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Diastereodivergent Synthesis of 3-Spirocyclopropyl-2-oxindoles through Direct Enantioselective Cyclopropanation of Oxindoles

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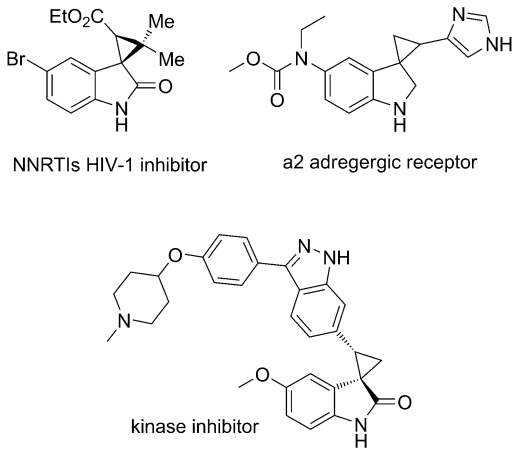
Oxindoles are structural motifs that are widely present in natural products and medicinally important agents.[1] In particular, spirocyclic oxindoles bearing a quaternary stereogenic center at the 3-position possess significant biological profiles. In this context, syntheses of 3-spirocyclic oxindoles bearing a five-[2] or six-membered[3] ring system have been intensively investigated due to the biological importance of these molecules. Spirocyclopropyl oxindoles have shown remarkable biological activities (Scheme 1),[4] and as such are molecules of high synthetic value.[2c,5] Surprisingly, methods



Scheme 1. Bioactive molecules containing a spirocyclopropyl oxindole/indoline motif.

for the preparation of 3-spirocyclopropane-2-oxindoles are very limited.[6] To the best of our knowledge, only one example of the enantioselective construction of cyclopropyl spirooxindoles has been reported recently; Bartoli, Bencivenni et al. utilized a Michael–alkylation cascade to realize the enantioselective nitrocyclopropanation of 3-alkylidene oxindoles.[7] As part of our ongoing efforts towards the efficient creation of quaternary stereogenic centers and chiral spirooxindole derivatives,[8] we became interested in developing an enantioselective synthetic method for the direct cyclopropanation of oxindole substrates.

Asymmetric cyclopropanation reactions have fascinated organic chemists for decades because the cyclopropane motif is both synthetically useful and biologically important.[9] Well-established synthetic strategies for asymmetric cyclopropanation include the Simmons–Smith reaction,[10] transition-metal-catalyzed decomposition of diazoalkanes,[11] Michael-initiated ring-closure reactions,[12] and many others.[13] In the past few years, organocatalytic cyclopropanation has emerged as a powerful approach for the construction of chiral cyclopropanes.[14] However, a direct cyclopropanation method to access spirocyclopropyl oxindoles has yet to be developed. In the reported organocatalytic cyclopropanation methods,[14] α-halogenated carbonyl compounds are commonly utilized as a C_1 synthon, which contains a nucleophilic/electrophilic center for the construction of cyclopropanes.

From a practical point of view, it would be ideal if simple oxindoles could be used directly as a C_1 synthon for the synthesis of cyclopropyl spirooxindoles. We envisioned that the employment of oxindoles containing a dinucleophilic center as a C_1 synthon, in combination with a suitable dielectrophilic C_2 synthon (e.g., halogenated nitroolefins), might provide a straightforward cyclopropanation strategy. In the presence of a suitable catalyst, oxindole can readily add to a nitroolefin. After intramolecular proton transfer, an S_N2 substitution is expected to generate the cyclopropane core. Ostensibly, the O-alkylation product[15] may be formed in addition to the desired C-alkylation product (Scheme 2). It is noteworthy that utilization of a dinucleophilic C_1 synthon in asymmetric organocatalytic cyclopropanation is unknown, and the use of halogenated nitroolefins in asymmetric cyclopropanation has also not been disclosed. Notably, Connon and co-workers have described a stereoselective synthesis of functionalized nitrocyclopropanes by employing nitroolefins as a reaction component. However, their attempt to utilize a halogenated nitroolefin in the asymmetric cyclopropanation led to disappointing results.[14f] Herein, we describe the first direct highly diastereoselective and enantioselective cyclopropanation of oxindoles by employing oxindoles as a readily available C_1 synthon and (*E*)-β-bromo-β-nitroolefins as a convenient C_2 synthon.

We initiated our study by examining the reaction between N-Boc-protected oxindole **1a** and (*E*)-β-bromo-β-nitrostyrene **2a** (Table 1). Tertiary amine–thiourea catalysts[16] were

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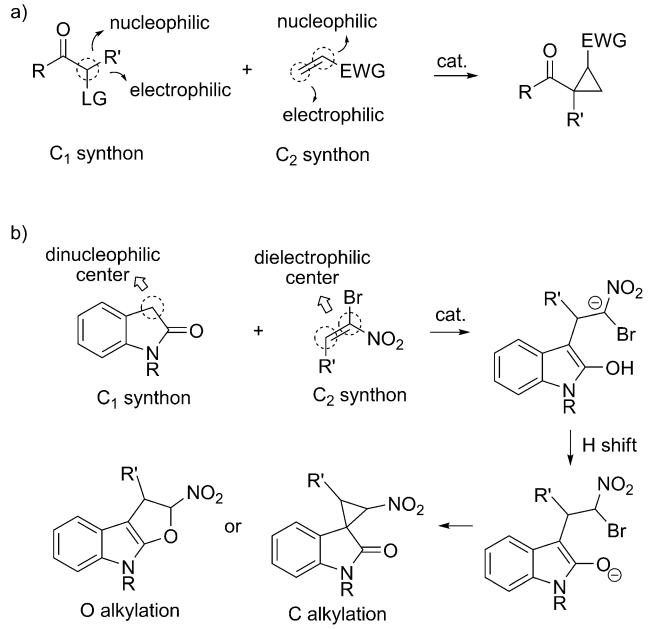
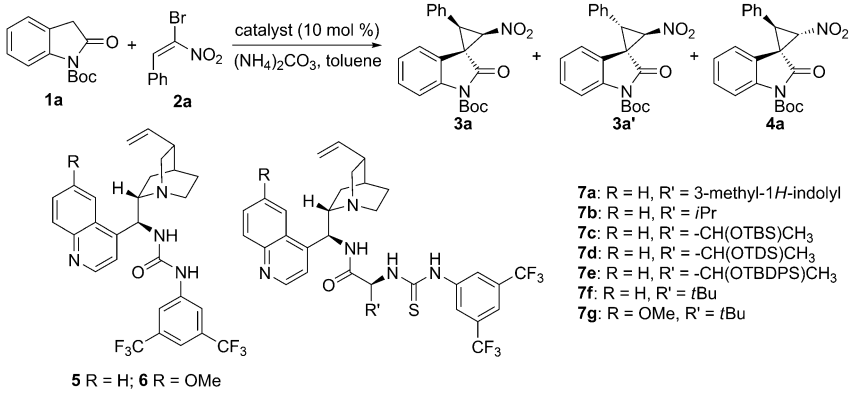


Scheme 2. Organocatalytic approaches to cyclopropanes and cyclopropyl spirooxindoles. a) The previously reported approach to organocatalytic cyclopropanation. b) The synthesis of cyclopropyl spirooxindoles, employing dinucleophilic and dielectrophilic synthons.

Table 1. The direct asymmetric cyclopropanation reaction of oxindole **1a**.[a]



Entry	Catalyst	Yield [%][b]	**3a**/**3a′**/**4a**[c]	*ee* [%][d]	
				3a/**3a′**	**4a**
1	**5**	95	28:58:14	90:93	n.d.
2	**6**	97	44:44:12	88:93	n.d.
3	**7a**	82	46:12:42	57:n.d.	80
4	**7b**	85	43:14:43	75:n.d.	87
5	**7c**	95	45:6:49	72:n.d.	85
6	**7d**	95	45:5:50	78:n.d.	86
7	**7e**	97	39:4:57	85:n.d.	86
8	**7f**	98	52:6:42	96:n.d.	92
9	**7g**	98	53:5:42	97:n.d.	92
10[e]	**7g**	98	67:9:24	97:n.d.	90

[a] Reactions were performed with **1a** (0.05 mmol), **2a** (0.06 mmol), $(NH_4)_2CO_3$ (0.05 mmol), and the catalyst (0.005 mmol, 10 mol%) in toluene (1.0 mL) at room temperature for 3 h. Products **3a** and **3a′** were obtained as a mixture, and product **4a** was easily separated from **3a** and **3a′** by column chromatography. [b] Combined isolated yield of the three stereoisomers. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis on a chiral stationary phase (n.d.: not determined). [e] $CHCl_3$ (1.0 mL) was used as the solvent and molecular sieves (5 Å, 10 mg) were added.

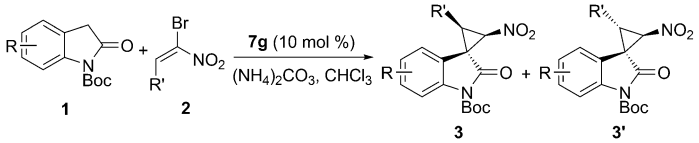
selected to promote the predicted reaction. As HBr would be generated during the reaction process, a stoichiometric amount of $(NH_4)_2CO_3$ was used as an HBr scavenger because $(NH_4)_2CO_3$ could capture the released HBr and not induce undesired background reactions.[17] Cinchona alkaloid derived compounds **5** and **6** promoted the reaction efficiently, furnishing three diastereomers **3a**, **3a′**[18] and **4a** in high yields with excellent enantioselectivities, but with very poor diastereoselectivities (Table 1, entries 1 and 2). To further improve the results, we chose to employ our recently developed amino acid incorporating multifunctional catalysts.[8c] All of the multifunctional catalysts could efficiently promote the reaction, affording the desired C-alkylation products **3a**, **3a′** and **4a** in high yields. Fine tuning of the side-chain structure of the amino acid moiety in the catalysts led to the formation of **3a** and **4a** with excellent enantio- and diastereoselectivity. However, the selectivity between **3a** and **4a** remained poor (Table 1, entries 3–9). Gratifyingly, further extensive additive and solvent studies[19] resulted in promising results; when the reaction was performed in chloroform in the presence of 5 Å molecular sieves, cyclopropyl spirooxindole **3a** was obtained in good yield and excellent *ee* (Table 1, entry 10).

The substrate scope was investigated next (Table 2). Both the oxindole and the bromonitroolefin could be varied, and cyclopropyl spirooxindoles **3** were obtained in good diastereomeric ratios and excellent enantioselectivities (Table 2, entries 1–10). When alkyl bromonitroolefin **2q** was employed, a product with high *ee* was obtained, although only in moderate yield and poor diastereoselectivity (Table 2, entry 11). When the reaction was performed on a larger scale, similar results were obtained (Table 2, entry 12).

Having stereoselectively obtained spirocyclopropanes **3**, our next task was to devise a diastereodivergent approach to selectively access cyclopropanes **4**. It is well-established that activated cyclopropanes can be readily opened by nucleophiles,[20] we therefore considered the possibility of converting **3** into **4** through a cyclopropane opening–closing process. We reasoned that the employment of a suitable nucleophile may lead to the opening of the cyclopropane ring in **3a**, and the highly stabilized oxindole enolate makes opening at the α-position of the nitro group favorable, and the subsequent ring closure may yield **4a** (Scheme 3).

The feasibility of converting **3a** into **4a** in the presence of a number of Lewis bases was studied (Table 3). When diisopropylethylamine (DIPEA) was used, only a trace amount of **4a** was observed, suggesting the importance of the nucleophilicity of the promoting base (Table 3, entry 1). Both

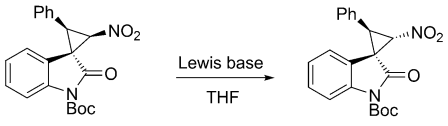
Table 2. The substrate scope of the direct cyclopropanation reaction.[a]



Entry	*t* [h]	Product (R, R′)	Yield [%][b]	**3**/**3′**[c]	*ee* [%][d]
1[e]	12	**3a** (H, Ph)	72	87:13	97
2[e]	12	**3c** (H, 3-BrC_6H_4)	81	81:19	90
3[e]	24	**3d** (H, 4-BrC_6H_4)	75	81:19[f]	95
4[e]	72	**3g** (H, 2-FC_6H_4)	63	86:14[f]	96
5	36	**3h** (H, 4-FC_6H_4)	76	82:18[f]	97
6	24	**3f** (H, 4-ClC_6H_4)	68	82:18[f]	98
7	36	**3i** (H, 2-MeC_6H_4)	60	>20:1	97
8	36	**3j** (H, 4-MeC_6H_4)	72	88:12[f]	98
9[e]	12	**3s** (6-Cl, Ph)	68	88:12	93
10	12	**3o** (6-Cl, 2-BrC_6H_4)	45	92:8	99
11	36	**3q** (H, phenethyl)	46	57:43	93
12[e,g]	12	**3a** (H, Ph)	68	85:15	95

[a] Reactions were performed with **1** (0.05 mmol), **2** (0.06 mmol), $(NH_4)_2CO_3$ (0.05 mmol), and **7g** (0.005 mmol, 10 mol%) in $CHCl_3$ (1.0 mL) at room temperature. [b] Isolated yield of **3** and **3′**. [c] Determined by ^{1}H NMR analysis. [d] The *ee* value of **3**, determined by HPLC analysis on a chiral stationary phase. [e] Molecular sieves (5 Å, 10 mg) were added. [f] Two diastereoisomers could be separated by silica gel column chromatography. [g] Reaction was performed with 0.5 mmol of oxindole **1**.

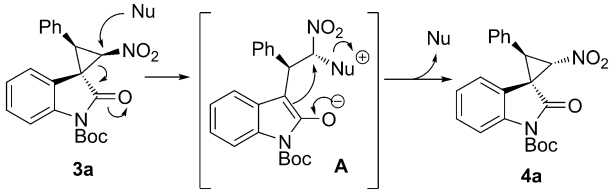
Table 3. Lewis base initiated conversion of **3a** into **4a**.[a]



Entry	Base	*t* [h]	Yield [%][b]	*ee* [%][c]
1	DIPEA	12	trace	–
2	Et_3N	6	42	94
3	DMAP	24	47	95
4	DABCO	6	73	95
5	PPh_3	24	–	–
6	quinine	6	22	86

[a] Reactions were performed with **3a** (0.05 mmol) and the base (0.05 mmol) in THF (0.5 mL) at room temperature. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase.

triethylamine and dimethylaminopyridine (DMAP) could promote conversion of **3a** into **4a** without affecting the *ee* values, however, the yields were unsatisfactory (Table 3, entries 2 and 3). 1,4-Diazabicyclo[2.2.2]octane (DABCO) was found to be the most effective promoter, leading to the formation of **4a** in good yield, and the enantiomeric excess of the product was maintained (Table 3, entry 4). Triphenylphosphine, however, was found to be completely ineffective (Table 3, entry 5). A chiral base (quinine) was also tested in the epimerization process. However, **4a** was obtained in very poor yield and with decreased *ee* (Table 3, entry 6). It is noteworthy that **3a′** remained unchanged in the epimerization process of **3a**. We believe that the conversion of **3a** into **4a** was initiated by the nucleophilic attack of the nucleophilic amine on the cyclopropane ring because the ammonium enolate intermediate[21] (Scheme 3, **A**: Nu = DABCO) was observed in mass spectra taken during the reaction.



Scheme 3. Conversion of **3a** into **4a** through a nucleophilic-catalyst-initiated cyclopropane ring opening–closing process.

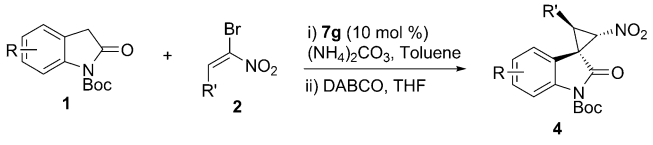
With an effective method for the creation of **4a** from **3a** in hand, we proceeded to prepare cyclopropanes **4a** directly from oxindoles **1a** and bromonitroolefins **2a** (Scheme 4). The reaction was carried out in a stepwise fashion. By using the reaction conditions we had established previously (Table 1, entry 9), a mixture of **3a** and **3a′** was isolated (**3a**/**3a′** = 53:5, **3a** 97% *ee*), and **4a** was obtained in 92% *ee*. DABCO was then introduced to effect the conversion of **3a** into **4a**. The **3a**/**3a′** mixture was subjected to epimerization by treatment with DABCO; **3a** was converted into **4a** with preservation of the *ee* value (97% *ee*), and **3a′** remained unchanged during the epimerization process. Finally, **4a** was obtained in 82% overall yield and 95% *ee* (Table 4, entry 1). It should be noted that the final product **4a** was derived from two sources, that is, through the direct cyclopropanation reaction and through epimerization from **3a**. Thus, the *ee* value obtained in this reaction sequence differs slightly from the result given in Table 2.

By following the same procedure described for the preparation of **4a**, the substrate scope of the synthesis of cyclopropyl spirooxindoles **4** was investigated (Table 4). Consistently high chemical yields and excellent diastereo- and enantioselectivities were obtained for a wide range of aryl bromonitroolefins (Table 4, entries 1–13). Variation of the substituents on the oxindole ring was also tolerated (Table 4, entries 14 and 15). Alkyl bromonitroolefins were suitable for the reaction; high *ee* values, chemical yields, and moderate diastereoselectivities were obtained (Table 4, entries 16 and 17) for these reagents. The reaction was also reproducible on a larger scale (Table 4, entry 18).

Deprotection of the final products could be easily achieved by treating them with trifluoroacetic acid (TFA) in dichloromethane (Scheme 5). The absolute configurations of products **3** and **4** were assigned based on the X-ray crystallographic analysis of a single crystal of de-Boc **3o** and product **4b**, respectively.

In summary, we have developed the first direct asymmetric cyclopropanation reaction of oxindoles. In our cyclopropanation strategy, we employed oxindoles with a dinucleophilic center as a C_1 synthon, and used bromonitroolefins, containing a dielectrophilic center, as a unique C_2 synthon. We believe that the cyclopropanation strategy reported herein will find widespread applications in synthetic organic chemistry. By using DABCO as a nucleophilic catalyst, a stereochemically retentive conversion of different diastereo-

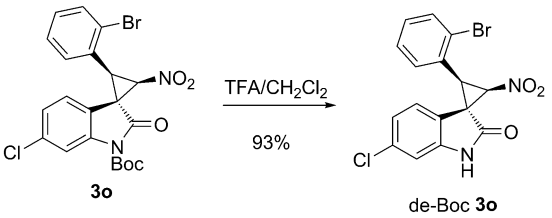
Table 4. Direct diastereoselective synthesis of cyclopropyl spirooxindoles **4**.[a]



Entry	Product (R, R′)	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**4a** (H, Ph)	82	>20:1	95
2	**4b** (H, 2-BrC_6H_4)	92	>20:1	94
3	**4c** (H, 3-BrC_6H_4)	84	>20:1	95
4	**4d** (H, 4-BrC_6H_4)	80	>20:1	96
5	**4e** (H, 2-ClC_6H_4)	85	>20:1	95
6	**4f** (H, 4-ClC_6H_4)	81	>20:1	94
7	**4g** (H, 2-FC_6H_4)	88	>20:1	94
8	**4h** (H, 4-FC_6H_4)	71	>20:1	96
9	**4i** (H, 2-MeC_6H_4)	90	>20:1	90
10	**4j** (H, 4-MeC_6H_4)	72	>20:1	95
11	**4k** (H, 1-naphthyl)	77	>20:1	97
12	**4l** (H, 2-naphthyl)	74	>20:1	96
13	**4m** (H, 2,4-ClC_6H_3)	86	>20:1	94
14	**4n** (5-Cl, 2-BrC_6H_4)	91	>20:1	98
15	**4o** (6-Cl, 2-BrC_6H_4)	95	>20:1	97
16[e]	**4p** (H, isobutyl)	69	4:1	92
17[e]	**4q** (H, phenethyl)	82	3:1	91
18[f]	**4o** (6-Cl, 2-BrC_6H_4)	93	>20:1	96

[a] Reactions were performed with **1** (0.05 mmol), **2** (0.06 mmol), $(NH_4)_2CO_3$ (0.05 mmol), and **7g** (0.005 mmol, 10 mol %) in toluene (1.0 mL) at room temperature for 6 h; in the subsequent step, crude **3** was separated and treated with DABCO (0.05 mmol) in THF (0.5 mL) at room temperature for 3 h. Compound **4** was obtained as a sum of the **4** obtained in the first step and the **4** obtained after epimerization. [b] Isolated combined yield. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis on a chiral stationary phase, *ee* value of the final combined product. [e] Reaction time was 18 h. [f] Reaction was performed with 0.5 mmol of oxindole **1**.

mers of cyclopropyl spirooxindoles was discovered. We achieved the highly diastereodivergent and enantioselective synthesis of 3-spirocyclopropyl-2-oxindoles, which are a class of compounds of great biological significance. Currently, we are extending this novel cyclopropanation approach to the preparation of other cyclopropanes, and the biological evaluation of the prepared cyclopropyl spirooxindoles is also underway.



Scheme 5. Removal of the Boc protecting group.

Acknowledgements

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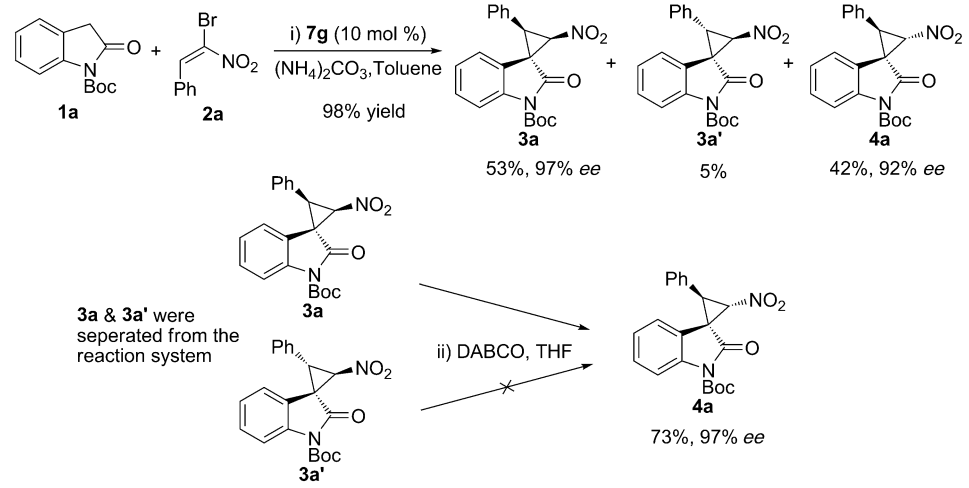
Keywords: asymmetric synthesis · cyclopropanation · domino reactions · organocatalysis · oxindole



Scheme 4. Reaction sequence for the synthesis of cyclopropyl spirooxindole **4a**.

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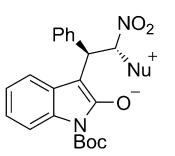

Nu=DABCO

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