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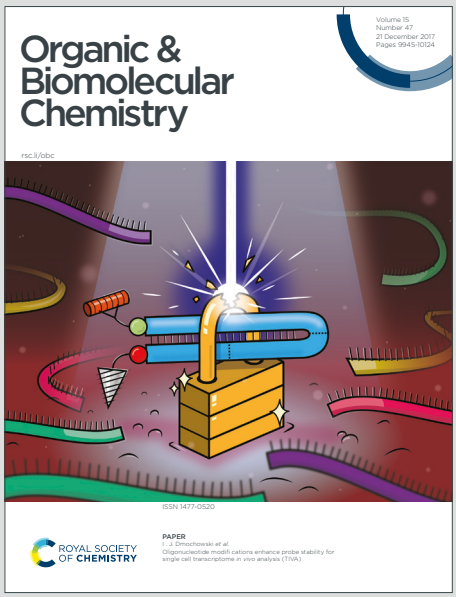

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Application of Isatin-derived Saturated Esters in the Synthesis of 3,3'-Spirooxindole γ-Butyrolactams

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Abstract: Stable while reactive isatin-derived saturated esters have been utilized as 3-carbon synthons in a base-promoted formal [3+2] annulation with *N*-Boc imines. The developed protocol offers a direct pathway for the rapid and divergent construction of two classes of 3,3'-spirooxindole γ-butyrolactam skeletons that are recognized as the privileged structures of various bioactive compounds. This protocol also has the advantages of mild reaction conditions, scalability and wide reaction scope.

Introduction

Spirooxindoles are well-recognized scaffolds that have attracted great attention from the scientific community owing to their challenging structural architecture and unique biological activities.[1] Among them, the structurally similar 3,3'-spirooxindole pyrrolidine[1h, 2] and 3,3'-spirooxindole γ-butyrolactam[3] frameworks are frequently found as the privileged structures in numerous natural products and synthetic compounds possessing significant pharmaceutical activities.

Over the past decades, a large number of synthetic methods for 3,3'-spirooxindole pyrrolidines have been developed.[1a, 1e, 1h, 4] Among these methods, the 1,3-dipolar cycloaddition of azomethine ylides with methyleneoxindoles is the most powerful and efficient strategy to access diverse 3,3'-spirooxindole pyrrolidines.[1d, 5] By contrast, there are limited documented synthetic approaches to 3,3'-spirooxindole γ-butyrolactams. [6]Therefore, in view of the importance of spirooxindole scaffolds, it is still in demand to develop direct and versatile new synthetic methods to access more structurally diverse 3,3'-spirooxindole γ-butyrolactams. As part of our interest in the development of new methodologies and substrates for the divergent synthesis of

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spirooxindoles,[7] we envisioned that the reactive while stable isatin-derived saturated esters **1** could undergo diverse annulations under basic conditions for the synthesis of spirooxindoles with structural diversity. Herein, we present a novel base-promoted catalyst-free [3+2] annulation of isatin-derived saturated esters **1** with two types of *N*-Boc imines for the divergent synthesis of spirooxindole γ-butyrolactams **3**/**4** and bispirooxindole γ-butyrolactams **6**/**7**.

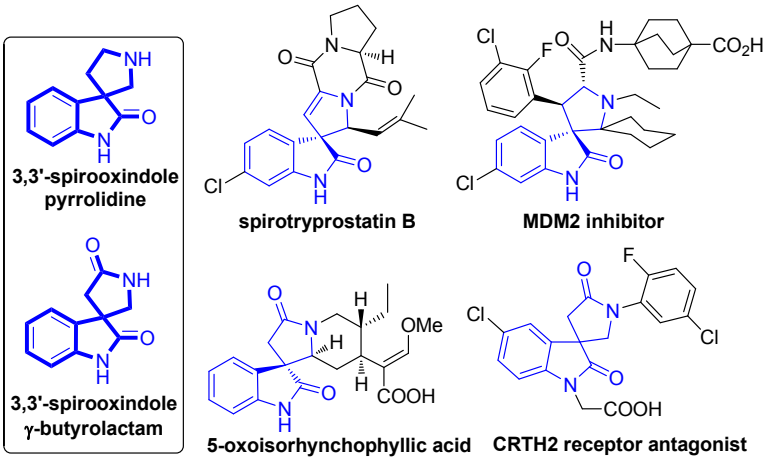
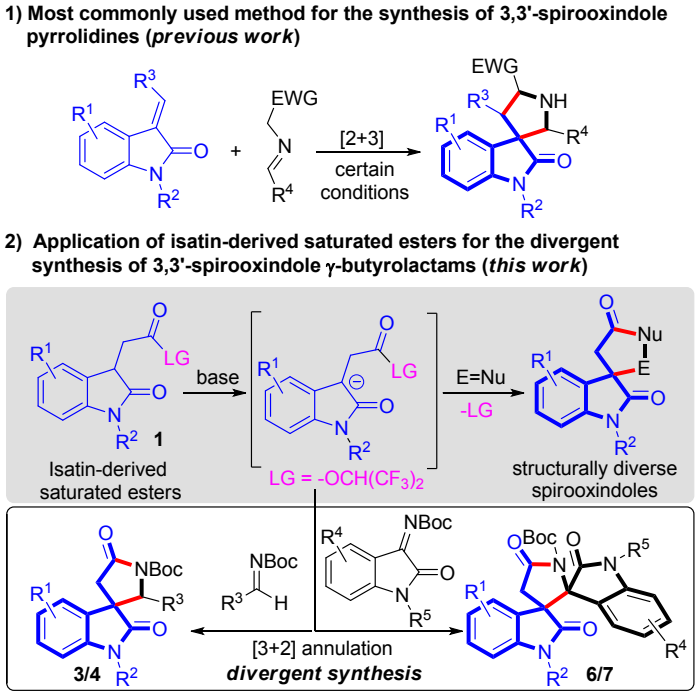


Figure 1. Representative bioactive 3,3'-spirooxindoles.



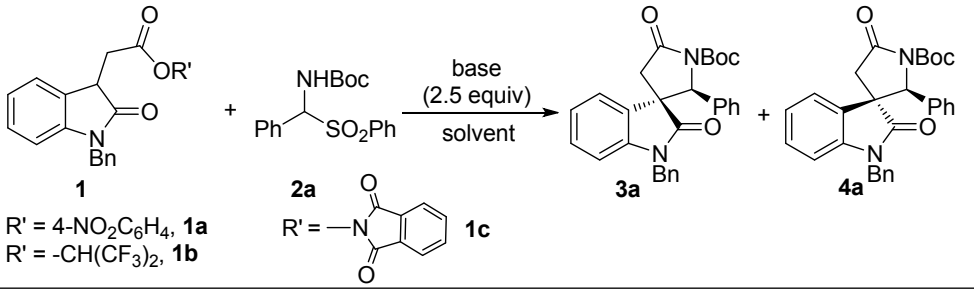
Scheme 1. Synthetic approaches to 3,3'-spirooxindole pyrrolidines and γ-butyrolactams.

Results and discussion

Our investigation started with the reaction between 4-nitrophenyl 2-(1-benzyl-2-

oxoindolin-3-yl) acetate **1a** and *N*-Boc aldimine precursor **2a** (Table 1). Initially, a variety of bases were tested using THF as a solvent (entries 1-8). It was found that inorganic bases were superior to organic bases, and Cs_2CO_3 was established as the optimal one (entry 4). After examination of several commonly used solvents (entries 9-13), desired product **3a** was obtained in 73% yield with excellent diastereoselectivity when the reaction was carried out in ethyl acetate (entry 13). Further variation of the leaving group of ester substrates convinced us that hexafluoroisopropyl ester **1b** was more suitable for this transformation resulting in a higher yield (83%) and equally excellent diastereoselectivity (entry 14). It is noteworthy that the *situ* activation of 2-(1-benzyl-2-oxoindolin-3-yl) acetic acid with pyBOP, HATU or DCC/DMAP in the presence of hexafluoroisopropanol and Cs_2CO_3 did not give the desired product.

Table 1. Optimization of the reaction conditions[a]



Entry	**1**	Base	Sol.	Temp.(°C)	Yield (%)[b]	Dr (**3a**/**4a**)[c]
1	**a**	DBU	THF	25	0	-
2	**a**	DIPEA	THF	25	0	-
3	**a**	DMAP	THF	25	0	-
4	**a**	Cs_2CO_3	THF	25	57	>95:5
5	**a**	K_2CO_3	THF	50	56	>95:5
6	**a**	K_3PO_4	THF	50	47	>95:5
7	**a**	*t*-BuOK	THF	25	0	-
8	**a**	NaOH	THF	25	44	>95:5
9	**a**	Cs_2CO_3	Toluene	25	0	-
10	**a**	Cs_2CO_3	DCM	25	trace	-
11	**a**	Cs_2CO_3	CH_3CN	25	0	-
12	**a**	Cs_2CO_3	dioxane	25	56	>95:5
13	**a**	Cs_2CO_3	EtOAc	25	73	>95:5
14	***b***	***Cs_2CO_3***	***EtOAc***	***25***	***83***	***>95:5***
15	**c**	Cs_2CO_3	EtOAc	25	complex	-

[a] Unless otherwise noted, all reactions were carried out with **1a** (0.2 mmol), **2a** (1.2 equiv) and a base (2.5 equiv) in an anhydrous solvent (2 mL) at room temperature typically for 30 mins. [b] Isolated yields based on **1a**. [c] *dr* values were determined by ^1H NMR analysis of the crude products.

With optimized conditions in hand, we then moved our attention to explore the reaction scope initially through variation of the aldimine precursors **2** (Table 2). It was found that the positions of the substituents on the benzene ring had great impact on the diastereoselectivities (entries 2-15). A wide range of substrates **2b-k** with diverse substituents at *p*- or *m*-position of the benzene ring were well tolerant to this reaction, affording the desired products **3b-k** in good to high yields and diastereoselectivities (entries 2-11). However, the reactions of 2-OMe- and 2-Me-substituted substrates **2l** and **2m** gave rise to the diastereomers **4l** and **4m**, respectively, in excellent diastereoselectivities (entries 12 and 13). The reactions of 2-Cl- and 2-Br-substituted substrates **2n** and **2o** afforded the desired products in poor diastereoselectivities (entries 14 and 15). To our delight, the reactions of naphthyl and heteroaromatic imine precursors **2p-s** worked equally well to produce the desired products in moderate yields (entries 16-19). In terms of more hindered 1-naphthyl, 2-furyl and 2-thienyl substrates, diastereomers **4p**, **4r** and **4s** were obtained as the major products in good to high diastereoselectivities (entries 16, 18 and 19). It might be concluded that the *ortho*-steric effect of phenyl ring or aromatic heterocycles have great impact on the stereoselectivity of this reaction, and diastereomers **4** were obtained in much higher ratios for these cases (entires 12-16, entries 18 and 19). The reaction of less hindered 2-naphthyl substrate **2q** afforded **3q** in an excellent diastereoselectivity (entry 17). We then evaluated the reactions between aldimine precursor **2a** and diverse esters **1d-g** with different substituents on the phenyl ring or nitrogen (entries 20-23). The reaction of 5-Cl substituted ester **1d** produced **3t** and **4t** in a good yield but with a lower diastereoselectivity (entry 20), while the reaction of 5-Me substituted ester **1e** afforded **3u** in a lower yield but with an excellent diastereoselectivity (entry 21). The reactions of *N*-Me- and *N*-Boc-protected esters **1f** and **1g** worked smoothly to give the corresponding products **3v** and **3w**, respectively, in excellent diastereoselectivities (entries 22 and 23). However, N-*H* free ester **1h** was not suitable to this protocol (entry 24). Remarkably, all these reactions completed typically in 30 mins, and several reactions were carried out under lower temperatures in order to gain better diastereoselectivities (entries 7-13 and 19). The structure of **3** and **4** was verified by

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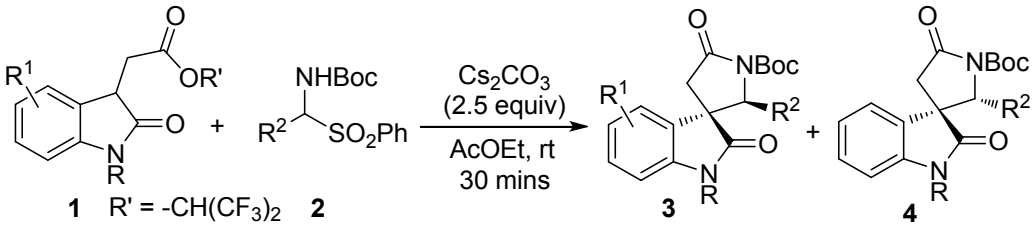
analysis of their NMR data and was further confirmed by X-ray crystallography of **3a**.

Table 2. Scope of the reaction between esters **1** and imine precursors **2** [a]



1 R' = -CH(CF$_3$)$_2$ **2** **3** **4**

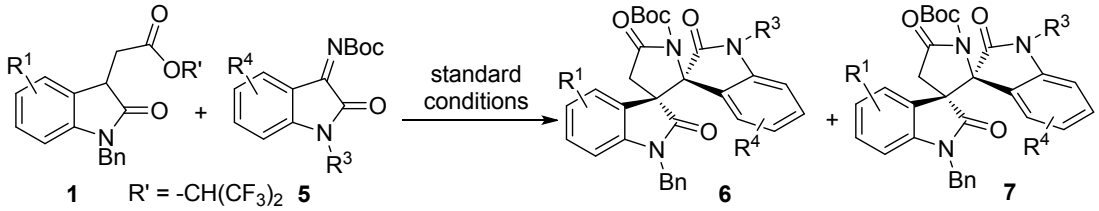
Entry	R, R^1, **1**	R^2, **2**	Yield (%),[b] **3/4**	Dr (**3**/**4**) [c]
1	Bn, H, **b**	C_6H_5, **a**	83, **a**	>95:5
2	Bn, H, **b**	4-OMeC_6H_4, **b**	90, **b**	83:17
3	Bn, H, **b**	4-MeC_6H_4, **c**	93, **c**	82:18
4	Bn, H, **b**	4-FC_6H_4, **d**	89, **d**	82:18
5	Bn, H, **b**	4-ClC_6H_4, **e**	82, **e**	80:20
6	Bn, H, **b**	4-BrC_6H_4, **f**	91, **f**	83:17
7 [d]	Bn, H, **b**	4-$CF_3C_6H_4$, **g**	65, **g**	80:20
8 [d]	Bn, H, **b**	3-FC_6H_4, **h**	86, **h**	92:8
9 [d]	Bn, H, **b**	3-ClC_6H_4, **i**	85, **i**	>95:5
10 [d]	Bn, H, **b**	3-MeC_6H_4, **j**	86, **j**	>95:5
11 [e]	Bn, H, **b**	3-OMeC_6H_4, **k**	87, **k**	85:15
12 [e]	Bn, H, **b**	2-OMeC_6H_4, **l**	85, **l**	<5:95
13 [d]	Bn, H, **b**	2-MeC_6H_4, **m**	88, **m**	<5:95
14	Bn, H, **b**	2-ClC_6H_4, **n**	87, **n**	51:49
15	Bn, H, **b**	2-BrC_6H_4, **o**	87, **o**	54:46
16	Bn, H, **b**	1-naphthyl, **p**	59, **p**	<5:95
17	Bn, H, **b**	2-naphthyl, **q**	60, **q**	>95:5
18	Bn, H, **b**	2-furyl, **r**	50, **r**	18:82
19 [e]	Bn, H, **b**	2-thienyl, **s**	49, **s**	<5:95
20	Bn, 5-Cl, **d**	C_6H_5, **a**	77, **t**	67:33
21	Bn, 5-Me, **e**	C_6H_5, **a**	47, **u**	>95:5
22	Me, H, **f**	C_6H_5, **a**	90, **v**	>95:5
23	Boc, H, **g**	C_6H_5, **a**	76, **w**	>95:5
24	H, H, **h**	C_6H_5, **a**	0	-

[a] Unless otherwise noted, all reactions were carried out with **1** (0.2 mmol), **2** (1.2 equiv) and Cs_2CO_3 (2.5 equiv) in anhydrous ethyl acetate (2 mL) at room temperature typically for 30 mins. [b] Combined isolated yields of **3** and **4** based on **1**. [c] *dr* values were determined by ^{1}H NMR analysis of the crude products. [d] The reaction temperature was -20°C. [e] The reaction temperature was 0°C.

Since bispirooxindole motifs are also frequently found in bioactive compounds,[9] we then focus on the extension of this protocol to isatin-derived ketimines **5** (Table 3).

Fortunately, the desired bispirooxindole γ-butyrolactams **6**/**7** were obtained in moderate to good yields through the reactions of ester **1b** and ketimines **5a-f** (entries 1-6). The reactions of the *N*-Bn- and *N*-Me-protected ketimines **5a** and**d 5b** had similar results in terms of the reaction yield and diastereoselectivity (entries 1 and 2). However, the diastereoselectivities of the reactions of ketimines **5c-f** varied with the different substituents on the benzene ring (entries 3-6). The reactions of 5-Me and 5-OMe-substituted imines **5c** and **5d** gave products **6c** and **6d**, respectively, in good diastereoselectivities (entries 3 and 4). The reaction of 5-F-substituted imine **5e** resulted in a poor diastereoselectivity (entry 5), while the reaction of 4-Cl-substituted imine **5f** afforded diastereomer **7f** with an excellent diastereoselectivity (entry 6). Finally, the reactions of two 5-substituted esters **1d** and **1e** were carried out to give the corresponding products in high yields with moderate diastereoselectivities (entries 7 and 8). The structure of **6** and **7** was established by analysis of their NMR data and was further confirmed by X-ray crystallography of **6b**.[10]

Table 3. Scope of the reaction between ester **1a** and isatin-derived ketimines **5**



Entry	R^1, **1**	R^3, R^4, **5**	Yield (%),[a] **6**/**7**	Dr (**6**/**7**)[b]
1	H, **b**	Bn, H, **a**	80, **a**	85:15
2	H, **b**	Me, H, **b**	86, **b**	84:16
3	H, **b**	Bn, 5-Me, **c**	74, **c**	87:13
4	H, **b**	Bn, 5-OMe, **d**	47, **d**	80:20
5	H, **b**	Bn, 5-F, **e**	58, **e**	42:58
6	H, **b**	Bn, 4-Cl, **f**	69, **f**	<5:95
7	5-Cl, **d**	Bn, H, **a**	94, **g**	87:13
8	5-Me, **e**	Bn, H, **a**	91, **h**	79:21

[a] Combined isolated yields of **6** and **7** based on **1b**. [b] *dr* values were determined by ^{1}H NMR analysis of the crude products.

A preliminary enantioselective study of this methodology was also undertaken by employing several commonly used chiral organocatalysts (see ESI). After screening the

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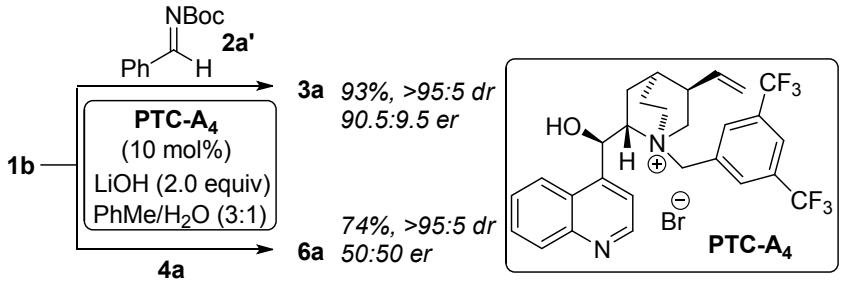
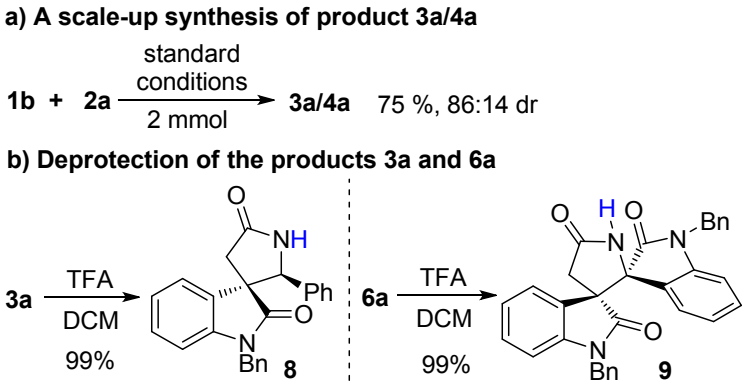
reaction conditions, we found that product **3a** could be obtained in 93% yield with an excellent diastereoselectivity and 90.5:9.5 er by the reaction of **1b** with imine **2a'** under the catalysis of chiral phase transfer reagent **PTC-A$_4$** (Scheme 2). Unfortunately, this reaction condition is not effective for the asymmetric synthesis of product **6a** that was obtained in 74% yield with an excellent diastereoselectivity but 50:50 er.



Scheme 2. A preliminary enantioselective study of this methodology.

To further explore the utility of this protocol, a scale-up synthesis of products **3a**/**4a** and deprotection of the *N*-Boc group were then carried out (Scheme 3). The reaction between **1b** and **2a** with 2 mmol scale under the standard conditions afforded desired products **3a**/**4a** in a slightly decreased yield (75 %) with 86:14 dr (Scheme 3a). The deprotection of the *N*-Boc group of **3a** and **6a** with trifluoroacetic acid (TFA) produced compound **8** and **9**, respectively, in quantitative yields (Scheme 3b).



Scheme 3. Synthetic applications.

Conclusions

In summary, we have designed a type of stable but reactive isatin-derived saturated esters that have been applied successfully in a base-promoted formal [3+2] annulation

for the divergent synthesis of two classes of structurally interesting 3,3' -spirooxindole γ-butyrolactams. The diversity-oriented protocol developed herein offers a direct and rapid access to a broad range of the desired spirooxindoles, especially the structurally complex bispirooxindoles which may be attractive for potential drug discovery. Moreover, this protocol has the advantages of mild reaction conditions and scalability for the synthesis of the target compounds that can easily undergo deprotection of *N*-Boc groups to afford *N*-H free lactams. A preliminary asymmetric synthesis study of this protocol through chiral phase transfer catalysis was also demonstrated. Research on the diversity-oriented synthesis of other spirooxindoles *via* diverse [3+m] annulations of esters **1** is currently underway in our laboratory.

Acknowledgements

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