



Highly efficient synthesis of spiro[oxazolidine-2-thione-oxindoles] with 3-isothiocyanato oxindoles and aldehydes via an organocatalytic cascade aldol-cyclization reaction



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ABSTRACT

A highly efficient method for the construction of a family of spiro[oxazolidine-2-thione-oxindoles] with 3-isothiocyanato oxindoles and aldehydes via a cascade aldol-cyclization process has been developed. This method provides access to spiro[oxazolidine-2-thione-oxindole] derivatives bearing two vicinal quaternary/tertiary stereocenters in up to 95% yield, 98:2 dr, and 89% ee with a chiral bifunctional thiourea–tertiary amine organocatalyst based on DPEN scaffold. Good reactivity was observed and the reaction could be completed within 1.0 min.

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1. Introduction

The spirooxindole scaffold defines the characteristic structure of a large number of natural and synthetic compounds possessing diverse and important biological functions (Fig. 1).¹ Motivated by the significant biological activities of this class of compounds, considerable efforts have been devoted toward the development of the asymmetric methods to construct various spirooxindole scaffolds.² Meanwhile, allowing for the relevant reports that sharing of the oxindole C3-position atom for the generation of spirocyclic oxindole derivatives can enhance the biological activity of the related compounds,³ thus exploring enantioselective strategies by fusing oxindoles with various heterocyclic motifs at the C3-position of oxindole have been the focus of intensive efforts for the construction of diverse chiral spirocyclic oxindoles. Despite some new reactions have been disclosed by numerous research groups in this realm,⁴ given that a different class of spirocycle ring system may show promise as medicinally relevant compounds in drug development,⁵ in this context, it is also significant and highly desirable to develop an effective catalytic system for the direct

construction of spirooxindoles bearing novel structure with respect to synthetic efficiency.

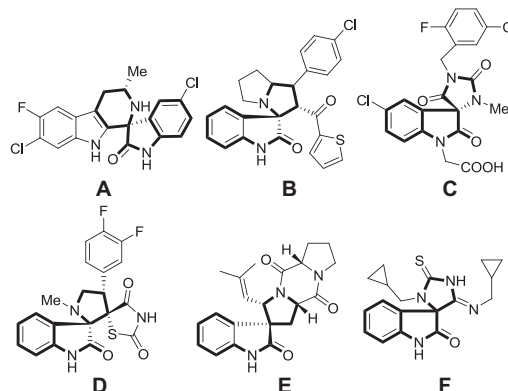
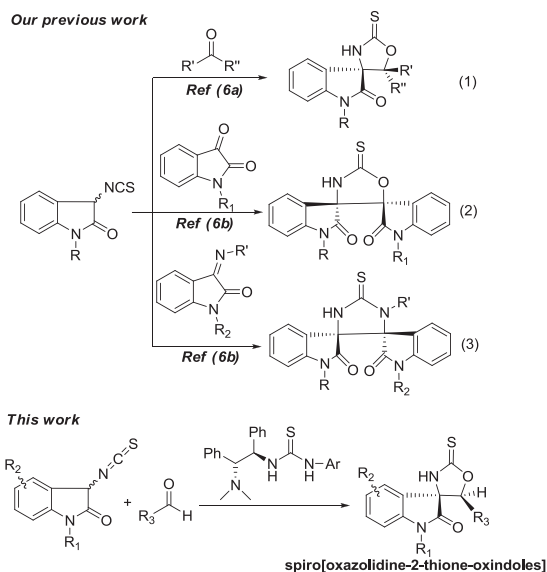


Fig. 1. Some bioactive compounds bearing the spirooxindole scaffold.

In 2011, we firstly reported that 3-isothiocyanato oxindoles could be used for enantioselective construction of chiral spirocyclic thioxazolidineoxindoles with organocatalysts via aldol-cyclization process (Scheme 1, (1)).^{6a} Immediately after, we also

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Scheme 1. Our studies on the synthesis of spirocyclic oxindoles with 3-isothiocyanato oxindoles as the donors.

reported that the synthesis of dispirocyclic bisoxindoles with 3-isothiocyanato oxindoles as nucleophiles through aldol- and Mannich-type reaction (Scheme 1, (2) and (3)).^{6b} Subsequently, the employment of such isothiocyanato oxindoles as donors for the synthesis of spiro[imidazolidine-4,3'-oxindole] core via an asymmetric Mannich-type reaction with a strontium/Schiff base complex was reported by Kanai and Matsunaga.⁷ Recently, the same 3-isothiocyanato oxindoles could serve as valuable substrates for the construction of bispirooxindole core through a cascade Michael-cyclization reaction was also demonstrated by some groups.⁸ Meanwhile, the application of α -isothiocyanato imides and esters in asymmetric synthesis for producing masked chiral β -hydroxyl- α -amino and α,β -diamino acid derivatives has been actively investigated over the last few years.^{4h,j,6–9} Based on the above research and as part of our ongoing investigation of the construction of various spirocyclic oxindoles,^{6,10} during our recently extensive studies, we have found that a series of spiro[oxazolidine-2-thione-oxindoles] can be readily obtained with 3-isothiocyanato oxindoles and aldehydes via an aldol-cyclization reaction by a bifunctional thiourea–tertiary amine organocatalyst based on DPEN scaffold (Scheme 1). Herein, we wish to present the results of our endeavors.

2. Results and discussion

Our initial studies started with the reaction of 3-isothiocyanato oxindoles **2a** and benzaldehyde (**3a**) in toluene at 0 °C for the examination of a series of organocatalysts **1a–I** (Fig. 2). We were

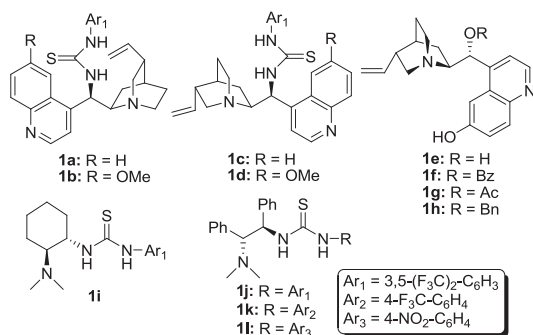


Fig. 2. Structures of organocatalysts examined in this study.

particularly pleased to find that all the reactions could proceed to completion even within 1 min (Table 1). Firstly, in the presence of 10 mol % chiral organocatalysts **1a–h** derived from cinchona alkaloids, respectively, the desired product **4aa** was able to be readily obtained in excellent yields and good diastereoselectivities, but the enantioselectivities were very poor (Table 1, entries 1–8). And then, the further investigation into various bifunctional thiourea–ter-

Table 1
Screening of catalysts and optimization of reaction conditions^a

Entry	Solvent	1	Yield ^b (%)	dr ^c	ee ^d (%)
1	Toluene	1a	92	82/18	–48
2	Toluene	1b	90	75/25	14
3	Toluene	1c	88	71/29	20
4	Toluene	1d	90	68/32	<1
5	Toluene	1e	93	72/28	–40
6	Toluene	1f	93	80/20	–56
7	Toluene	1g	92	75/25	–49
8	Toluene	1h	91	78/22	–30
9	Toluene	1i	87	68/32	–12
10	Toluene	1j	90	85/15	57
11	Toluene	1k	92	79/21	34
12	Toluene	1l	88	78/22	43
13	Toluene	1j	90	87/13	67 ^e
14	Toluene	1j	88	87/13	67 ^f
15	Mesitylene	1j	94	93/7	75 ^e
16	THF	1j	88	82/18	–3 ^e
17	Et ₂ O	1j	90	89/11	58 ^e
18	MTBE	1j	86	88/12	34 ^e
19	Mesitylene	1j	94	92/8	73 ^{e,g}
20	Mesitylene	1j	88	84/16	70 ^{e,h}
21	Mesitylene	1j	90	93/7	76 ^{e,i}

^a Unless otherwise noted, the reactions were run with 0.1 mmol of **2a** and 0.2 mmol of **3a** in 2.0 mL of specified solvent with 10 mol % catalyst at 0 °C.

^b Isolated yields of both diastereoisomers.

^c Determined by chiral HPLC.

^d Determined by chiral HPLC for the major diastereoisomer.

^e Run at –40 °C.

^f Run at –78 °C.

^g 20 mol % **1j** was used.

^h 5 mol % **1j** was used.

ⁱ In 4.0 mL of mesitylene. MTBE=methyl *tert*-butyl ether.

tiary amine organocatalysts **1i–l** based on chiral 1,2-diamine scaffold revealed that the reaction could take place efficiently and afforded product **4aa** in high yields and good diastereoselectivities, but with poor to moderate enantioselectivities (Table 1, entries 9–12). After considering various factors including reactivity, diastereoselectivity, and enantioselectivity, we chose thiourea–tertiary amine catalyst **1j** based on DPEN scaffold as the optimal catalyst for further investigation (Table 1, entry 10). Subsequently, the probe of reaction temperature was carried out in toluene at –40 °C and –78 °C, respectively (Table 1, entries 13 and 14). It was observed that product **4aa** could be obtained in 90% yield with a slight increase in diastereo- and enantioselectivity at –40 °C (Table 1, entry 13), but no further increase at –78 °C (Table 1, entry 14). Additionally, the effect of solvent on the aldol-cyclization reaction was tested. It was observed that mesitylene was the best solvent for the reaction (Table 1, entry 15 vs entries 13, 16–18). Finally, the survey of catalyst loading and concentration indicated that the reaction conducted with 10 mol % **1j** in 4.0 mL mesitylene at –40 °C could give the best results (Table 1, entry 21 vs entries 15, 19, and 20). In addition, the relative configuration of major diastereoisomers of product **4aa** could be determined by NOE

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