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Highly Efficient and Stereocontrolled Construction of 3,3′-Pyrrolidonyl Spirooxindoles via Organocatalytic Domino Michael/Cyclization Reaction

Xiong-Li Liu,[†,‡] Wen-Yong Han,[†,‡] Xiao-Mei Zhang,[†] and Wei-Cheng Yuan*[,†]

National Engineering Research Center of Chiral Drugs, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, China, and University of Chinese Academy of Sciences, Beijing, 100049, China

yuanwc@cioc.ac.cn

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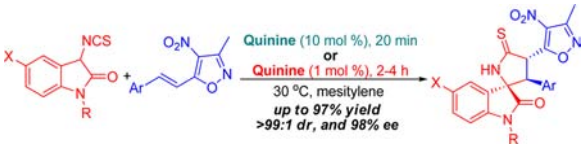
ABSTRACT



A wide range of structurally diverse 3,3′-thiopyrrolidonyl spirooxindoles bearing three contiguous stereogenic centers can be smoothly obtained via a domino Michael/cyclization reaction between 3-isothiocyanato oxindoles and 3-methyl-4-nitro-5-alkenyl-isoxazoles with commercially available quinine as the catalyst under mild conditions. The protocol is significantly characterized by high reactivity, a low catalyst loading (1 mol %), and an excellent diastereo- and enantioselectivity (up to >99:1 dr and 98% ee).

Highly efficient, diastereoselective, and enantioselective reactions generating complex chiral heterocyclic compounds in one step are unusually valuable and remain a challenging goal in organic synthesis. Spirocyclic oxindoles in particular have emerged as attractive synthetic targets because of their prevalence in numerous natural products and significant biological activity.[1] Intense efforts have been made on the development of various elegant methods to access the structurally diverse family of spirocyclic oxindoles.[2] Undoubtedly, any of the known strategies should result in a different class of spirocycle oxindoles that may show promise as biologically active compounds. In this context, searching for creative procedures that could achieve high reactivity and stereoselectivity for the construction of structurally diverse spirocycle oxindoles is still challenging and interesting, because it might be practically applied not only to natural products synthesis but also to library synthesis in medicinal chemistry.[1,2a,3]

A family of potentially promising spirocyclic oxindole frameworks common to many bioactive molecules are the 3,3′-pyrrolidonyl spirooxindoles (Figure 1),[3,4] which are an intriguing fusion of two privileged motifs, the pyrrolidone and 2-indolinone substructures. The frameworks

[†] Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences.
[‡] University of Chinese Academy of Sciences.

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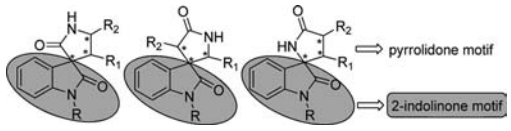
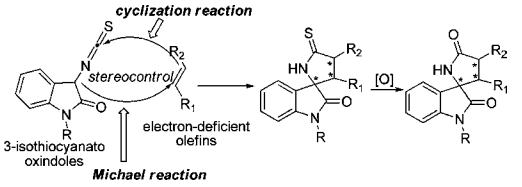


Figure 1. Diversely structured 3,3′-pyrrolidonyl spirooxindoles.

are characterized by a spiro ring fusion at the C3-position of the oxindole core with more substitution variants (Figure 1). Although many exquisite approaches to various spirocyclic oxindoles have been developed, to the best of our knowledge, the examples that can efficiently produce structurally diverse 3,3′-pyrrolidonyl spirooxindoles in a catalytic asymmetric manner are still limited.[2f,i,4] Thus, the development of novel asymmetric methods for the synthesis of various stereoenriched 3,3′-pyrrolidonyl spirooxindole derivatives is of paramount importance.

Recently, we have synthesized a series of 3-isothiocyanato oxindoles and employed them as attractive reactants to perform some domino reactions for the construction of various spirocyclic oxindoles.[5,6] The successes of the domino tactics lead us to speculate the possibility of a catalytic asymmetric domino process regarding a Michael addition/cyclization reaction between 3-isothiocyanato oxindoles and somewhat appropriate electron-deficient olefins (Scheme 1).[7] If this idea is viable, we can imagine that a library of chiral 3,3′-thiopyrrolidonyl spirooxindoles will be formed via a domino Michael addition/cyclization sequence under the elegant stereocontrol of chiral catalysts. Surely, the 3,3′-thiopyrrolidonyl spirooxindoles are liable to be transformed into corresponding 3,3′-pyrrolidonyl spirooxindoles by oxidizing (Scheme 1). Therefore, as part of our ongoing effort to develop new strategies for the construction of diversely structured oxindoles bearing a tetrasubstituted stereogenic center at C3,[5,8] we have found that a wide range of 3,3′-thiopyrrolidonyl spirooxindoles bearing three contiguous stereogenic centers can be obtained from the reactions between 3-isothiocyanato oxindoles and 3-methyl-4-nitro-5-alkenyl-isoxazoles[9] with excellent diastereo- and enantioselectivity in very high yields in the presence of very low loadings of an organocatalyst. Herein, we wish to report our preliminary results on this subject.

Scheme 1. Strategy for the Reaciton of 3-Isothiocyanato Oxindoles and Appropriate Electron-Deficient Olefins via a Domino Michael Addition/Cyclization Sequence



Our initial studies started with the reaction of *N*-methyl-3-isothiocyanato oxindole **1a** and (*E*)-3-methyl-4-nitro-5-styrylisoxazole (**2a**)[10] in dichloromethane for the optimization of the catalyst. We were pleased to find that the commercially available quinine was the most powerful catalyst.[11] Subsequently, to further find the optimal conditions for the reaction, a screening was performed using different solvents, temperatures, substrate concentrations, and additives (Table 1). Firstly, we decided to screen a number of solvents to examine the effect on the yield and selectivity of this process. The reaction proceeded at −40 °C and was complete after only 30 min in each solvent (Table 1, entries 1−6), but mesitylene appeared optimal in terms of yield and diastereo- and enantioselectivity (Table 1, entry 6). Perfoming the reaction in mesitylene at different temperatures (Table 1, entries 6−10) revealed that the process gave full conversion into **3a** in 97% yield with 96:4 dr and 92% ee only after 10 min at 30 °C (Table 1, entry 9). Afterward, among the substrate concentrations probed (Table 1, entries 9, 11−13), it was observed that a lower concentration was beneficial to the enantioselectivity and without sacrificing the yield and diastereoselectivity with a slight extension of reaction time (20 min, Table 1, entry 13). Additionally, it was noted that adding different types of molecular sieve (MS) into the reaction system was favorable to obtain a slightly higher ee (Table 1, entries 14−16). As a result, these studies provided the optimal reaction conditions: addition of **1a** (0.1 mmol) and **2a** (0.13 mmol) in 8.0 mL of mesitylene in the presence of 10 mol % quinine and 50 mg of 5 Å MS at 30 °C for 20 min (Table 1, entry 16).

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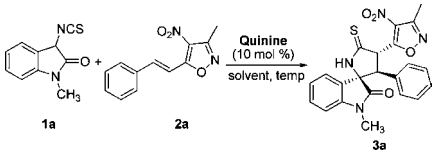
Table 1. Optimization of Various Reaction Conditions[a]

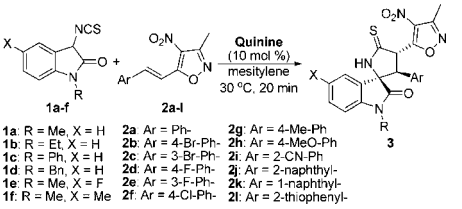


entry	solvent	temp (°C)	time (min)	yield (%)[b]	dr[c]	ee (%)[d]
1	CH_2Cl_2	−40	30	94	73:27	59
2	$CHCl_3$	−40	30	91	89:11	64
3	THF	−40	30	89	77:23	42
4	CH_3CN	−40	30	90	64:36	7
5	toluene	−40	30	95	94:6	82
6	mesitylene	−40	30	96	94:6	84
7	mesitylene	0	30	94	97:3	86
8	mesitylene	18	10	94	96:4	89
9	mesitylene	30	10	97	96:4	92
10	mesitylene	60	10	97	94:6	90
11	mesitylene	30	10	96	95:5	89[e]
12	mesitylene	30	10	94	97:3	93[f]
13	mesitylene	30	20	95	96:4	94[g]
14	mesitylene	30	20	92	94:6	95[g,h]
15	mesitylene	30	20	94	94:6	95[g,i]
16	mesitylene	30	20	96	>99:1	96[g,j]

[a] Unless noted, the reactions were carried out with **1a** (0.1 mmol), **2a** (0.13 mmol), and quinine (0.01 mmol) in 2.0 mL of solvent. [b] Yield of isolated product as a mixture of diastereoisomers. [c] Determined by chiral HPLC analysis. [d] Ee of major diastereomer as determined by chiral HPLC analysis. [e] Run in 1.0 mL of mesitylene. [f] Run in 6.0 mL of mesitylene. [g] Run in 8.0 mL of mesitylene. [h] 50 mg of 3 Å MS were used. [i] 50 mg of 4 Å MS were used. [j] 50 mg of 5 Å MS were used.

A subsequent experiment began to define the substrate scope of this reaction. As shown in Table 2, the domino Michael addition/cyclization sequence with the optimal reaction conditions can be extended to a wide variety of 3-isothiocyanato oxindoles **1a**−**f** and 3-methyl-4-nitro-5-alkenyl-isoxazoles **2a**−**l** to give diversely structured 3,3′-thiopyrrolidonyl spirooxindoles **3a**−**t** in 91−97% yield with 92:8−> 99:1 dr and 92−98% ee. Importantly, in all cases, the reaction showed very high reactivity and reached completion only within 20 min. Various *N*-protecting groups of the 3-isothiocyanato oxindoles having different steric parameters were well tolerated (Table 2, entries 1−4). A variety of aromatic 3-methyl-4-nitro-5-alkenyl-isoxazoles underwent reaction with *N*-methyl-3-isothiocyanato oxindole **1a** in high to excellent yields and diastereo- and enantioselectivity regardless of their electronic properties (Table 2, entries 5−10). Notably, the 2- and 1-naphthyl-based 3-methyl-4-nitro-5-alkenyl-isoxazoles (**2j** and **2k**) also gave rise to the corresponding products (**3k** and **3l**) in very high yields and ee values (Table 2, entries 11−12). Additionally, the thiophene derived reactant **2l** also reacted smoothly with **1a** and delivered product **3m** in 95% yield with 97:3 dr and 93% ee (Table 2, entry 13). Nevertheless, the substitution, whether electron-withdrawing or -donating, on the 3-isothiocyanato oxindole aromatic ring did not affect the reactivity and selectivity of the reaction (Table 2, entries 15−17). Finally, we also surveyed some other 3-isothiocyanato oxindole/3-methyl-4-nitro-5-alkenyl-isoxazole combinations and obtained satisfactory results similar to those from the above-mentioned studies (Table 2, entries 14, 18−20).

Table 2. Scope of the Reaction between **1** and **2** with 10 mol % Quinine[a]

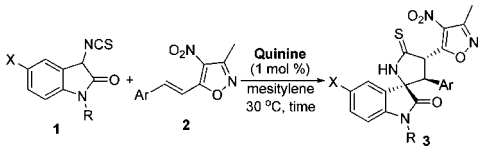


entry	1	2	3	yield (%)[b]	dr[c]	ee (%)[d]
1	**1a**	**2a**	**3a**	96	>99:1	96
2	**1b**	**2a**	**3b**	92	96:4	96
3	**1c**	**2g**	**3c**	93	99:1	95
4	**1d**	**2a**	**3d**	95	95:5	95
5	**1a**	**2b**	**3e**	93	94:6	93[e]
6	**1a**	**2c**	**3f**	94	97:3	96
7	**1a**	**2d**	**3g**	97	94:6	95
8	**1a**	**2e**	**3h**	92	95:5	94
9	**1a**	**2f**	**3i**	92	97:3	94
10	**1a**	**2g**	**3j**	95	96:4	94
11	**1a**	**2j**	**3k**	97	>99:1	96
12	**1a**	**2k**	**3l**	96	92:8	96
13	**1a**	**2l**	**3m**	95	97:3	93
14	**1c**	**2b**	**3n**	92	98:2	95
15	**1e**	**2a**	**3o**	93	99:1	96
16	**1f**	**2b**	**3p**	94	99:1	98
17	**1f**	**2g**	**3q**	95	>99:1	95
18	**1d**	**2g**	**3r**	94	97:3	97
19	**1d**	**2h**	**3s**	92	95:5	96
20	**1d**	**2i**	**3t**	91	93:7	92

[a] The reactions were carried out with **1** (0.1 mmol), **2** (0.13 mmol), quinine (0.01 mmol), and 5 Å MS (50 mg) in 8.0 mL of mesitylene at 30 °C for 20 min. [b] Yield of isolated product as a mixture of diastereoisomers. [c] Determined by chiral HPLC analysis. [d] Ee of major diastereomer as determined by chiral HPLC analysis. [e] The absolute configuration of **3e** was assigned (*C7R,C8S,C9S*).[12] The absolute configurations of remaining products shown in this work were tentatively proposed by analogy.

Encouraged by the gratifying results summarized in Table 2, we attempted to examine our protocol with a lower catalyst loading considering the remarkably high reactivity of the reactions illustrated in Table 2. Decreasing the quinine loading from 10 to 5 mol % had hardly any effect on the properties of the reaction (Table 3, entry 1). Surprisingly, when we further lowered the catalyst loading to 1 mol % for the same reaction, similar results to those with 5 mol % catalyst also could be obtained smoothly just with an extended reaction time to 2 h (Table 3, entry 2). Subsequently, in the presence of 1 mol % catalyst, we performed a series of reactions with different 3-isothiocyanato oxindole/3-methyl-4-nitro-5-alkenyl-isoxazole combinations in 4.0 mL of mesitylene at 30 °C (Table 3, entries 3−13). Gratifyingly, the desired 3,3′-thiopyrrolidonyl spirooxindole products were also able to be well obtained in very high yields (90−96%) with excellent diastereoselectivities ranging from 92:8 to 99:1 and very high enantioselectivities ranging from

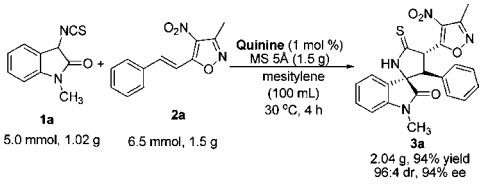
Table 3. Scope of the Reaction between **1** and **2** with 1 mol % Quinine[a]



entry	1	2	time (h)	3	yield (%)[b]	dr[c]	ee (%)[d]
1	**1a**	**2a**	0.5	**3a**	94	97:3	95[e]
2	**1a**	**2a**	2	**3a**	95	95:5	94[f]
3	**1a**	**2a**	4	**3a**	92	96:4	96
4	**1b**	**2a**	4	**3b**	93	96:4	95
5	**1c**	**2g**	2	**3c**	90	98:2	92
6	**1d**	**2a**	4	**3d**	90	93:7	91
7	**1a**	**2b**	4	**3e**	96	96:4	95
8	**1a**	**2g**	4	**3j**	95	95:5	94
9	**1a**	**2k**	4	**3l**	94	92:8	96
10	**1a**	**2l**	4	**3m**	96	99:1	93
11	**1c**	**2b**	2	**3n**	92	98:2	90
12	**1f**	**2b**	4	**3p**	95	95:5	97
13	**1f**	**2g**	4	**3q**	95	99:1	93

[a] Unless noted, the reactions were carried out with **1** (0.1 mmol), **2** (0.13 mmol), quinine (0.001 mmol), and 5 Å MS (30 mg) in 4.0 mL of mesitylene at 30 °C. [b] Yield of isolated product as a mixture of diastereoisomers. [c] Determined by chiral HPLC analysis. [d] Ee of major diastereomer as determined by chiral HPLC analysis. [e] The reactions were carried out with **1** (0.1 mmol), **2** (0.13 mmol), quinine (0.005 mmol), and 5 Å MS (50 mg) in 8.0 mL of mesitylene at 30 °C. [f] The reactions was carried out with **1** (0.1 mmol), **2** (0.13 mmol), quinine (0.001 mmol), and 5 Å MS (50 mg) in 8.0 mL of mesitylene at 30 °C.

Scheme 2. Reaction of **1a** and **2a** on Gram Scale



90% to 97% (Table 3, entries 3−13). It is noteworthy that various functional groups were also well-tolerated when the reaction time is slightly prolonged to 2−4 h.

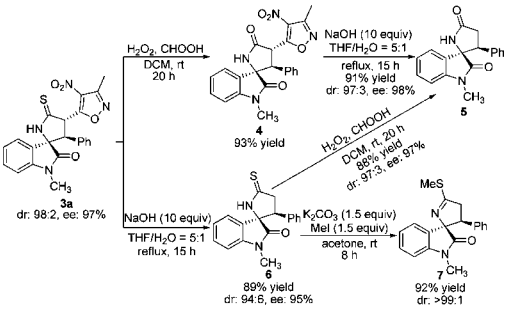
To examine the utility of the catalytic system, gram scale quantities of **1a** and **2a** were carried out with 1 mol % quinine as the catalyst in 100 mL of mesitylene at 30 °C. The reaction proceeded to completion within 4 h and the corresponding product **3a** also could be obtained in 94% yield, 96:4 dr, and 94% ee (Scheme 2). Surely, when comparing the gram scale reaction with the milligram scale reaction, in the presence of the same loading of catalyst, the product was able to be obtained almost without any loss of yield or diastereo- or enantioselectivity (Scheme 2 vs Table 3, entry 3).

(12) CCDC-869022 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(13) See the Supporting Information for more details.

The synthetic utility of the current reaction was illustrated by the versatile conversion of the 3,3′-thiopyrrolidonyl spirooxindole **3a** into other 3,3′-spirocyclic oxindoles (Scheme 3).[13] The treatment of **3a** with 30% aqueous hydrogen peroxide and formic acid in CH_2Cl_2 readily accomplished an oxidation reaction to give 3,3′-pyrrolidonyl spirooxindole **4** by transforming the thiolactam moiety into lactam. Then, **4** was treated with a NaOH solution of a solvent mixture of THF and water at reflux for 15 h, resulting in the elimination of the isoxazole moiety, in turn generating the 3,3′-pyrrolidonyl spirooxindole **5** in 91% yield without loss of diastereo- and enantioselectivity. Nevertheless, the structural diversity of the products also could be further demonstrated by the sequential transformations of **3a** into other spirooxindoles **6** and **7**.[13] Notably, when **6** was subjected to the same reaction conditions as those for the transformation of **3a** into **4**, **5** could be smoothly obtained.

Scheme 3. Transformation of Cycloadduct **3a** into other 3,3′-Spirocyclic Oxindoles



In conclusion, we have developed a highly efficient, stereocontrolled method for the construction of enantioenriched 3,3′-pyrrolidonyl spirooxindole derivatives with commercially available quinine as the catalyst under mild reaction conditions. The reactions are accomplished via a domino Michael addition/cyclization reaction between 3-isothiocyanato oxindoles and 3-methyl-4-nitro-5-alkenyl-isoxazoles to deliver a wide range of structurally diverse 3,3′-thiopyrrolidonyl spirooxindoles bearing three contiguous stereogenic centers. Most importantly, the process is significantly characterized by high reactivity, a low catalyst loading (1 mol %), and an excellent diastereo- and enantioselectivity (up to 97% yield, >99:1 dr and 98% ee). The utilities of the protocol have been demonstrated by the gram scale reaction and the versatile conversion of the cycloadduct into other 3,3′-spirocyclic oxindoles.

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Supporting Information Available. Experimental details, characterization data for new compounds, and X-ray crystal structure of **3e**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.