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Organocatalytic enantioselective tandem Michael addition-oxidation of 3-substituted oxindoles with 1,4-benzoquinone

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ABSTRACT

By employing a chiral bifunctional thiourea-tertiary amine as catalyst, enantioselective tandem Michael addition-oxidation of 3-monosubstituted oxindoles with 1,4-benzoquinones were realized. The reactions afforded a wide range of 3,3-disubstituted oxindoles with moderate to good yields (up to 87%) in moderate to good enantioselectivities (up to 96%).

1. Introduction

Enantioenriched 3,3-disubstituted oxindoles are important core structures found in many natural products and pharmaceutical lead compounds.[1] Consequently, considerable efforts have been devoted to development of asymmetric synthesis of 3,3-disubstituted oxindoles. Over the past decade, impressive progress has been made in asymmetric construction of enantioenriched 3,3-disubstituted oxindoles.[1g,2] However, up to now, very limited examples involving asymmetric direct α-arylation of 3-monosubstituted oxindoles has been studied.[2a–c] Buchwald et al. presented the first highly efficient Pd-catalyzed enantioselective α-arylation and α-vinylation of 3-monosubstituted oxindoles with an axially chiral, P-chirogenic ligand.[2a] Wang et al. reported an indane amine-thiourea promoted highly enantioselective tandem Michael addition-oxidation of 3-monosubstituted oxindoles with naphthoquinones through which a series of 3,3-disubstituted oxindoles were prepared in good to excellent enantioselectivities.[2b] Zhou and et al. employed $(DHQD)_2PYR$ to catalyze the reaction of unprotected 3-monosubstituted oxindoles with naphthoquinones and the products were obtained with moderate to good yields in low to moderate ee values.[2c] We demonstrated an indirect asymmetric α-heteroarylation of 3-substituted oxindoles through conjugated addition of 3-monosubstituted oxindoles followed by Paal–Knorr cyclization.[2d] Recently, Pietruszka et al. reported a Laccase-catalyzed arylation of 3-substituted oxindoles via an oxidation/Michael addition sequence through which a series of racemic 3,3-disubstituted oxindoles were prepared efficiently.[3]

Quinones are important intermediates in organic synthesis. Owing to the good electrophilicity of quinones, they are usually employed as Michael acceptors. In recent years, quinones have attracted increasing attention in asymmetric reactions,[2b,c,4] through which numerous valuable complex chiral compounds were prepared in good stereoselectivities.

Herein we describe an enantioselective tandem Michael addition-oxidation of 3-monosubstituted oxindoles with 1,4-benzoquinone promoted by bifunctional chiral thiourea-tertiary amine organocatalysts. The reactions proceeded smoothly to provide various 3,3-disubstituted oxindoles in moderate to good yields (up to 87%) and moderate to good enantioselectivities (up to 96% ee).

2. Results and discussion

First, a range of bifunctional organocatalysts **1a**–**j** (Fig. 1) were screened in the reaction of *tert*-butyl-2-oxo-3-phenylindoline-1-carboxylate (**2a**) and 1,4-benzoquinone (**3a**) in dichloromethane at 0 °C to RT for 12 h. All of the reactions resulted in a main product

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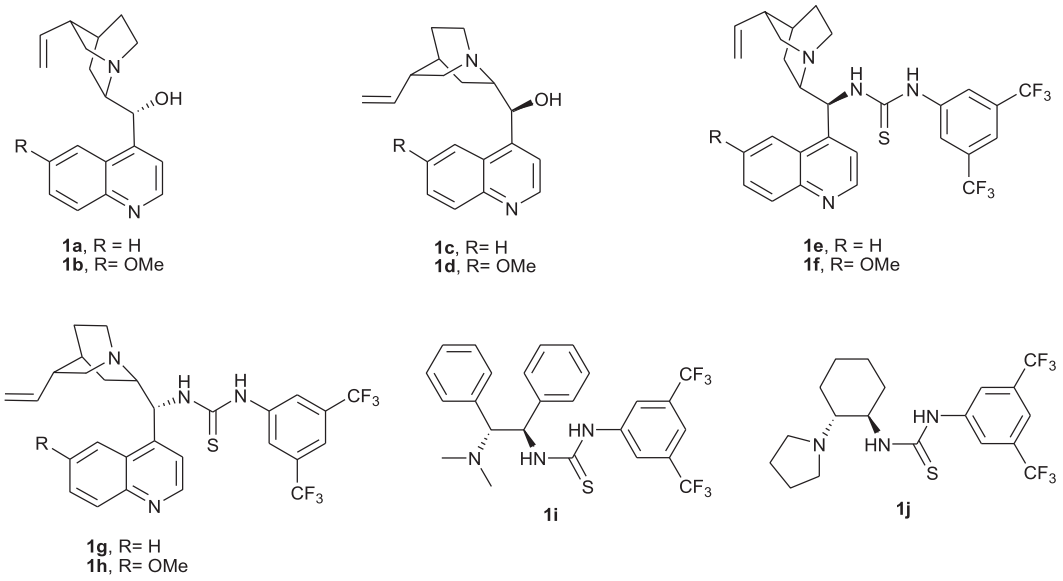
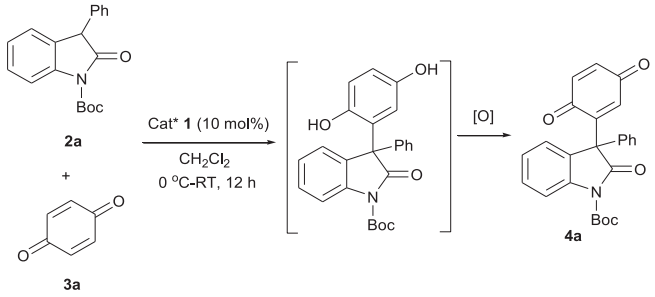


Fig. 1. Chiral bifunctional organocatalysts evaluated in this study.

3-quinone oxindole **4a** and some inseparable materials. The intermediate biphenol could not be detected. It was assumed that the biphenol was oxidized by 1,4-benzoquinone immediately. This assumption was confirmed by a GC–MS analysis of the reaction system, in which *p*-hydroquinone was detected (See Supplementary data). The results are summarized in Table 1.

As can be seen in Table 1, cinchona alkaloids **1a**–**d** provided the product **4a** in poor yields as well as low enantioselectivities (Table 1, entries 1–4). Better results were observed with cinchona alkaloids derived thiourea-tertiary amine catalysts **1e**–**h**[5] (Table 1, entries 5–8), in which **1e** provided remarkably superior ee value of 79% (Table 1, entry 10). Meanwhile thiourea-tertiary amine catalysts **1i**[6] and **j**[7] delivered much lower enantioselectivities (Table 1, entries 9 and 10).

Table 1
Screening of the chiral organocatalysts[a]

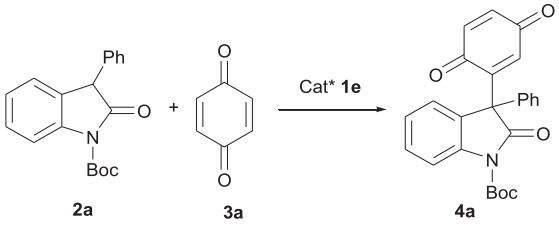


Entry	Cat*	Yield (%)[b]	ee (%)[c]
1	**1a**	39	7
2	**1b**	47	15
3	**1c**	25	26
4	**1d**	25	36
5	**1e**	52	79
6	**1f**	49	57
7	**1g**	58	45
8	**1h**	61	40
9	**1i**	54	31
10	**1j**	46	30

[a] Unless specified otherwise, reactions were carried out with **2a** (0.2 mmol), **3a** (0.4 mmol), and 10 mol % of catalyst **1** in 2 mL of dichloromethane at 0 °C to rt for 12 h.
[b] Isolated yield based on **2a**.
[c] The ee values were determined by using chiral HPLC.

Hence **1e** was determined as the optimal catalyst and was employed in further investigations. Subsequently, the other conditions were modified. The results are summarized in Table 2. First, various solvents were evaluated. Chloroform gave much lower ee value (Table 2, entry 2). 1,2-Dichloroethane resulted in slightly lower ee value (Table 2, entry 3). To our delight, reaction in several aromatic solvents provided the product with good enantioselectivities (Table 2, entries 4–6), in which mesitylene delivered the highest ee value of 89% (Table 2, entry 6). Non-polar solvent hexane provided only moderate enantioselection (Table 2, entry 7). Ether gave similar result to the aromatic solvents (Table 2, entry 8 vs

Table 2
Modification of the reaction conditions[a]



Entry	Solvent	T (°C)	Yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	0–rt	52	79
2	$CHCl_3$	0–rt	46	54
3	$ClCH_2CH_2Cl$	0–rt	42	74
4	Toluene	0–rt	41	84
5	Xylene	0–rt	37	85
6	Mesitylene	0–rt	45	89
7	Hexane	0–rt	40	65
8	Et_2O	0–rt	45	85
9	THF	0–rt	42	53
10[d]	MeOH	0–rt	40	0
11	Mesitylene	0	87	91
12	Mesitylene	−10	65	92
13[e]	Mesitylene	0	51	86
14[f]	Mesitylene	0	84	91

[a] Unless specified otherwise, reactions were carried out with **2a** (0.2 mmol), **3a** (0.4 mmol), and 10 mol % of catalyst **1e** in 2 mL of the solvent for 12 h.
[b] Isolated yield based on **2a**.
[c] The ee values were determined by using chiral HPLC.
[d] The reaction was carried out for 24 h.
[e] 5 mol % of **1e** was employed.
[f] 15 mol % of **1e** was employed.