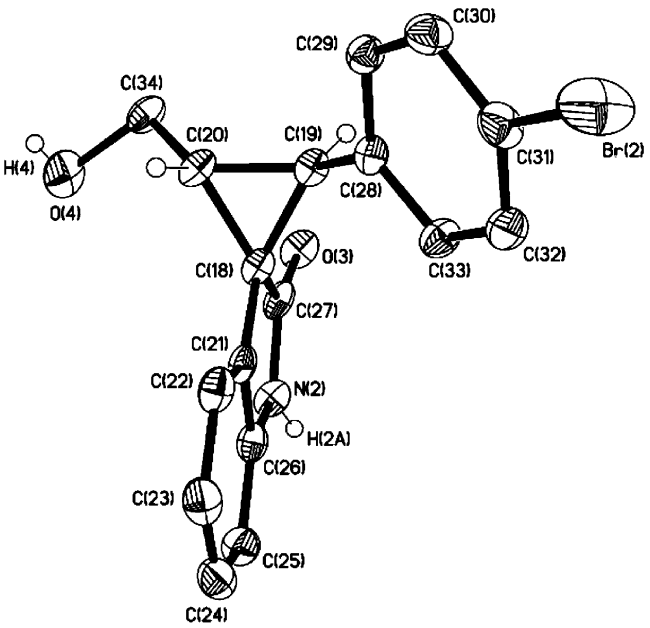



**Figure 3.** X-ray structure of spirooxindole **9ac** (one of two similar molecules in the asymmetric unit).[24,25]

acted smoothly, almost with no changes in reactivity and selectivity (Table 3, **10df** and **10dg**).

The relative stereochemistry of spirooxindoles **7** (both major and minor isomer) and bis-spirooxindoles **10** was established by NMR NOE experiments, the absolute stereochemistry by X-ray diffraction (Figure 3) and VCD experiments, respectively (for details see the Supporting Information).

In summary, we have demonstrated that 3-chlorooxindoles **7** can serve as useful precursors in the synthesis of spirocyclopropyl oxindoles under conditions of two different activation modes and, hence, employing two different classes of catalysts. We have developed a general methodology to access both spirooxindoles **9** and bis-spirooxindoles **10** in good to excellent yields and high diastereo- and enantioselectivities. Both reaction pathways feature a wide substrate scope including various substitution patterns at the indole ring.

## Experimental Section

### General Procedure for Spirocyclopropanation (Table 2)

α,β-Unsaturated aldehyde **8** (0.40 mmol), oxindole **7** (0.20 mmol), amine **12** (26 mg, 20 mol%, 0.04 mmol), and $NaHCO_3$ (1.1 equiv., 18 mg, 0.22 mmol) were dissolved in toluene (2 mL) and stirred at room temperature. The reaction was monitored by TLC. Upon completion, the mixture was diluted with MeOH (2 mL) and cooled in an ice bath. $NaBH_4$ (2 equiv., 15 mg, 0.40 mmol) was added and the reaction mixture stirred for 30 min. The mixture was poured into 10 mL of saturated aqueous $NH_4Cl$ solution, extracted with DCM (3×10 mL). The organics were combined, concentrated and directly purified by silica gel column chromatography using a mixture of heptane and EtOAc as eluent. Diastereomeric ratios were determined from the crude reaction mixture by $^1$H NMR and enantiomeric purity by chiral HPLC analysis.

### General Procedure for the Formation of Bis-spirooxindoles (Table 3)

3-Chlorooxindole **7** (1 equiv., 0.1 mmol), methyleneindolinone **4** (1.2 equiv., 0.12 mmol), $NaHCO_3$ (1 equiv., 8.4 mg, 0.1 mmol) and squaramide **18** (5 mol%, 3.2 mg) were dissolved in chloroform (0.5 mL) and stirred at room temperature. The reaction was monitored by TLC. Upon completion of the reaction, the mixture was directly purified by silica gel column chromatography using a mixture of heptane and EtOAc as eluent. The diastereomeric ratio was determined by $^1$H NMR and the enantiomeric purity by chiral HPLC analysis.

### Supporting Information

Experimental details, NMR spectral characterization data for all compounds are given in the Supporting Information.

## Acknowledgements

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[18] For organometallic example see: B. M. Trost, K. Hirano, *Org. Lett.* **2012**, *14*, 2446–2449.
[19] In our previous paper, the configuration of spirooxindoles **6** was assumed by analogy from the calculated VCD data for dimethyl malonate derivative, herein, we present X-ray evidence for ethyl acetoacetate analogue (for details see the Supporting Information), unambiguously confirming the absolute configuration. CCDC 916342 contains the supplementary crystallographic data for compounds **6**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
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[24] *Crystal data* for **9ac**: $C_{17}H_{14}BrNO_2$, $M=344.20$, colourless tablet, $0.96\times0.66\times0.12\ mm^3$, orthorhombic, $P2_12_12_1$, $a=8.2115(7)$, $b=13.4656(12)$, $c=26.810(2)$ Å, $V=2964.5(4)$ Å$^3$, $Z=8$, $\mu$(Mo-K$\alpha$)$=2.78\ mm^{-1}$, $\rho_{calcd}=1.542\ g\,cm^{-3}$, 8968 reflections measured with graphite monochromated Mo-K$\alpha$ radiation at $T=150$ K ($\lambda=0.71073$ Å), 7553 unique, $R_{int}=0.051$, solved by direct methods,[25] $R_1[F^2>2\sigma(F^2)]=0.039$, $wR_2$ (all data)$=0.096$. Largest difference map features within $\pm0.86\ e\,Å^{-3}$. Two similar molecules in the asymmetric unit. Flack $x=0.000(8)$; absolute structure reliably determined. CCDC 916343 contains the supplementary crystallographic data for compound **9ac**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
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