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Quinine-catalyzed asymmetric domino Mannich-cyclization reactions of 3-isothiocyanato oxindoles with imines for the synthesis of spirocyclic oxindoles

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ABSTRACT

A range of structurally diverse chiral spiro[imidazolidine-2-thione-4,3′-oxindole] compounds could be obtained via a domino Mannich-cyclization reaction of 3-isothiocyanato oxindoles and imines with commercial quinine as catalyst under mild conditions. The protocol is significantly characterized by simple process, easily available catalyst, high reactivity, low catalyst loading (1 mol%), and good to excellent diastereo- and enantioselectivity (up to>99:1 dr and 97% ee). A plausible dual activation working model was tentatively proposed to account for the stereochemistry of the domino Mannich-cyclization process.

1. Introduction

The spirocyclic oxindole moiety is a core structure in many complex natural products and biologically active compounds.[1] This privileged structural motif has also captured the attention of medicinal chemists due to its potential as an important pharmacophore.[2] Inspired by the special scaffolds, various synthetic methods for producing chiral spirocyclic oxindoles have been documented over the last decade.[1,3] In general, different synthetic strategies are able to result in a class of spirocyclic system that may show promise as biologically active compounds. Particularly, we noticed that the spirocyclic oxindole scaffolds with a nitrogen atom at the C3-position of the oxindole unit were frequently occurring structure motifs in medicinally active compounds.[4] Some efforts have been made for the construction of novel spirocyclic oxindoles fusing with nitrogen-containing heterocycles at the C3-position of the oxindole unit.[5] Given that the development of creative methods to access various spirocyclic oxindoles would be valuable because it could be applied not only to natural products synthesis but also to library synthesis in medicinal chemistry, it is highly desirable to develop efficient methods to generate structurally diverse chiral spirocyclic oxindoles, especially bearing a nitrogen atom at the C3-position of the oxindole unit.

Notably, α-isothiocyanato compounds recently have been employed in various asymmetric domino reactions[6] for the synthesis of chiral amino acid derivatives and spirocyclic oxindoles.[7] In this study area, we reported that 3-isothiocyanato oxindoles could served as versatile nucleophiles in domino reactions for the construction of diverse spirocyclic oxindole compounds.[8] Encouraged by these results and our own laboratory's success in the asymmetric synthesis of oxindole compounds with organocatalysts,[8,9] we envisaged that the reaction of 3-isothiocyanato oxindoles and imines should be catalyzed by certain chiral organocatalyst to construct a class of spirocyclic oxindole derivatives through a domino Mannich-cyclization process (Scheme 1). Although the similar reaction catalyzed by a Sr/Schiff base complex was reported by Kanai, Matsunaga, and co-workers,[5d] we know that the reaction with an organocatalyst is less explored.[10] In this context, here we present the results of our endeavours on the development of a diastereo- and enantioselective synthesis of a class of spiro[imidazolidine-2-thione-4,3′-oxindole] derivatives based on domino

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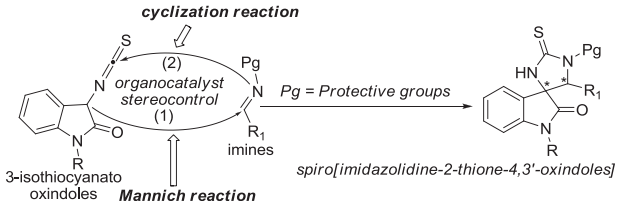
Mannich-cyclization reactions of 3-isothiocyanato oxindoles and imines with commercial quinine as catalyst.



Scheme 1. The strategy for the reaciton of 3-isothiocyanato oxindoles and imines via a domino Mannich-cyclization process.

2. Results and discussion

Our experiments began with a screening of a variety of chiral organocatalysts (Fig. 1) for their ability to promote enantioselective domino reaction of **1a** and tosyl-protected aldimine **2a**. As shown in Table 1, the expected reaction proceeded smoothly in toluene at room temperature in the presence of 10 mol% cinchonidine (**A**), affording the spirocyclic product **3a** in 80% yield with 70:30 diastereomeric ratio (dr) but only 41% ee (entry 1). And then, we were pleased to see that the reaction was indeed accelerated with quinidine (**B**) as catalyst, proceeding to completion within 10 min to give **3a** in 93% yield with 83:17 dr and 87% ee (entry 2). More delightedly, quinine (**C**) could give **3a** in 95% yield with 85:15 dr and 92% ee (entry 3). However, further studies revealed that chiral bifunctional thiourea-tertiary amine catalysts **D** and **E** provided worse activity and stereoselectivity in toluene than that by quinine (entries 4–5 vs entry 3). Thus commercially available quinine (**C**) was proved to be the best catalyst for the domino Mannich-cyclization reaction in terms of activity, diastereo- and enantoselectivity (entry 3). Solvent screening showed toluene to be the most suitable solvent comparing with CH_2Cl_2 and mesitylene (entry 3 vs entries 6–7). Reaction temperature investigation revealed that 0 °C was the optimal temperature for the reaction (entry 3 and entries 8–11). Decreasing the catalyst loading from 10 mol% to 5 mol% and 1 mol%, respectively (entries 12–13), we were pleased to observe that the reaction also gave acceptable results using only 1 mol% quinine (entry 13). When different concentrations were screened (entries 14–17), it was observed that the reaction worked well in the presence of 1 mol% **C** under 0.1 M substrate concentration, giving **3a** in 95% yield with 79:21 dr and 93% ee (entry 16). Ultimately, with 50 mg 4 Å activated molecular sieve (MS) as additive for the reaction system, **3a** could be obtained smoothly in 95% yield with 78:22 dr and 94% ee (entry 18).

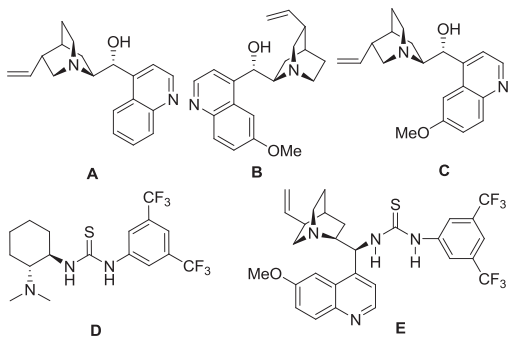
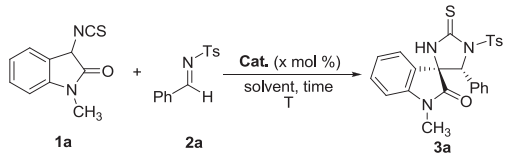


Fig. 1. Chiral organocatalysts screened in the Mannich-cyclization reaction of **1a** and **2a**.

Table 1
Optimization of reaction conditions[a]



Entry	Cat.	*x*	Solvent	Time (min)	*T* (°C)	Yield[b] (%)	dr[c]	ee[d] (%)
1	**A**	10	Toluene	20	rt	80	70:30	41
2	**B**	10	Toluene	10	rt	93	83:17	87
3	**C**	10	Toluene	10	rt	95	85:15	92
4	**D**	10	Toluene	30	rt	82	54:46	43
5	**E**	10	Toluene	10	rt	91	70:30	71
6	**C**	10	CH_2Cl_2	10	rt	95	55:45	39
7	**C**	10	Mesitylene	10	rt	82	87:13	89
8	**C**	10	Toluene	10	0	95	84:16	93
9	**C**	10	Toluene	10	−10	94	83:17	90
10	**C**	10	Toluene	30	−20	94	82:18	90
11	**C**	10	Toluene	30	−40	93	84:16	93
12	**C**	5	Toluene	10	0	95	80:20	90
13	**C**	1	Toluene	10	0	95	68:32	91
14	**C**	1	Toluene	10	0	90	64:36	77[e]
15	**C**	1	Toluene	10	0	90	52:48	60[f]
16	**C**	1	Toluene	10	0	95	79:21	93[g]
17	**C**	1	Toluene	10	0	90	77:23	85[h]
18	**C**	1	Toluene	10	0	95	78:22	94[g,i]

[a] Unless otherwise noted, the reactions were carried out with 0.1 mmol **1a** and 0.11 mmol **2a** in the presence of specified amount of catalyst in 2.0 mL (0.05 M) solvent at room temperature for the specified reaction time.
[b] Isolated yields.
[c] Determined by HPLC analysis.
[d] Enantiomeric excess for major diastereoisomers determined by chiral HPLC analysis.
[e] Reaction performed at 0.025 M.
[f] Reaction performed at 0.0125 M.
[g] Reaction performed at 0.1 M.
[h] Reaction performed at 0.2 M.
[i] 4 Å MS (50 mg) was used.

With the optimized conditions in hand, we turned our focus to the substrate scope and generality of the domino Mannich-cyclization reaction. As shown in Table 2, all of the tested reactions could go to completion within 10 min just with 1 mol% quinine at 0 °C. This point indicates that the domino Mannich-cyclization reaction of 3-isothiocyanato oxindoles and tosyl-protected aldimines has very high activity. The reactivity and stereoselectivity were scarcely affected by the incorporation of various electron-withdrawing substituents on the aryl group of aldimines, the corresponding spirocyclic oxindoles could be obtained in 89–95% yield with 68:32–94:6 dr and 61–94% ee (entries 1–9). Meanwhile, the presence of diverse electron-donating groups on the aromatic ring led to similar results for the spirocyclic products (entries 10–14). With 2-methoxy substituted tosyl-protected aldimine **2m** as a substrate, the reaction affords product **3m** in 95% yield with even up to>99:1 dr and 92% ee (entry 12). Furthermore, a heteroaromatic aldimine **2p** was successfully employed, thereby broadening the scope of the reaction (entry 15). Nevertheless, 2-naphthyl-substituted aldimine **2q** could be smoothly converted into the corresponding spirocyclic oxindole **3q** with good results (entry 16). Notably, the domino reaction between **1a** and tosyl-protected aliphatic aldimine **2r** could still proceed smoothly under the standard conditions and furnished product **3r** in 99% yield with 72:28 dr and only 24% ee (entry 17). On the other hand, we also examined the scope of the reaction with regard to the 3-isothiocyanato oxindoles (entries 18–21). The steric size of the N-protecting group seems to be important as methyl (**1a**), ethyl (**1b**), and benzyl (**1c**) gave distinctively different enantioselectivity by reacting with aldimine **2a**. Ultimately, we also observed that