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Enantioselective Organocatalytic *anti*-Mannich-Type Reaction of *N*-Unprotected 3-Substituted 2-Oxindoles with Aromatic *N*-Ts-aldimines

Liang Cheng,[†,‡] Li Liu,*[,†] Han Jia,[†] Dong Wang,[†] and Yong-Jun Chen*[,†]

Beijing National Laboratory for Molecular Sciences (BNLMS), CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China, and Graduate School of Chinese Academy of Sciences, Beijing 100049, China

lliu@iccas.ac.cn; yjchen@iccas.ac.cn

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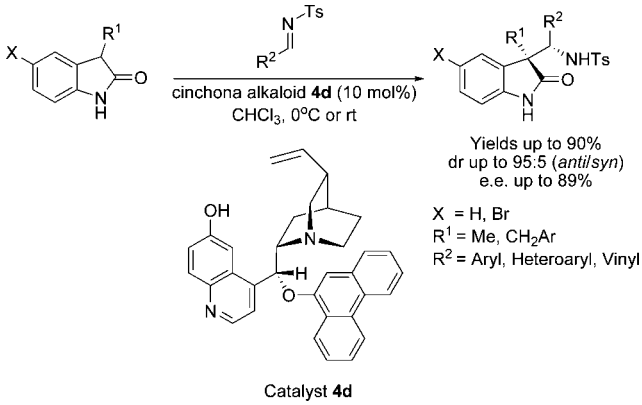

The modified cinchona alkaloid-catalyzed direct Mannich-type reaction of *N*-unprotected 2-oxindoles with *N*-Ts-imine was developed to afford *anti*-3,3-disubstituted 2-oxindoles with vicinal chiral quaternary and tertiary carbon centers in yields up to 90% with excellent diastereoselectivities (*anti*/*syn* up to 95:5) and good enantioselectivies (up to 89% ee). A transition model for the *anti*-diastereo- and enantioselectivity of the reaction was proposed.

Stereoselective (diastereo- and enantioselective) formation of quaternary centers is one of the key issues that are encountered during the synthesis of the center of complex molecules. Consequently, the installation of a specific fully substituted chiral center has been a challenging task for synthetic organic chemists for decades.[1] Due to the unique biological and pharmacological proprieties, the framework of 2-oxindole is extensively incorporated in substructures of natural products and synthetic intermediates of bioactive molecules.[2] Numerous oxindole alkaloids with strong bioactive profiles and interesting structural properties, such as salacin (**1**),[3a] uncarine E (**2**),[3b,c] and spirotryprostatin A (**3**),[3e,f] contain a 3,3-disubstituted 2-oxindole subunit in their backbones and an *anti*-diastereomeric structure (Figure 1). Though a handful of synthetic methods are available for creating the single quaternary carbon centers at the C-3 position with complete control, the challenge still lies primarily in the efficient construction of a vicinal chiral tertiary carbon center.[4]

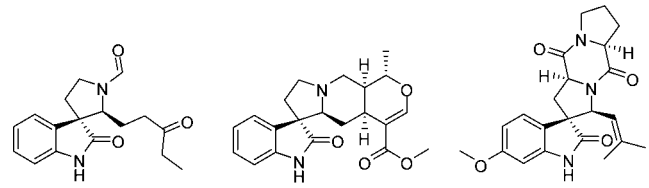

FIGURE 1. Biologically active 2-oxindoles bearing 3,3-disubstituted centers.

Direct Mannich-type reaction is one of the most powerful methods for carbon−carbon bond formation, and the versatility of this process has been widely exploited in the development of asymmetric methods for the synthesis of chiral β-aminocarbonyl compounds.[5] Inspired by the success in asymmetric reactions of imine derivatives,[6] we were encouraged to ascertain whether the daunting problem that the formation of chiral quaternary carbon center and an adjacent tertiary center could be processed concurrently by employing an appropriate 3-monosubstituted oxindole. While direct organocatalytic asymmetric Mannich-type reaction giving *syn*-adducts has been well established, the development of an *anti*-Mannich-type reaction is considerably sluggish.[7] The exploitation of a highly efficient

† Beijing National Laboratory for Molecular Sciences (BNLMS), CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China.

‡ Graduate School of Chinese Academy of Sciences, Beijing 100049, China.

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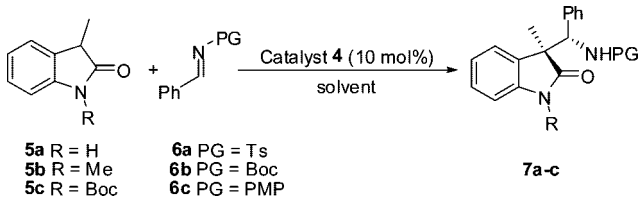
SCHEME 1. Asymmetric Addition of 2-Oxindoles 5 with Imines 6



anti-diastereoselective Mannich-type reaction is still a challenge in contemporary asymmetric synthesis. Recently, Chen and coworker disclosed a novel transformation between *N*-Boc-oxindoles and *N*-Boc-imines catalyzed by thiourea−tertiary amine to generate the *syn*-diastereoisomers with high enantioselectivities.[8] Herein, we describe the asymmetric *anti*-Mannich-type reaction of *N*-unprotected 2-oxindole with aromatic *N*-tosylimine in the presence of modified cinchona alkaloids as the catalysts.[9] The highly functionalized chiral oxindole derivatives obtained from this reaction will surely provide versatile building blocks for the preparation of oxindole alkaloids with biological activities.

In light of the thiourea−tertiary amine-catalyzed asymmetric Mannich-type reaction of *N*-Boc-2-oxindole **5c**,[8] at first the reaction of 3-methyl-2-oxindole (**5a**, R = H) with *N*-Ts-imine **6a** was carried out in CH_2Cl_2 at room temperature in the presence of quinine−thiourea catalyst **4i** (Scheme 1, Figure 2). Unfortunately, **4i** exhibited relatively lower reactivity and provided the product **7a** with poor diastereo- and enantioselectivity (Table 1, entry 1).

Subsequently, the asymmetric additions of **5a** with **6a** under the catalysis of chiral natural cinchona alkaloids (**4a**,**b**,**e**,**f**) proceeded smoothly to give the desired adduct **7a** in moderate yields but with poor diastereo- and enantioselectivities (Table 1, entries 2−5). It was found that QN-1-naphthoate **4c** was totally inactive in the reaction of **5a** with **6a** (entry 6) in spite of its highly catalytic ability in enantioselective aldol-type reaction of 2-oxindoles with ethyl trifluoropyruvate.[10] As to the limited conformational flexibility, β-ICD **4h** was another catalyst with increased basicity, nucleophilicity, and reduced steric hindrance of the quinuclidine nitrogen center.[11] However, it

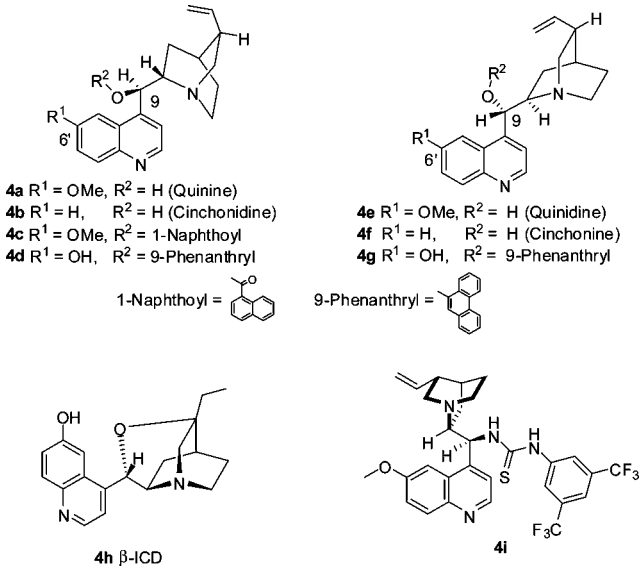


FIGURE 2. Catalyst library for screening.

TABLE 1. Optimization of Mannich-Type Reaction of 2-Oxindole 5 with Imine 6 Catalyzed by Cinchona Alkaloids 4[a]

entry	5	6	4	solvent	*T* (°C)	yield (%)	*anti*/*syn*[b]	ee[c] (%)
1[d]	**5a**	**6a**	**4i**	CH_2Cl_2	rt	74	75:25	−20
2[d]	**5a**	**6a**	**4a**	CH_2Cl_2	rt	65	49:51	−6
3[d]	**5a**	**6a**	**4b**	CH_2Cl_2	rt	86	42:58	8
4[d]	**5a**	**6a**	**4e**	CH_2Cl_2	rt	70	46:54	25
5[d]	**5a**	**6a**	**4f**	CH_2Cl_2	rt	70	54:46	−11
6[d]	**5a**	**6a**	**4c**	CH_2Cl_2	rt	<5	23:77	nd[e]
7[d]	**5a**	**6a**	**4h**	CH_2Cl_2	rt	<10	84:16	nd[e]
8[f]	**5a**	**6a**	**4d**	CH_2Cl_2	rt	90	92:8	82
9	**5a**	**6a**	**4g**	CH_2Cl_2	rt	83	93:7	−80
10	**5a**	**6a**	**4d**	$CHCl_3$	rt	99	94:6	84
11	**5a**	**6a**	**4d**	DCE	rt	83	93:7	80
12	**5a**	**6a**	**4g**	THF	rt	15	92:8	−79
13	**5a**	**6a**	**4g**	Et_2O	rt	99	94:6	−79
14	**5a**	**6a**	**4g**	PhMe	rt	41	90:10	nd[e]
15	**5a**	**6a**	**4d**	$CHCl_3$	0	77	95:5	86
16	**5a**	**6a**	**4d**	$CHCl_3$	−10	68	94:6	86
17	**5a**	**6a**	**4d**	$CHCl_3$	−30	40	94:6	81
18	**5b**	**6a**	**4d**	$CHCl_3$	rt	trace		
19	**5c**	**6a**	**4d**	CH_2Cl_2	rt	NR[g]		
20	**5a**	**6b**	**4d**	$CHCl_3$	rt	trace		
21	**5a**	**6c**	**4d**	$CHCl_3$	rt	NR[g]		

[a] Oxindole **5** (0.2 mmol), imine **6** (0.2 mmol), catalyst **4** (0.02 mmol), solvent (200 μL), 48 h. [b] dr (*anti*/*syn*) determined by ^{1}H NMR or chiral HPLC of the reaction mixture. [c] Determined by chiral HPLC and refer to the major diastereoisomers. [d] Solvent (2 mL). [e] nd: not determined. [f] Reaction time: 60 h. [g] NR: no reaction.

could barely catalyze the addition (entry 7), which indicates the crucial transition-state structure of the substrate−catalyst complex (vide infra).

On the basis of these results, it was found that both of natural cinchona alkaloid catalysts (**4a**,**b**,**e**,**f**) disfavored for highly stereoselective reaction of **5** with **6** and appropriate bulky group on C9 should be introduced. To our delight, when the catalyst **4d** bearing a 6′-hydroxyquinoline ring with a bulky phenanthrene group on C9 position (R^2 = 9-PHN) was employed, the desired product **7a** was isolated with an excellent yield of 90% and high diastereoselectivity (8:92) (entry 8). The enantiomeric excess of the major diastereoisomer could reach 82%. To the best of our knowledge, this is the first example of asymmetric direct Mannich-type reactions catalyzed by 6′-OH cinchona alkaloid catalysts bearing 9-OR groups, which have been widely applied in organocatalytic asymmetric reactions.[12] The pseudoenantiomeric quinidine derivative **4g** gave results similar to those for **4d**, but with opposite configuration (entry 9) as determined by chiral HPLC analysis.

To examine the effect of solvents, various solvents were employed in the reaction of **5a** with **6a**. Compared with that in

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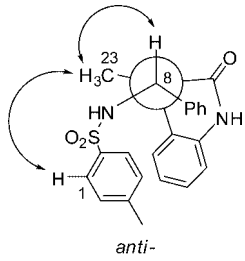
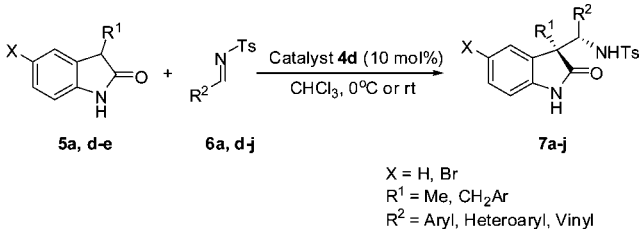


FIGURE 3. Key NOESY correlations (double-headed arrows) observed for adduct **7a** established the relative stereochemistry as the *anti*-configuration.

SCHEME 2. Asymmetric Addition of 2-Oxindoles 5 to *N*-Ts-imines 6 under the Catalysis of 4d



CH_2Cl_2 (entry 8) or DCE (entry 11), the reaction performed in $CHCl_3$ gave better results (entry 10). For polar oxygen-containing solvents (such as THF, Et_2O), the ee values of the product decreased slightly (entries 12 and 13).

The use of a nonpolar solvent (e.g., toluene) would make the yield of **7a** decrease to only 41% (entry 14). The reaction temperature also influenced the yield and selectivity notably. The reaction performed at 0 or −10 °C afforded **7a** with better diastereo- and enantioselectivities than that at room temperature, albeit with inferior yields (entries 15 and 16). By lowering the temperature to −30 °C, the reaction was evidently impeded (entry 17).

The assignment of relative configuration of the product **7a** was achieved by NMR experiments. Key NOESY correlations were observed from H-23 to H-1 and H-8, but not to the protons in the phenyl ring (Figure 3), which confirmed the *anti*-relationship (see the Supporting Information for details).

We further examined the effect of *N*-substitution of 2-oxindole in the reaction process. For *N*-methyl-2-oxindole **5b** and *N*-Boc-2-oxindole **5c**, no addition products were detected in the reaction with **6a** (entries 18 and 19), which indicates that the *N*-H subunit of oxindole is necessary for this reaction. On the other hand, *N*-substitution in the aldimines also influenced the Mannich-type reaction strongly. Although *N*-Boc-benzaldimine **6b** exhibited comparable activity in many kinds of reactions, it was totally inactive in the reaction system employed here. Less reactive *N*-methoxyphenyl (*N*-PMP) benzaldimine **6c** gave the same results (entries 20 and 21).

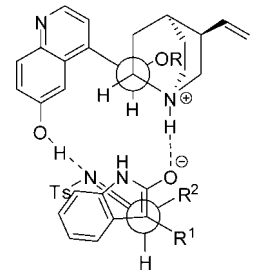


FIGURE 4. Proposed transition state of the *anti*-Mannich-type reaction of *N*-unprotected oxindole with *N*-Ts-imine catalyzed by cinchona alkaloid **4d**.

Employing the optimal conditions, a wide range of aldimines (**6a**,**d**−**j**) derived from aryl, heteroaryl, and vinyl aldehydes were treated with 3-substituted 2-oxindoles (**5a**,**d**,**e**) in $CHCl_3$ at 0 °C or room temperature in the presence of catalyst **4d** to give the products **7a**−**j** (Scheme 2, Table 2). Good to excellent diastereo- and enantioselectivities of the products were obtained. The substituents with either multifarious electronic properties or steric effect in aldimines were found to be well tolerated in this transformation (entries 2−7), while the aldimine derived from piperonal **6h** gave the best results (dr *anti*/*syn* 95:5, ee 89%) (entry 6). Interestingly, α,β-unsaturated imine **6j** was a good substrate for the Mannich-type reaction with **5a** and exclusively afforded 1,2-addition product **7h** in moderate yield with good *anti*-diastereo- and enantioselectivity (entry 8). Other 3-substituted-2-oxindoles were also found to be effective for the asymmetric Mannich-type reaction catalyzed by cinchona alkaloid. 3-(4-Bromobenzyl)-2-oxindole **5d** was facilely converted to the product **7i** with an 88% yield, of which the ee could reach 97% after recrystallization. Substitution in the phenyl ring of 2-oxindole has less effect on the yield of the product, albeit with moderate enantioselctivity of the *anti*-diastereoisomer (entry 10).

As indicated above, although *N*-Boc-protected 2-oxindoles provided *syn*-Mannich products under the catalysis of thiourea,[8] an excess of *anti*-diastereomeric isomers were detected in the Mannich-type reaction of *N*-unprotected 2-oxindole with *N*-Ts-aldimines in the presence of cinchona alkaloid catalyst. Meanwhile, the X-ray single-crystal structure analysis of the adduct **7i**[13] also demonstrated that the major Mannich product had an

TABLE 2. Catalytic Enantioselective Addition of 2-Oxindoles 5 to *N*-Ts-imines 6[a]

entry	X	R^1	R^2	yield (%)	*anti*/*syn*[b]	ee[c] (%)
1	H	**5a**, Me	**6a**, Ph	**7a**, 77	95:5	86
2	H	**5a**	**6d**, 2-Cl-C_6H_4	**7b**, 65	79:21	81
3[d]	H	**5a**	**6e**, 3-Cl-C_6H_4	**7c**, 90	83:17	80
4	H	**5a**	**6f**, 4-Br-C_6H_4	**7d**, 88	84:16	85
5	H	**5a**	**6g**, 2-OMe-C_6H_4	**7e**, 79	80:20	85
6	H	**5a**	**6h**, 3,4-OCH_2O-C_6H_3	**7f**, 90	95:5	89
7	H	**5a**	**6i**, 2-furyl	**7g**, 71	89:11	83
8[d]	H	**5a**	**6j**, Ph-CH=CH	**7h**, 57	90:10	80
9	H	**5d**, 4-Br-C_6H_4-CH_2	**6a**	**7i**, 88	80:20	71 (97)[e]
10	Br	**5e**, Me	**6a**	**7j**, 70	88:12	70

[a] Oxindole **5**/imine **6** = 1:1; catalyst **4d** loading = 10 mol %; reaction performed at 0 °C unless otherwise noted. [b] Determined by ^1H NMR or chiral HPLC of the reaction mixture. [c] Determined by chiral HPLC and refer to the *anti* diastereoisomers. [d] Reaction performed at room temperature. [e] After recrystallization from petroleum ether/CH_2Cl_2.

anti-diastereomeric structure, while the configurations of the two newly formed chiral carbon centers were deduced as (*C*8*S*, *C*15*S*).

Based on experimental results, we proposed a model of the transition state to rationalize the observed *anti*-diastereoselection and asymmetric induction (Figure 4). The bulky 9-phenanthryl ether substituent at C9 position as well as the utilization of polar solvent (chloroform) facilitated the catalyst **4d** to adapt its conformation[12d] to simultaneously close and activate the deprotonated enolated oxindole and *N*-Ts-imine in favoring the *re*-face attack of the imine. Remarkably, the unprotected *N*-H of oxindole was found to be essential for the transition state and hence the catalytic process.[14] The use of *N*-substituted 2-oxindoles (*N*-Me, *N*-Boc) gave nothing or trace addition product. The network of hydrogen bonding forced the substituents of the two bond-forming carbons in a staggered arrangement to afford the *anti*-diastereoisomers. Deduced from the X-ray analysis of the **7i**, the *re*-face of the imine was preferably attacked by the *re*-face of enolated oxindole, which is consistent with the observed *anti*-diastereoselection in this transformation (see the Supporting Information for details).

In summary, we have developed a highly *anti*-diastereoselective and enantioselective direct Mannich-type reaction of *N*-unprotected 2-oxindoles with *N*-Ts-aldimines catalyzed by a modified cinchona alkaloid to give versatile chiral 2-oxindole derivatives bearing chiral amino functional moiety and a chiral quaternary carbon center, and a transition model was proposed for the *anti*-diastereoselectivity.

Experimental Section

Representative Procedure for the Synthesis of 3,3-Disubstituted 2-Oxindoles. To the mixture of 2-oxindole **5a** (30 mg, 0.2 mmol) and *N*-Ts-aldimine **6a** (52 mg, 0.2 mmol) in $CHCl_3$ (200 μL) at 0 °C was added the catalyst **4d** (10 mg, 0.02 mmol). The resulting mixture was continuously stirred until TLC showed consumption of starting materials and was then directly purified by column chromatography on silica gel (elute: petroleum ether/ethyl acetate) to obtain the product **7a** as a white solid (63 mg, yield 77%). The ee was determined by HPLC analysis (Chiralcel AD-H column, 5% 2-propanol in *n*-hexane at 1 mL·min^{-1}; λ = 254 nm; T = 25 °C; t_R = 36.1 min for the *S*,*S*- and 86.5 min for the *R*,*R*-enantiomer): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.62 (s, 3H), 2.27 (s, 3H), 4.42−4.53 (d, 1H, J = 9.0 Hz), 5.39 (br, 1H), 6.44−6.46 (d, 2H, J = 7.2 Hz), 6.65−6.68 (d, 1H, J = 7.8 Hz), 6.84−6.89 (t, 2H, J = 7.6 Hz), 6.98−7.10 (m, 5H), 7.20−7.23 (d, 1H, J = 7.5 Hz), 7.29−7.31 (m, 1H), 7.41−7.44 (d, 2H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 21.4, 53.1, 62.8, 109.7, 122.7, 124.5, 127.3, 127.4, 127.6, 127.7, 128.8, 129.2, 130.7, 136.1, 136.6, 140.4, 143.2, 179.5; HRMS (EI) *m*/*z* calcd for $C_{23}H_{22}N_2O_3S$ 406.1351 (M^+), found 406.1348.

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Supporting Information Available: Experimental procedures, characterization data, chiral chromatographic analysis for all new compounds, and single-crystal structure data for **7i** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Crystal data for compound **7i**: $C_{29}H_{25}BrN_2O_3S$, MW = 561.48, tetragonal, space group $P4(3)2(1)2$, final R indices [$I > 2\sigma(I)$], R1 = 0.0357, wR2 = 0.0785, R indices (all data) R1 = 0.0854, wR2 = 0.0855, a = 13.4440(19) Å, b = 13.4440(19) Å, c = 32.156(6) Å, α = 90°, β = 90°, γ = 90°, V = 5811.9(16) Å^3, T = 173(2) K, Z = 8. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, CCDC 712210.

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