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Enantioselective Synthesis of Spirooxindole α-*exo*-Methylene-γ-butyrolactones from 3-OBoc-Oxindoles

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Chiral Lewis bases facilitated the synthesis of highly functionalized spirooxindoles containing α-*exo*-methylene-γ-butyrolactones in high yields (76–92 %) and excellent enantioselectivities (up to 98 % *ee*) at ambient temperature.

Introduction

The presence of spirooxindoles in various pharmacologically active compounds stimulates interest of organic chemists in developing new methodologies for the synthesis of highly functionalized spirooxindoles.[1] The ever-increasing number of publications on the enantioselective synthesis of these scaffolds highlight their importance. Spirooxindoles bearing γ-butyrolactones (**I**; Figure 1) are formidable synthesis targets, as only a few protocols are available to prepare them in a stereoselective manner.[2] Bergonzini et al. accomplished the enantioselective synthesis of spirooxindole γ-butyrolactones by an enamine strategy with 3-hydroxyoxindole as a nucleophile (Figure 1; Route A).[2a] Racemic spirocyclic γ-butyrolactones **I** were generated by N-heterocyclic carbene (NHC) catalysis in 2006.[2b] Sun et

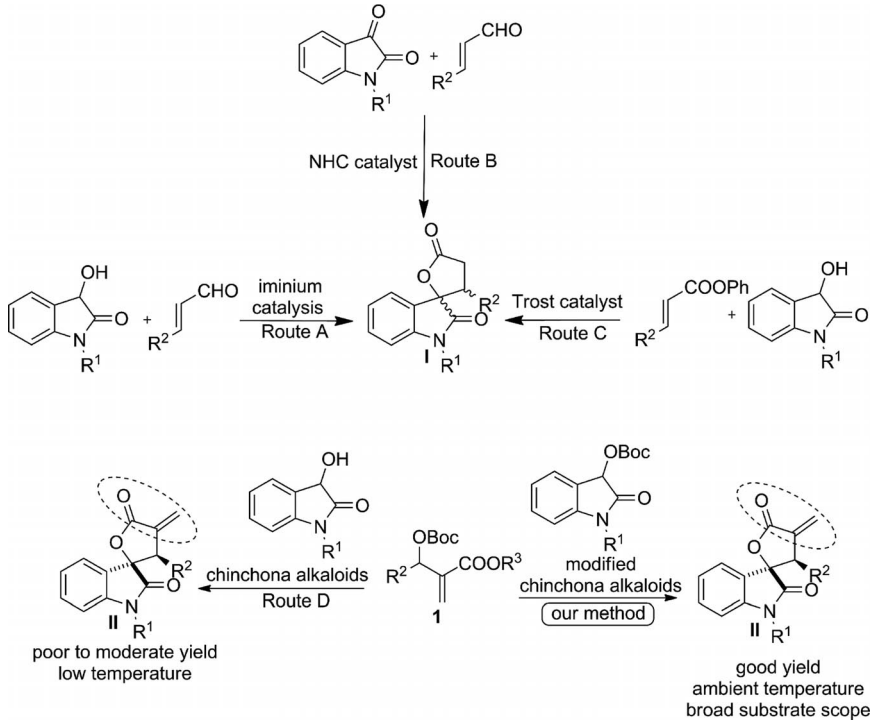

Figure 1. Strategies to create spirooxindoles bearing γ-butyrolactone.

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al.[2c] and Dugal-Tessier et al.[2d] developed an NHC-catalyzed enantioselective version that involves annulation of 1,2-dicarbonyl compounds to construct oxindole spirolactones **I** (Figure 1; Route B). Trost et al. employed an umpolung strategy in a spiroannulation reaction to synthesis oxindole-containing spiro-γ-butyrolactones **I** (Figure 1; Route C).[2e] Despite these developments, it is necessary to expand the diversity of the oxindole skeleton to improve their pharmacological properties.

α-*exo*-Methylene-γ-butyrolactone is a privileged scaffold that displays a wide range of biological activities[3] and is an important constituent of various natural products.[4] It is noteworthy that this scaffold can form covalent bonds with cysteine residues and thereby inhibit the function of proteins.[5] Among the various electrophiles that have been employed to impair the function of proteins,[6] inhibitors appended with Michael acceptors are quite common and well explored.[7]

Apart from increasing the diversity in the oxindole skeleton, the fusion of α-*exo*-methylene-γ-butyrolactone to oxindole may pave the way to the generation of more promising covalent inhibitors. Despite various efforts to construct spirooxindole γ-butyrolactones, there has been little effort to obtain enantioenriched spirooxindoles bearing α-*exo*-methylene-γ-butyrolactone (**II**) scaffolds. Hence, the development of an efficient methodology to synthesize this valuable scaffold is very much needed. To the best of our knowledge, there was no literature precedent when we commenced the enantioselective synthesis of spirooxindoles containing α-*exo*-methylene-γ-butyrolactones. While we were completing our experiments, Wang et al. described the enantioselective synthesis of identical compounds in moderate yields (Figure 1; Route D).[8] The low yield of this methodology can be attributed to the dimerization of 3-hydroxyoxindole under basic conditions[2a] and the possibility of competitive *C*,*O*-alkylation. Furthermore, the addition of 3 equiv. of Morita–Baylis–Hillman (MBH) carbonate is required to afford the corresponding lactone in moderate yield. To overcome all these shortcomings, we describe herein a simple protocol to synthesize optically enriched spirooxindole scaffolds containing α-*exo*-methylene-γ-butyrolactone (**II**) in very good yield by using 3-OBoc-oxindoles **2** as nucleophiles.

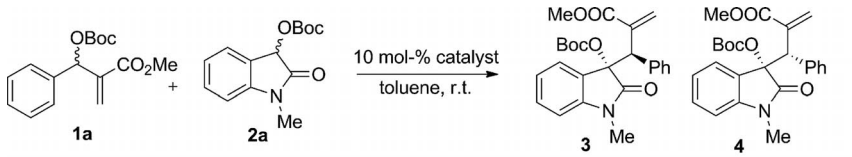
Results and Discussion

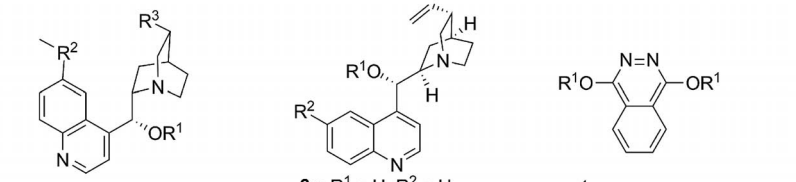
The combination of a chiral tertiary amine catalyst and MBH carbonates **1** has been well exploited to create structurally diverse compounds.[9] The asymmetric allylic alkylation of 3-aryloxindole with MBH carbonates[10] led us to apply an umpolung strategy to achieve the target spirolactones **II** in two steps. The 3-OBoc-protected *N*-methyloxindole **2a** was chosen as a nucleophile, because the resulting alkylated product **3** can be cyclized under trifluoroacetic acid conditions with ease.[11] The OBoc protection of 3-hydroxyoxindole may avoid both dimerization and competitive *O*-alkylation. Our efforts were dedicated to the identification of suitable tertiary amines to catalyze the asymmetric alkylation of MBH carbonate **1a** with 3-OBoc-oxindole **2a**. We performed the model alkylation reaction in the presence of a tertiary amine catalyst (10 mol-%), and the results are presented in Table 1.

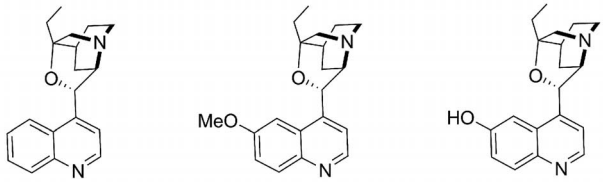
It is evident from Table 1 that quinine derivatives **5a**–**5d** failed to catalyze the alkylation reaction of MBH carbonates efficiently. Only moderate yields and enantioselectivities were obtained (Table 1, Entries 1–4). Among the cinchonine derivatives, quinidine (**6b**) afforded the expected product **3** in fair yield with very good enantioselectivity, and the diastereomeric ratio (*dr*) was 9.5:1 (Table 1, Entry 6). Efforts to increase the enantioselectivity further by using $(QN)_2$PHAL (**7a**) and $(QD)_2$PHAL (**7b**) did not produce the desired results (Table 1, Entries 10 and 11). Further attempts to enhance the enantioselectivity by using catalysts **8** (β-ICN) and **9** (β-IQD) were not fruitful. In those experiments – although good yields were obtained – only moderate to fair enantioselectivity was observed (Table 1, Entries 12 and 13). The alkylation proceeded with very good enantioselectivity and yield, but the diastereoselectivity was lower when β-ICD (**10**) was employed as the catalyst (Table 1, Entry 14). Both **6b** and **10** were chosen as catalysts for other experimental optimization studies. As the one-pot cyclization of the alkylated products (**3** and **4**) to yield α-*exo*-methylene-substituted spiro-γ-butyrolactones **II** under acidic conditions in toluene was sluggish, the identification of a suitable reaction medium was undertaken by using **6b** as the catalyst. The choice of solvent had a profound effect on both the stereoselectivity and the yield, and the results are summarized in Table 2. The use of chlorinated solvents lowered both the yield and the enantioselectivity (Table 2, Entries 1 and 2). Neither the enantioselectivity nor the diastereoselectivity improved when ethereal solvents such as methyl *tert*-butyl ether (MTBE), tetrahydrofuran (THF), and dioxane were used (Table 2, Entries 3–5). It is evident that increasing the number of methyl substituents on the benzene ring affected both the enantioselectivity and the diastereoselectivity in the desired manner (Table 2, Entries 6–10). Thus, we have identified mesitylene as the most suitable reaction medium in which excellent yield (88%) and diastereoselectivity (20:1) in addition to admirable enantioselectivity were obtained for the expected product **3** (Table 2, Entries 10 and 11). Although very good diastereo- and enantioselectivity were obtained in mesitylene, the one-pot cyclization of the alkylated product did not proceed as expected. Hence, the diastereomeric mixture **3/4** was isolated by flash column chromatography and subjected to cyclization in dichloromethane under acidic conditions to quantitatively afford the corresponding lactone of the major diastereomer with no loss of enantiopurity. Thus, we have identified a suitable tertiary amine catalyst and reaction medium to accomplish the enantioselective synthesis of α-*exo*-methylene-γ-butyrolactones **II** in good yield in two steps.

We were also curious to check whether the ester group of the MBH carbonate and the *N*-substitution of 3-OBoc-oxindole may influence the enantioselectivity (Table 3). Initially, we studied the steric effect of the ester functional

Table 1. Ligand optimization.[a]







Entry	Catalyst	Yield [%][b]	*dr* (**3**/**4**)[c]	*ee* (**3**) [%][d]
1	**5a**	64	6.2:1	–2
2	**5b**	45	5.2:1	–50
3	**5c**	trace	n.d.	n.d.
4	**5d**	63	6.1:1	–40
5	**6a**	60	8.1:1	70
6	**6b**	71	9.5:1	84
7	**6c**	54	5:1	36
8	**6d**	52	1.8:1	39
9	**6e**	trace	n.d.	n.d.
10	**7a**	trace	n.d.	n.d.
11	**7b**	trace	n.d.	n.d.
12	**8**	81	6.5:1	50
13	**9**	77	8.6:1	72
14	**10**	87	6:1	86

[a] Unless otherwise indicated, the reaction was performed with **1a** (0.18 mmol), **2a** (0.15 mmol), and 10 mol-% catalyst in toluene (1 mL). [b] Isolated yields of diastereomers **3** and **4**. [c] Determined by ^{1}H NMR spectroscopy. [d] Enantiomeric excess of major diastereomer determined by chiral HPLC.

Table 2. Influence of solvents.[a]

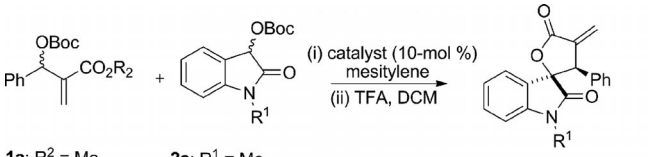
Entry	Catalyst	Solvent	Yield [%][b]	*dr* (**3**/**4**)[c]	*ee* (**3**) [%][d]
1	**6b**	$ClCH_2CH_2Cl$	40	19:1	46
2	**6b**	CH_2Cl_2	53	8.2:1	53
3	**6b**	MTBE	61	8:1	40
4	**6b**	THF	40	16.5:1	56
5	**6b**	dioxane	86	6:1	74
6	**6b**	benzene	80	2.3:1	64
7	**6b**	toluene	71	9.5:1	84
8	**6b**	xylene	92	15.2:1	84
9	**10**	xylene	92	15:1	82
10	**6b**	mesitylene	95	21.5:1	86
11	**10**	mesitylene	95	20:1	88

[a] Unless otherwise indicated, the reaction was performed with **1a** (0.18 mmol), **2a** (0.15 mmol), and 10 mol-% catalyst in the appropriate solvent (1 mL). [b] Isolated yields of diastereomers **3** and **4**. [c] Determined by ^{1}H NMR spectroscopy. [d] Enantiomeric excess of major diastereomer determined by chiral HPLC.

group of the MBH carbonates **1a**–**1c** in the presence of either **6b** or **10**. Methyl ester **1a** and ethyl ester **1b** were well tolerated when **6b** was used (Table 2, Entries 1 and 3), but the *tert*-butyl ester led to decreased enantioselectivity (Table 3, Entry 5). β-ICD (**10**) performed better than quinidine (**6b**) irrespective of ester substituents. Excellent diastereo- and enantioselectivity were observed in the presence of the *tert*-butyl ester of the MBH carbonate **1c** when **10** was employed (Table 3, Entry 6).

Having established the optimal structural requirements of the MBH carbonate and chiral catalyst, we next focused on the synthesis of spiro-α-*exo*-methylene-γ-butyrolactones from oxindoles with varying *N*-protecting groups. As unprotected oxindoles may exhibit better pharmacological activities than their protected counterparts, it is imperative to generate spirooxindole α-*exo*-methylene-γ-butyrolactones in

Table 3. Substrate optimization study.[a]



Entry	Catalyst	1	2	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**6b**	**a**	**a**	90	21:1	86
2	**10**	**a**	**a**	91	20:1	88
3	**6b**	**b**	**a**	84	17:1	80
4	**10**	**b**	**a**	86	12:1	88
5	**6b**	**c**	**a**	71	12:1	70
6	**10**	**c**	**a**	92	20:1	92
7	**10**	**c**	**b**	81	14:1	88
8	**10**	**c**	**c**	86	12:1	80
9	**10**	**c**	**d**	82	11:1	92
10	**10**	**c**	**e**	92	20:1	95

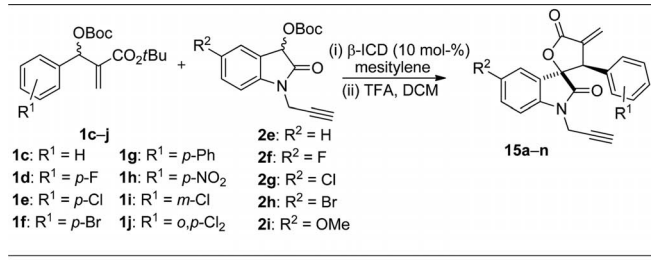
[a] Unless otherwise indicated, the reaction was performed with **1a**–**1c** (0.18 mmol), **2a**–**2e** (0.15 mmol), and 10 mol-% catalyst in mesitylene (1 mL). [b] Isolated yields of mixture of diastereomers. [c] Determined by ^{1}H NMR spectroscopy. [d] Enantiomeric excess of major diastereomer determined by chiral HPLC.

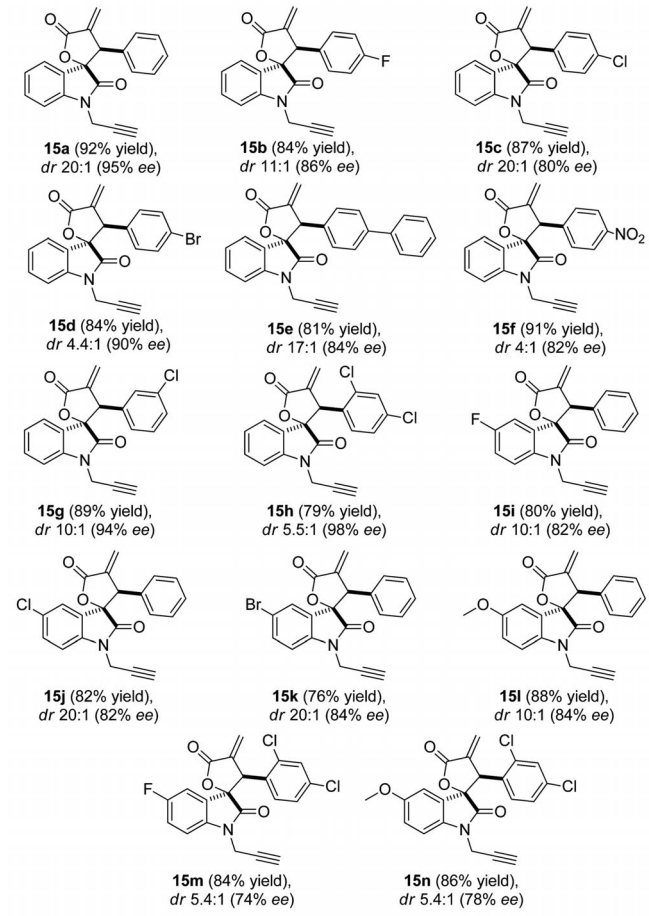
which facile deprotection of N-1 can be accomplished with ease. 3-OBoc-Oxindoles with different protecting groups, such as benzyl (**2b**), allyl (**2c**), and methyl acetate (**2d**), rendered the cyclized products **12a**–**14a** with slightly decreased enantioselectivities (Table 3, Entries 7–9) in the presence of **10**. We were delighted to observe that the *N*-propargyl-protected oxindole derivative **2e** afforded the desired lactone **15a** in high selectivity (*dr* 20:1, 95% *ee*) and yield (92%; Table 3, Entry 10). It is easier to deprotect *N*-propargyl groups than to deprotect *N*-methyl groups.[12] *N*-Propargyl protection can also be utilized for activity-based proteome profiling (ABPP) in addition to target identification by pull-down assay.[13] These experiments led to the identification of the optimal substituents on the oxindole moiety as well as on the MBH carbonates. In all of these reactions, **10** was a superior catalyst over **6b** (Table 3, Entries 1–10).

Having identified the suitable protecting group on the oxindole moiety and the substituent effects on the MBH carbonates, the investigation of the substrate scope of the MBH carbonates and oxindoles was undertaken (Table 4). Under the established catalytic conditions, nucleophile **2e** was treated with various MBH carbonates **1c**–**1j** with 10 mol-% of **10**. Halogen substituents at the *para* position (**1d**–**1f**) of the MBH carbonates did not hamper the efficiency of **10** in inducing very good enantioselectivity. The *para*-halogen-substituted spirooxindole lactones **15b**–**15d** were obtained in very good yields (84–87%), although stereoselectivity varied a little (80–90% *ee*) when the corresponding MBH carbonates **1d**–**1f** were employed. The replacement of the halogen substituent with a phenyl ring at the *para* position of MBH carbonate **1g** did not exert any negative influence, and **15e** was isolated in very good yield (81%) and high stereoselectivity (*dr* 17:1, 84% *ee*). Almost similar enantioselectivity (82% *ee*) with a significant change in the diastereoselectivity (*dr* 4:1) was noticed with an electron-withdrawing *para*-NO_2 group (**15f**).

The presence of a chloro substituent at the *meta* position (**1i**) is well accommodated, unlike a *para* substituent (**1e**), and the resulting cyclized product **15g** was isolated in good yield and with excellent enantioselectivity (94% *ee*). Interestingly, even the presence of an *ortho*-chloro substituent in the 2,4-dichloro-substituted MBH carbonate **1j** did not pose any negative impact on the enantioselectivity (98% *ee*), and the corresponding butyrolactone **15h** was isolated

Table 4. Substrate scope.[a]





[a] Unless otherwise indicated, the reaction was performed with **1c**–**1j** (0.18 mmol), **2e**–**2i** (0.15 mmol), and 10 mol-% **10** in mesitylene (1 mL).

in 79% yield. We would like to highlight that the presence of two chlorine atoms on the phenyl ring of MBH carbonate **1j** decreased the diastereoselectivity despite excellent enantioselectivity for the respective diastereomer.

After we examined the substituent effects on various MBH carbonates, we also studied the impact of different groups at the 5-position of the oxindole moiety. β-ICD can endure the presence of different substituents such as F, Cl, Br, and OMe at the 5-position of the oxindole **2f**–**2i**. In all these cases, cyclized products were isolated with similar enantioselectivities (**15i**–**15l**). The 5-chloro- and 5-bromo-substituted oxindoles **2g** and **2h** rendered the corresponding spirooxindole α-*exo*-methylene-γ-butyrolactones **15j** and **15k** with exquisite diastereoselectivity (*dr* 20:1). To study the effect of 5-fluoro and 5-methoxy substituents on the diastereoselectivity, oxindoles were treated with MBH carbonate **1j** under the established reaction conditions. It is apparent that dihalo substitution lowered the diastereoselectivity as in the case of product **15h**. The corresponding butyrolactones **15m** and **15n** were isolated with diminished diastereoselectivity. Although we obtained very good enantioselectivity for dihalo-substituted MBH carbonate **1j** with oxindole **2e**, decreased enantioselectivity was noticed for substrates **2f** and **2i** in combination with MBH carbonate **1j**.

Conclusions

We have established a simple and high-yielding protocol to access spirooxindoles comprising α-*exo*-methylene-γ-butyrolactones with excellent diastereo- and enantioselectivities (*dr* up to 20:1, 98% *ee*) at ambient temperature. By using the modified cinchona alkaloid β-ICD (**10**) as a catalyst, we created highly functionalized spirolactones in very good yields of 76–92% under the optimized conditions. Newly synthesized spirolactones are currently being evaluated against various cancer cell lines, and the results will be reported in due course. We expect that these compounds may act as covalent inhibitors owing to the presence of α-*exo*-methylene-γ-butyrolactones, and the *N*-propargyl handle may pave a way to identify biological targets.

Experimental Section

General Experimental Procedure for Catalytic Reactions: A flame-dried reaction vial was charged with *N*-protected 3-OBoc-oxindole **2a**–**2i** (0.15 mmol), MBH carbonate **1a**–**1j** (0.18 mmol), and **10** (10 mol-%) in mesitylene (1 mL). The reaction mixture was stirred under argon at ambient temperature (25 °C). The completion of the conversion (24–48 h) was ascertained by TLC, and the alkylated product was isolated by filtration column chromatography (petroleum ether/ethyl acetate, 95:5). The isolated diastereomeric mixture was treated with TFA (0.1 ml) in dry DCM (2 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred further for 3–4 h. After the completion of the reaction, the solvent was evaporated, and the crude product was purified by column chromatography with silica gel 230–400 mesh (petroleum ether/ethyl acetate, 9:1) to afford the corresponding spirooxindole-bearing α-*exo*-methylene-γ-butyrolactone in very good yield.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of all compounds and HPLC data for all substrates.

Acknowledgments

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