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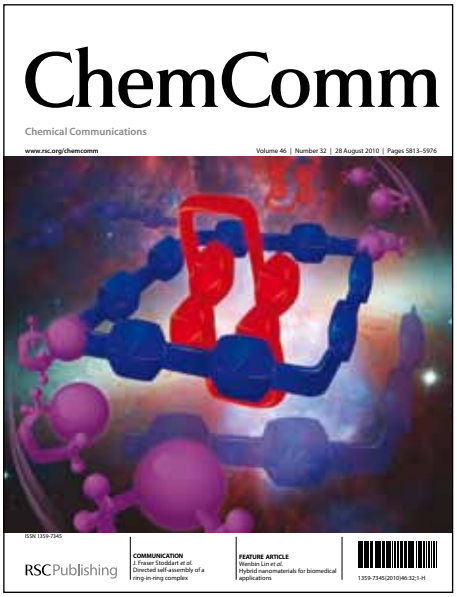

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3-Bromooxindoles as Nucleophiles in Asymmetric Organocatalytic Mannich Reactions with *N*-Ts-imines

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The direct asymmetric Mannich reaction of *N*-unprotected 3-bromooxindoles with *N*-Ts-imines catalyzed by bifunctional thiourea derived from 2-substituted cinchona alkaloid. The products with vicinal chiral tertiary and brominates quaternary stereogenic centers were achieved in excellent diastereo- and enantioselectivity (up to 99:1 *dr*, 99% *ee*).

Oxindoles bearing a quaternary stereocenters at the C_3 are prevalent in biologically relevant alkaloid natural products and pharmaceuticals.[1] For this reason, the development of methodologies to access various of chiral 3,3'-disubstituted oxindoles derivatives has become a hot topic.[2-5] Thus, great efforts and achievements have been made in catalytic asymmetric reactions to afford those chiral promising target compounds involving 3-alkyl-[3] or 3-aryloxindoles,[4] 3-hydroxyoxindoles,[5] and 3-halo 3,3'-disubstituted oxindoles[6] which could be easily elaborated to other functional derivatives and have exhibited potential use in the construct of complex bioactive compounds. Amongst the chiral 3-halo 3,3'-disubstituted oxindoles, the 3-chloro-[7,8] and 3-fluoro-[9] analogues have been successfully accessed by asymmetric reactions. However, to our knowledge, the chiral 3-bromo 3,3'-disubstituted oxindoles, which could have more potential and be broadly used as versatile synthetic intermediates, have no general asymmetric catalytic method to access.[10]

Racemic 3-bromooxindoles, with both eletrophilicity as alkylating agents and nucleophilicity in the enolate tautomer, were first reported by Hinman and Baumann.[11] The eletrophilicity of 3-bromooxindole and its derivatives has been successfully realized.[12] Stoltz group has exploited it in preparing racemic 3,3'-disubstituted oxindoles.[12a] Subsequently, the enantioselective variant was achieved and used in constructing the core structures of an important biologically active alkaloid.[12b] In contrast, 3-bromooxindoles have rarely been employed as nucleophiles. We hypothesized that if racemic 3-bromooxindoles could be successfully applied as nucleophilic partners in asymmetric Mannich reactions with *N*-Ts-imines, then those densely functionalized products with vicinal chiral tertiary and brominates quaternary centers could be accessed. Those products could be further transformed into chiral spiroaziridine oxindoles. The synthesis of highly strained optical activity spiroaziridine oxindoles remains a significant challenge, and until now, no report has documented a success. Those spiroaziridine oxindoles represent an important class of nitrogen-containing heterocycles with potential synthetic utility and biological activity.[13]

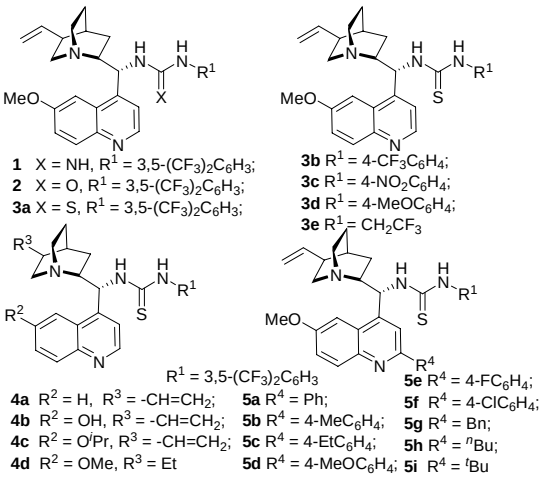


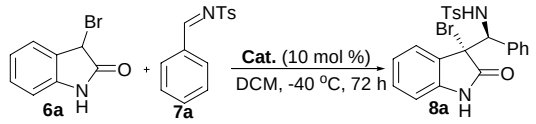
Figure 1 Screened catalysts derived from cinchona alkaloids.

Herein, we report the first example of a highly enantioselective direct asymmetric Mannich reaction of *N*-unprotected 3-bromooxindoles with *N*-Ts-imines catalyzed by bifunctional cinchona alkaloid catalysts, and further allow for construction of chiral spiroaziridine oxindoles.

The reaction of **6a** with benzaldehyde *N*-Ts-imine **7a** was selected as a model reaction. We exploited bifunctional cinchona alkaloid catalysts **1–5** (Figure 1) to concomitantly activate the two reactive partners through the tertiary nitrogen to deprotonate the 3-position proton of 3-bromooxindole and the hydrogen bond donating ability to interact with nitrogen of the imine. When the catalyst **3a** was investigated at rt, initial test had found the phenomena that the catalyst had been deactivated during the reaction procedure, we ascribed this to the electrophilic ability of 3-bromooxindole and with the propensity to alkylate the tertiary nitrogen to form quaternary ammonia salt to deactivate the catalyst. Thus the basicity of the tertiary nitrogen must be exerted and its nucleophilicity must be restrained by varying the reaction temperature and solvent with the help of the different effect of the two factors on them. After preliminary screening, we had delighted to find that good reactivity (79% yield) and stereoselectivities (90:10 *dr* and 88% *ee*) were achieved when the reaction was

performed at low temperature (-40 °C) in DCM after 72 h (Table 1, entry 3). By changing the catalyst into guanidine (**1**) and urea (**2**), the yields and stereoselectivities decreased greatly (Table 1, entries 1 and 2). The effect of the substituent at the terminal aromatic ring of thiourea on the reaction was further investigated. When **3a** was changed into **3b**, **3c**, or **3d**,

Table 1 Catalysts screened in asymmetric Mannich reaction of 3-bromooxindole to *N*-Ts-imine [a]

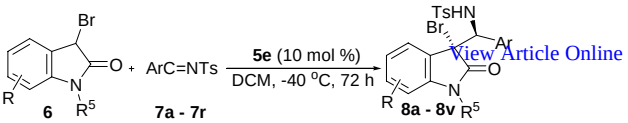


Entry	Cat.	Yield/%[b]	Dr[c]	Ee/%[c]
1	**1**	42	85:15	53
2	**2**	47	84:16	45
3	**3a**	79	90:10	88
4	**3b**	53	89:11	80
5	**3c**	42	90:10	88
6	**3d**	32	95:5	78
7	**3e**	53	86:14	75
8	**4a**	40	84:16	85
9	**4b**	30	93:7	77
10	**4c**	59	94:6	88
11	**4d**	64	92:8	87
12	**5a**	72	93:7	90
13	**5b**	70	95:5	93
14	**5c**	66	93:7	91
15	**5d**	72	94:6	93
16	**5e**	76	96:4	94
17	**5f**	66	96:4	94
18	**5g**	66	95:5	90
19	**5h**	NR	-	-
20	**5i**	66	88:12	90

[a] Reaction conditions: **6a** (0.1 mmol), **7a** (0.12 mmol), **Cat.** (0.01 mmol), c = 0.20 M, -40 °C, 72 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

the yields of the reaction decreased gradually with slightly fluctuated stereoselectivities (Table 1, entries 3–6). This may be caused by the hydrogen bond donating ability of the thiourea, which is associated and governed by the electronic status of the aromatic substituent. When we introduced an aliphatic trifluoroethyl into the terminal of thiourea (**3e**), no better results were observed (Table 1, entry 7). On the base of catalyst **3a**, we changed the group of R^2 to hydrogen (**4a**), hydroxyl (**4b**), and isopropoxyl (**4c**), and we also changed the group of R^3 to ethyl (**4d**), but the performance of those catalysts did not improve. When phenyl (R^4 = Ph) was introduced into the 2-position of the catalyst (**5a**), better diastereoselectivity (93:7 *dr vs* 90:10 *dr*) and stereoselectivity (90% *ee vs* 88% *ee*) were achieved with slightly lower yield (72% *vs* 79%) (Table 1, entries 3 and 12). Encouraged by this promising result, a series of other substituents on the 2-position of the catalysts (**5b**–**5i**) were investigated systematically (Table 1, entries 13–20). **5e** was identified as the best catalyst in steric control ability and had a 76% yield, 96:4 *dr* and 94% *ee* (Table 1, entry 16). Other bifunctional catalysts were screened, but none performed better than catalyst **5e** (see ESI: Electronic Supplementary Information). Reaction conditions were further optimized and the best result was achieved when the concentration of **6a** was 0.2 M and the ratio of **7a** to **6a** was 1.5 : 1 in DCM at -40 °C (see ESI).

Table 2 Asymmetric Mannich reaction of 3-bromooxindoles to *N*-Ts-imines [a]



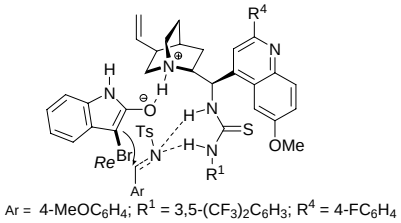
Entry	R	R^5	Ar	Product	Yield/%[b]	Dr[c]	Ee/%[c]
1[d]	H	H	Ph	**8a**	91 (86)	96:4 (95:5)	94 (95)
2	H	H	*o*-FC_6H_4	**8b**	94	94:6	82
3	H	H	*m*-FC_6H_4	**8c**	99	96:4	82
4	H	H	*p*-FC_6H_4	**8d**	96	97:3	90
5	H	H	*o*-ClC_6H_4	**8e**	84	93:7	82
6	H	H	*m*-ClC_6H_4	**8f**	99	92:8	75
7	H	H	*p*-ClC6H4	**8g**	94	93:7	87
8	H	H	*o*-MeC_6H_4	**8h**	89	99:1	92
9	H	H	*m*-MeC_6H_4	**8i**	99	83:17	93
10	H	H	*p*-MeC_6H_4	**8j**	87	97:3	94
11	H	H	*o*-$MeOC_6H_4$	**8k**	90	99:1	94
12	H	H	*m*-$MeOC_6H_4$	**8l**	99	78:22	91
13	H	H	*p*-$MeOC_6H_4$	**8m**	88	97:3	98
14	H	H	*p*-HOC_6H_4	**8n**	Trace	-	-
15	H	H	Furan-2-yl	**8o**	99	79:21	93
16	H	H	1-Naphthyl	**8p**	81	95:5	95
17	H	H		**8q**	89	94:6	90
18	H	Me	Ph	**8r**	64	92:8	79
19	5-F	H	*p*-$MeOC_6H_4$	**8s**	89	99:1	95
20	5-Cl	H	*p*-$MeOC_6H_4$	**8t**	90	99:1	95
21	5-Br	H	*p*-$MeOC_6H_4$	**8u**	93	99:1	96
22	6-Cl	H	*p*-$MeOC_6H_4$	**8v**	75	95:5	99

[a] Reaction conditions: **6** (0.1 mmol), **7** (0.15 mmol), **5e** (0.01 mmol), c = 0.20 M, -40 °C, 72 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Results of reaction magnified to 30 times are in parentheses.

Having established the optimal reactive conditions, the reaction was expanded to a wide variety of 3-bromooxindoles **6** and *N*-Ts-imines **7**. The results are summarized in Table 2. Generally, *N*-Ts-imines with electron donating substituents gave better enantioselectivity than those with electron withdrawing groups. The position of the substituent on the *N*-Ts-imines phenyl group had a slight influence on the reaction. *N*-Ts-imines with a *meta* substituent on the phenyl proceeded smoothly to give the corresponding products with slightly higher yields (Table 2, entries 3, 6, 9 and 12). Better enantioselectivities were achieved when substituents were in the *para* position of *N*-Ts-imines rather than in the *meta* or *ortho* position (Table 2, entries 2–13). When the substituent in the para position was –OH, no reaction occurred, which was ascribed to the acidity of the –OH, which neutralized the basicity of the tertiary nitrogen in the catalyst thus deactivating it (Table 2, entry 14). Imines with heteroaromatic and naphthalene substituents were also tested, and were suitable for the asymmetric Mannich reactions. The furyl imine showed slightly lower diastereoselectivity. Product **8o** was obtained in excellent yield (99%), good enantioselectivity (93% *ee*), and with moderate diastereoselectivity (79:21 *dr*) (Table 2, entry 15). Excellent stereoselectivities were observed in product **8p** (Table 2, entry 16). When the reaction was scaled up to 30 times, the stereoselectivities kept the same level (Table 2, entry 1). Distinct reactive performance between the protected and unprotected 3-substituted oxindoles has been documented.[14] The same phenomenon was also

identified in this catalytic system. *N*-Me-protected 3-bromooxindole resulted in lower yield and enantioselectivity (Table 2, entry 18). Various halo-substituted 3-bromooxindoles (**6b**–**6e**) were further investigated in the asymmetric reactions with imine **7m**. The desired products (**8s**–**8v**) were achieved with good yields (75–93%), and excellent stereoselectivities (95:5–99:1 *dr*; 95–99% *ee*) (Table 2, entries 19–22). Regrettably, this process didn't accommodate to aliphatic imines.

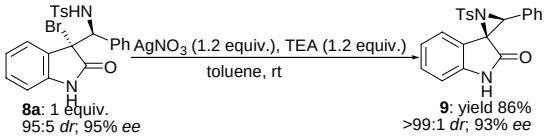
The absolute configuration of the major diastereomer of product **8u** was confirmed by X-ray analysis (See ESI).[15] To account for the stereochemical outcome, a transition state model was proposed (Figure 2). The two reactive partners were activated concurrently by the catalyst and the nucleophilic attack from both the *Re*-faces of the enolate anion and the *N*-Ts-imine afford the observed products. Other product configurations were deduced based on analogy.



Ar = 4-MeOC$_6$H$_4$; R^1 = 3,5-(CF$_3$)$_2$C$_6$H$_3$; R^4 = 4-FC$_6$H$_4$

Figure 2 Proposed transition state model.

Attempt to transform the chiral Mannich products into the corresponding spiroaziridine oxindoles.[16] After a series of tests and found that the target compound **9** could be achieved successfully by an intramolecular S_N2 reaction in 86% yield, >99:1 *dr* and 93% *ee* in the presence of $AgNO_3$ (1.2 equiv.) and TEA (1.2 equiv.) at rt in toluene (1.0 mL) for 1 h (Scheme 1).



8a: 1 equiv. 95:5 *dr*; 95% *ee*

9: yield 86% >99:1 *dr*; 93% *ee*

Scheme 1 Synthesis of chiral spiroaziridine oxindole

In conclusion, a series of bifunctional thiourea catalysts first derived from cinchona alkaloid with substituents at 2-position had been employed in the direct asymmetric Mannich reaction of *N*-unprotected 3-bromooxindoles with *N*-Ts-imines. The products bearing vicinal chiral tertiary and brominates quaternary stereogenic centers were attainable in the catalysis of **5e** with excellent stereoselectivities (up to 99:1 *dr*, 99% *ee*) for the first time. Thus, a novel general methodology to access chiral spiroaziridine oxindoles was further developed.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Catalysts synthesis, spectroscopic data, enantioselectivities measurement, and absolute configuration determinations for **8u**. See DOI: 10.1039/b000000x/

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15 CCDC 885433 (**8u**) contains the supplementary crystallographic data could be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.

16 No spiroaziridine oxindole was observed in the Mannich reaction procedure, even deal with the Mannich products with various bases.