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Synthesis of Spiro[chroman/tetrahydrothiophene-3,3′-oxindole] Scaffolds *via* Heteroatom-Michael–Michael Reactions: Easily Controlled Enantioselectivity *via* Bifunctional Catalysts

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Abstract: An efficient method for the construction of chiral spirooxindole-chroman and spirooxindole-tetrahydrothiophene scaffolds with three consecutive chiral centers including an all-carbon quaternary spirocenter has been developed. This method features an asymmetric thia/oxa-Michael–Michael cascade sequence in a single operation in the presence of chiral tertiary amine-thioureas as the catalysts, providing the desired products in good chemical yields and optical purities.

Keywords: asymmetric catalysis; cascade reactions; heteroatom-Michael–Michael reaction; organocatalysis; spirooxindoles

Spirocyclic oxindoles have recently emerged as attractive synthetic targets because of their prevalence in an array of fascinating natural products and pharmaceutical candidates.[1] For this reason, the development of general and efficient methodologies to access this family of alkaloids is of great interest in organic synthesis.[2,3] Moreover, it has been reported that the presence of the spirocyclic center is highly beneficial to the biological activity of relevant compounds.[4] Thus, the building of these fused spiroheterocycles has been intensively studied by organic chemists, and some impressive progress in the construction of densely functionalized spiroheterocycle compounds has been achieved.[3]

The asymmetric organocatalytic cascade reaction has emerged as a powerful tool in constructing chiral molecule scaffolds bearing multiple stereocenters from simple and readily available starting materials in a single operation.[5] In recent years, very many innovative and impressive cascade sequences to afford compounds with highly molecular complexity have been reported.[6] Among these sequences, the domino Michael–Michael reaction can be considered as one of the most powerful and reliable tools for the stereocontrolled assembly of molecular architectures, as demonstrated by numerous examples in which it has also been used as a key transformation in total synthesis.[7]

Very recently, we have developed an organocatalyzed aza-Michael–Michael cascade reaction to construct spirooxindole-tetrahydroquinolines with high yields and stereoselectivities.[8] As an extension of this work, we reported herein asymmetric organocatalytic oxa/thia-Michael–Michael cascade reactions to synthesize highly useful spirooxindole-chroman and spirooxindole-tetrahydrothiophene scaffolds[9] which have been found as core structural motifs in numerous natural products with intriguing biological and pharmaceutical activities (< Figure 1).[10,11]

The asymmetric oxa-Michael-Michael cascade reaction was first evaluated and the reaction between methyleneindolinone **1a** and *ortho*-hydroxychalcone **2a** was selected as the model. As we expected, *Cinchona* alkaloid-derived thiourea catalyst **4a** provided the desired product with 67% *ee* and 85% yield (Table 1, entry 1). A further screening of the solvents indicated that toluene was the best one with regard to enantioselectivity (Table 1, entries 1–5). On lowering the reaction temperature to 0 °C, the reaction was completely inhibited (Table 1, entry 6). Based on exciting reports about amine-acid derived thioureas from our group and others,[12] we then turned our attention to the various amino acid-based bifunctional catalysts (Table 1, entries 7–18). The examination of a variety of catalysts with different chiral backbones showed that the selectivity of the reaction was dependent on the steric hindrance of the R group. The catalyst **4f** with a bulky *tert*-butyl group provided the highest distereoselectivity and enantioselectivity (Table 1, entries 9–11). As for the tertiary amine

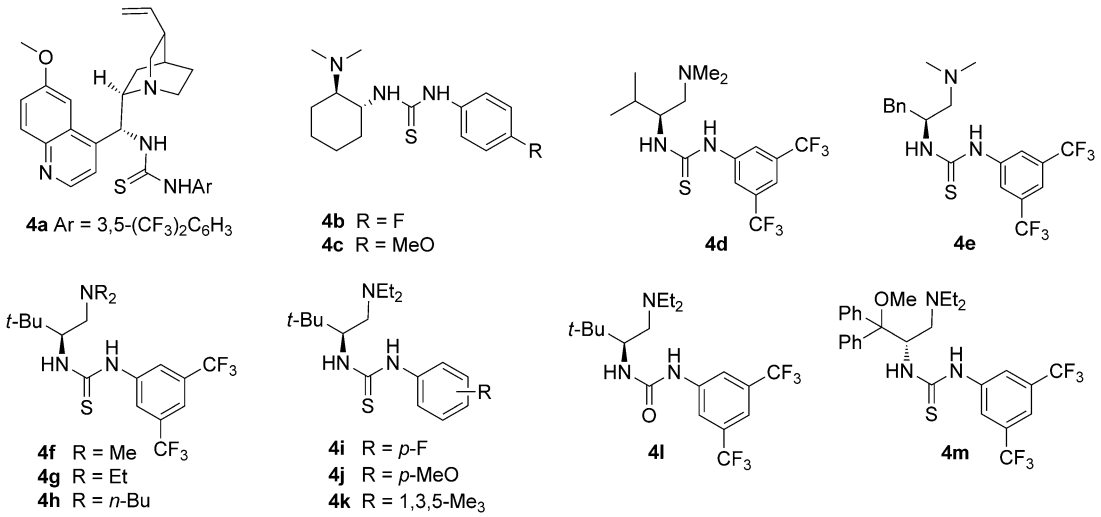
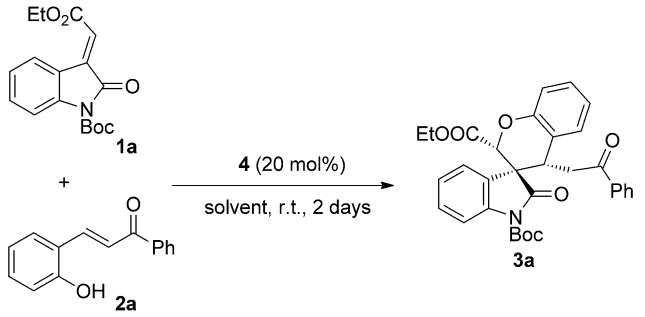


Figure 1. Structures of chiral catalysts used in the cascade reactions.

moiety, the catalyst **4g** endowed with diethylamine gave a slightly higher *ee* value (Table 1, entry 12). Notably, replacement of the 3,5-bis(trifluoromethyl) phenyl group in the thiourea part with other aryl groups had a deleterious effect on yield and selectivity (Table 1, entries 14–17). In order to further improve the above results, we presumed that an increase in the size of the R group would probably enhance the stereoselectivity based on the experience from catalysts **4d**–**4f**. Recently Ye and co-workers reported the Michael addition of substituted rhodanines to α,β-unsaturated ketones by bulky amino-acid derived primary-tertiary amine catalysts with good results.[13] Inspired by their work, we synthesized a novel bulky tertiary amine-thiourea catalyst **4m**. Pleasingly, reaction using this catalyst provided the corresponding product with a *dr* of >20:1 and an enantiomeric excess of 88% (Table 1, entry 18). As we observed, the best catalysts **4g** and **4m** gave the two enantiomers, respectively, with high yields and selectivities. Considering the potential utilization of both isomers in the synthesis, we decide to evaluate the generality of this reaction with catalysts **4g** and **4m**.

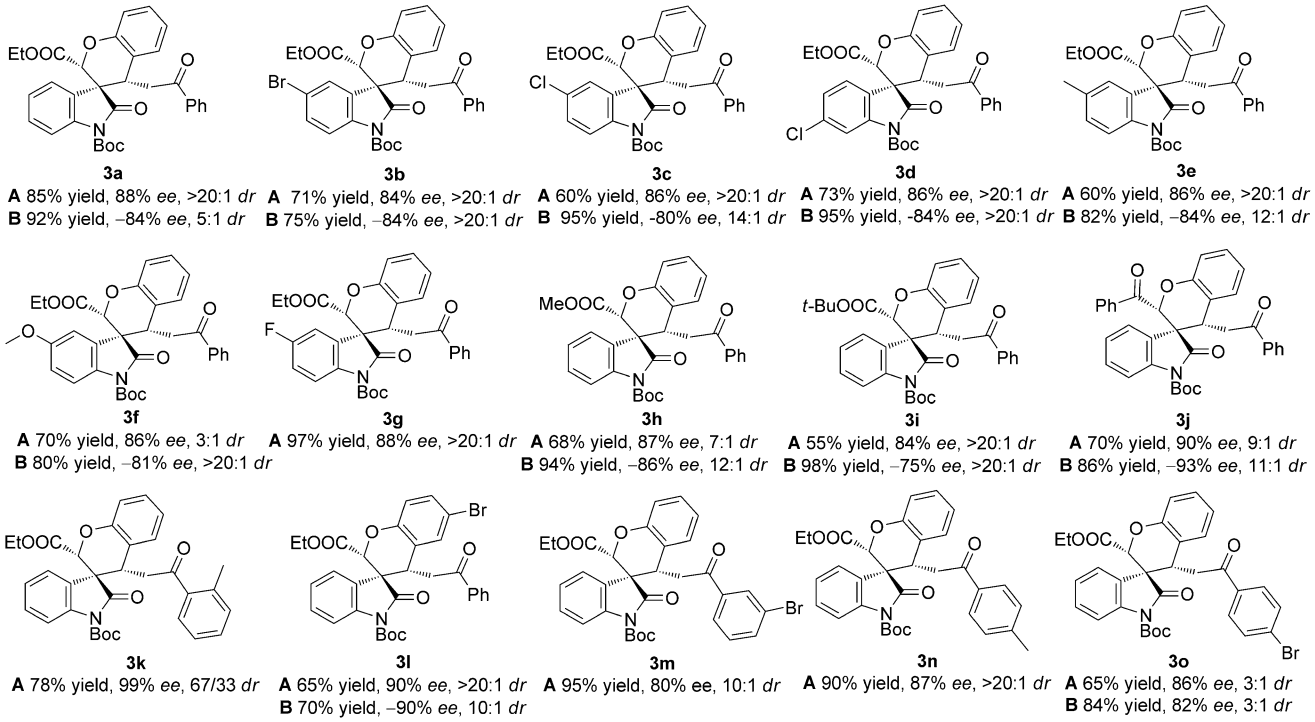
The experiment to construct different spirooxindole chromans is shown in Scheme 1. Several methyleneindolinones **1** were reacted with *ortho*-hydroxychalcone **2a** under the two optimized conditions, respectively (Scheme 1). As for the catalyst **4m** (Conditions **A**), the presence of electron-withdrawing or electron-donating substituents on the aromatic ring of the oxindoles had little effect on the stereoselectivity (**3a**–**3g**). Ester and ketone groups at the carbon-carbon double bond were well tolerated under these conditions (**3h**–**3j**). Notably, when the N-protecting groups of the methyleneindolinone was replaced by Ac or Bn, the reaction could not proceed.[14] *ortho*-Hydroxychalcones with various substituents on the benzene ring also gave the corresponding products with excellent

Table 1. Optimization of the reaction conditions of the oxa-Michael-Michael reaction.[a]



Entry	Catalyst	Solvent	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**4a**	$PhCH_3$	85	1.2/1	67
2	**4a**	$PhCF_3$	95	3/1	48
3	**4a**	CH_2Cl_2	70	4/1	18
4	**4a**	DCE	95	6/1	30
5	**4a**	Et_2O	95	2/1	50
6[f]	**4a**	$PhCH_3$	trace	–[e]	–[e]
7	**4b**	$PhCH_3$	63	3/1	60
8	**4c**	$PhCH_3$	26	3/2	47
9	**4d**	$PhCH_3$	88	3/1	−70
10	**4e**	$PhCH_3$	95	3/2	−67
11	**4f**	$PhCH_3$	94	4/1	−82
12	**4g**	$PhCH_3$	92	5/1	−84
13	**4h**	$PhCH_3$	87	4/1	−80
14	**4i**	$PhCH_3$	60	2/1	−59
15	**4j**	$PhCH_3$	54	3/1	−63
16	**4k**	$PhCH_3$	38	3/2	−54
17	**4l**	$PhCH_3$	85	4/1	−80
18	**4m**	$PhCH_3$	85	>20/1	88

[a] *Reaction conditions:* **1a** (1.2 equiv.), **2a** (1.0 equiv.), **4** (20 mol%), toluene (1.0 mL).
[b] Yield of the isolated product after column chromatography.
[c] Determined by ^{1}H NMR of crude product.
[d] Determined by chiral HPLC.
[e] Not determined.
[f] The reaction was carried out at 0 °C.

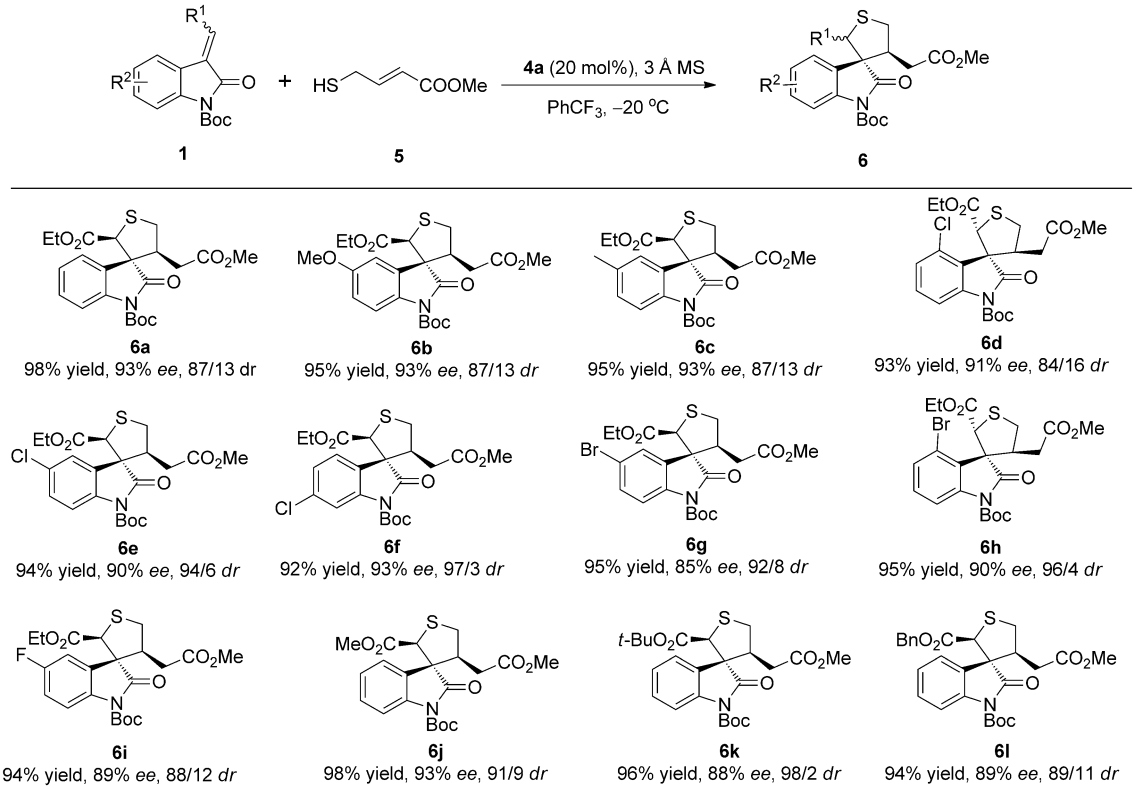


Scheme 1. Substrate scope of the oxa-Michael–Michael reaction. *Reaction conditions:* **1** (0.05 mmol), **2** (0.06 mmol), **4g** or **4m** (0.01 mmol), toluene (1.0 mL). Conditions **A**: with catalyst **4m**; conditions **B**: with catalyst **4g**. Yield reporteds after isolation. Diastereomeric ratios (*dr*) were determined by ^{1}H NMR of the crude product. Enantiomeric excesses (*ee*) were determined by chiral HPLC.

ee and moderate to excellent *dr* (**3k**–**3o**), regardless of their electronic nature or positions. When the catalyst **4g** was used (Conditions **B**), we found that the reactions provided the corresponding enantiomers in relatively higher yields than that under conditions **A** albeit with slightly decreased stereoselectivities indicated by the substrates examined. The absolute configuration of **3b** was unambiguously determined by single-crystal X-ray analysis and others can therefore be assigned by analogy.

After we had established the methodologies for the oxa-Michael–Michael reaction, the related thia-Michael–Michael reaction with methyleneindolinone came to mind and *trans*-ethyl 4-mercapto-2-butenoate **5** was chosen as the reaction partner. Based on the results we had obtained above, various reaction conditions including the catalysts, solvents were also examined in the same manner and finally the optimal conditions were obtained when methyleneindolinone **1a** (1.0 equiv.) was treated with *trans*-ethyl 4-mercapto-2-butenoate **5** (1.5 equiv.) in trifluorotoluene at −20 °C in the presence of catalyst **4a** (20 mol%) and 3 Å MS, providing the desired spriooxindole-tetrahydrothiophene in high yield and stereoselectivity (see the Support Information for details).

Having established the optimized reaction conditions, the generality of the reaction with different methyleneindolinones was explored. Changing the substituents at the C-4 to C-6 positions on the aromatic ring gave invariably excellent yields ranging from 92% to 98% and enantioselectivities ranging from 85% to 93% (Scheme 2, products **6a**–**6i**), irrespective of their electronic nature. A little more influence was observed on the diastereoselectivities which altered from 88:12 *dr* to 97:3 *dr*. A variety of ester substituents attached to the carbon-carbon double bond centers was also tolerated, providing the corresponding compounds in excellent yields, moderate to good diastereoselectivities, and good to excellent enantioselectivities (Scheme 2, products **6j**–**6l**). It should be noted that when we prepared the 4-substituted methyleneindolinones as the substrates (see **6d** and **6h**), we observed *cis*-alkenes in the compounds, which are different from other substituted methyleneindolinones we synthesized (*trans*-alkenes were observed), probably due to the steric hindrance between the ester and the 4-substituents. In view of the transition state the absolute configuration of **6d** and **6h** should also be altered compared with the others (see the Supporting Information for details). Unfortunately, efforts to get a crystal of **6g** failed although we can determine the configurations of the products **6h** and **6d** by X-ray analysis. In an alternative pathway, we presumed that the stereochemistry of the spiro carbon center is the same in all the products **6a**–**6l**. Thus we can determine the absolute configuration of the products **6a**–**6c**, **6e**–**6g** and **6i**–**6l** with an additional



Scheme 2. Substrate scope of the thia-Michael–Michael reaction. *Reaction conditions:* **1** (1.0 equiv.), **5** (1.5 equiv.), **4a** (20 mol%), $PhCF_3$ (1.0 mL). Yields reported after isolation. Diastereomeric ratios (*dr*) were determined by ^1H NMR of crude product. Enantiomeric excesses (*ee*) were determined by chiral HPLC.

NOE experiment (see the Supporting Information for details).

In summary, we have successfully developed a highly enantioselective oxa/thia-Michael–Michael cascade reaction for the construction of spirooxindole-chroman and spirooxindole-tetrahydrothiophene scaffolds. The novel amino acid-derived steric thiourea **4m** was identified as a highly efficient catalyst in the oxa-Michael–Michael cascade reaction. With the best catalysts **4g** and **4m** used, two enantiomers with high yields and selectivities were obtained, respectively. The reactions between *trans*-ethyl 4-mercapto-2-butenoate and methyleneindolinones were also developed, providing the spirooxindole-tetrahydrothiophenes with high yields and excellent enantioselectivities. Studies on the development of novel and concise methods to construct divergent heterocyclic oxindoles are still ongoing in our laboratory.

Experimental Section

General Procedure for the Oxa-Michael–Michael Reaction

Methyleneindolinone **1** (0.06 mmol, 1.2 equiv.) was added to a solution of thiourea **4** (0.01 mmol, 20 mol%) in toluene (0.5 mL). Then the *ortho*-hydroxychalcone **2** (0.05 mmol, 1.0 equiv.) was added and the resulting mixture was stirred for 4 days at room temperature. The crude mixture was directly subjected to column chromatography to provide the corresponding product **3** (with hexanes/ethyl acetate = 4/1).

General Procedure for the Thia-Michael–Michael Reaction

Methyleneindolinone **1** (0.05 mmol, 1.0 equiv.) was added to a solution of thiourea **4** (0.01 mmol, 0.2 equiv) in $PhCF_3$ (1 mL). The resulting solution was cooled down to −20 °C, then the *trans*-methyl 4-mercapto-2-butenoate **5** (0.075 mmol, 1.5 equiv.) and 10 mg of 3 Å MS were added. The progress of the reaction was monitored by TLC analysis. At the end of the reaction, the mixture was purified by flash column chromatography to afford the corresponding product **6** (with hexanes/ethyl acetate = 5/1).

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[14] Results not shown in Scheme 1. Actually, no products were observed by TLC analysis after the two reaction mixtures had been stirred at the optimum conditions for 5 days.

