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Construction of Chiral Quaternary Carbon through Morita–Baylis–Hillman Reaction: An Enantioselective Approach to 3-Substituted 3-Hydroxyoxindole Derivatives

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3-Substituted 3-hydroxy-2-oxindoles are the core structures in a variety of alkaloid natural products that have recently emerged as an important class of therapeutic compounds with a broad spectrum of biological activities.[1] Chiral 3-substituted 3-hydroxyindolin-2-ones are particularly important molecules in the field of medicinal chemistry since their biological activities have been considered to be derived from the substituted group at C3 position as well as the absolute configuration of the stereogenic center. Therefore, the development of new synthetic protocols to a C3-hydroxy-bearing stereogenic center with control of the absolute configuration is of paramount importance. Although several synthetic approaches have been recently reported to construct 3-aryl or alkyl 3-hydroxy-2-oxindoles based on transition-metal-catalyzed reactions[2] or organocatalytic reactions,[3] there are still a lot of challenges to develop new catalytic asymmetric reactions and new efficient synthetic methodologies.

During the investigations on Morita–Baylis–Hillman (MBH) or aza-MBH reaction[4,5] which is one of the most useful and interesting carbon–carbon bond-forming reactions to give enantiomerically enriched α-hydroxy carbonyl compound or α-amino carbonyl compound bearing an α-alkylidene group, several groups have achieved to synthesize 3-substituted 3-hydroxyindolin-2-ones via MBH reaction.[6] However, to the best of our knowledge, there has no report on the asymmetric MBH reaction of isatin derivatives with electron-deficient alkenes to construct chiral 3-substituted 3-hydroxyindolin-2-ones. Moreover, besides aldehydes and activated imines, the MBH reactions of substituted ketones having electron-withdrawing substituents (activated ketones), such as halogenated ketones, α-diketones, α-keto esters and α-keto lactones with activated vinyl compounds, have also been extensively studied.[7] However, as far as we know, there has been no report about asymmetric MBH reaction between activated ketones and activated vinyl compounds either. Herein we wish to report the asymmetric MBH reaction of isatin derivatives with acrylates to afford the desired chiral 3-hydroxyindolin-2-ones in good yields with high enantioselectivities, which also represents a good example for the asymmetric MBH reaction of activated ketones with activated vinyl compounds.

Isatin and a number of its derivatives, which possess a reactive keto-carbonyl group, have been proved to be reactive electrophilic components for the MBH reaction.[6] According to the previous reports, the acrylates are often less reactive in MBH reaction. The DABCO-catalyzed MBH reaction of methyl acrylate with isatin derivatives would cost several days to give the adducts in moderate yields.[6] 2-Naphthyl acrylate which has been successfully employed in asymmetric aza-MBH reaction,[8] could accelerate the rate of MBH reaction,[9] therefore it was chosen in our asymmetric MBH reaction using isatin derivatives as the substrates. As shown in Table 1, reaction of *N*-benzylisatin **1a** with 2-naphthyl acrylate **2a** in CH_2Cl_2 in the presence of 4-(3-ethyl-4-oxa-1-azatricyclo[4,4,0,$0^{3,8}$]dec-5-yl)quinolin-6-ol (TQO), which has been proved as an efficient catalyst for asymmetric MBH reaction,[10] could give the corresponding adduct **3a** in 97% yield with 91% *ee* for 40 h at room temperature. Encouraged by these results, several other substituted acrylates were tested in this reaction. Phenyl acrylate **2b** was also a suitable substrate, but hexafluoroisopropyl acrylate **2d** gave the worst result. 1-Naphthyl acrylate **2c** could give the corresponding adduct **3c** with higher enantio-

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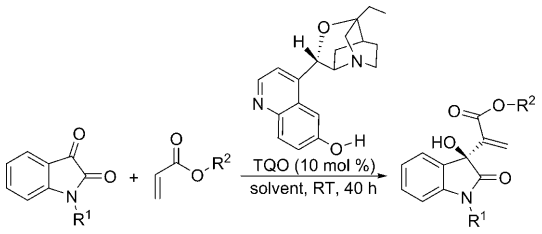
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201002240: Spectroscopic data of all new compounds shown in Tables 1 and 2, the detailed descriptions of experimental procedures, spectroscopic data, chiral HPLC traces and X-ray data for compounds **3v**.

Table 1. Survey of the reaction parameters for the TQO-catalyzed asymmetric MBH reaction of isatin derivatives **1** with acrylates **2**.



1 2 3

Entry[a]	R^1	R^2	Solvent	Yield [%][b]	*ee* [%][c]	Sign of optical rotation
1	Bn, **1a**	2-naphthyl, **2a**	CH_2Cl_2	**3a**, 97	91	+
2	Bn, **1a**	Ph, **2b**	CH_2Cl_2	**3b**, 99	87	–
3	Bn, **1a**	1-naphthyl, **2c**	CH_2Cl_2	**3c**, 92	94	–
4	Bn, **1a**	hexafluoroisopropyl, **2d**	CH_2Cl_2	**3d**, 83	61	–
5	9-anthracenylmethyl, **1b**	1-naphthyl, **2c**	CH_2Cl_2	**3e**, 90	93	–
6	allyl, **1c**	1-naphthyl, **2c**	CH_2Cl_2	**3f**, 67	92	–
7	Me, **1d**	1-naphthyl, **2c**	CH_2Cl_2	**3g**, 84	93	–
8	H, **1e**	1-naphthyl, **2c**	CH_2Cl_2	**3h**, 17	46	–
9	Tr, **1f**	1-naphthyl, **2c**	CH_2Cl_2	**3i**, 88	94	–
10	Bn, **1a**	1-naphthyl, **2c**	THF	**3c**, 97	83	–
11	Bn, **1a**	1-naphthyl, **2c**	toluene	**3c**, 92	91	–
12	Bn, **1a**	1-naphthyl, **2c**	dioxane	**3c**, 94	66	–
13	Bn, **1a**	1-naphthyl, **2c**	DMF	**3c**, 69	63	–
14	Bn, **1a**	1-naphthyl, **2c**	DCE	**3c**, 64	93	–
15	Bn, **1a**	1-naphthyl, **2c**	$CHCl_3$	**3c**, 85	94	–
16[d]	Bn, **1a**	1-naphthyl, **2c**	CH_2Cl_2	**3c**, 76	93	–
17[e]	Bn, **1a**	1-naphthyl, **2c**	CH_2Cl_2	**3c**, 60	86	–
18[f]	Bn, **1a**	1-naphthyl, **2c**	CH_2Cl_2	**3c**, 48	63	–

[a] All reactions were carried out with **1** (0.1 mmol) and **2** (0.2 mmol) in the presence of TQO in 1.0 mL of solvent. [b] Isolated yields. [c] Determined by chiral HPLC. [d] At 0 °C. [e] At −20 °C. [f] At −40 °C.

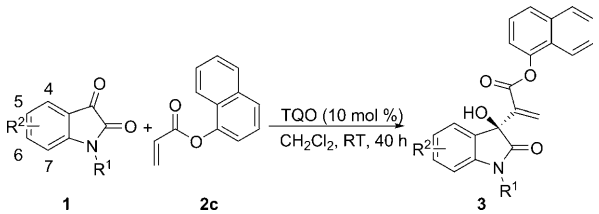
selectivity along with a slight sacrifice in yield. Next, we chose **2c** as the acrylate and a series of isatin derivatives with different N-substituents such as 9-anthracenylmethyl, allyl, methyl and trityl (Tr) to investigate the effects of steric hindrance. It was found that using different isatin derivatives there were no significant effects on the enantioselectivity. However, employing isatin without N-substituent led to the low yield and *ee*. Solvent effects were subsequently examined using *N*-benzyl isatin **1a** and 1-naphthyl acrylate **2c** as the reactants. Toluene and other chlorinated solvents such as 1,2-dichloroethane (DCE) and chloroform were suitable for this reaction to give **3c** with high *ee* value. But 1,4-dioxane and DMF gave poor enantioselectivities. In the presence of CH_2Cl_2, decreasing the temperature to 0 or −40 °C, both the yields and *ee* value declined remarkably. The reason why both the yields and *ee* value declined remarkably at lower temperature (Table 1, entries 16–18) is probably ascribed to the alteration of hydrogen-bond strength between phenolic hydroxyl group and the in situ generated enolate intermediate at lower temperature which might introduce detriment to the activity and enantioselectivity. Another possibility is that the rate of the retro-aldol process from intermediate **B** becomes rather slow at lower temperature. Namely, at lower temperature, intermediate **B** is difficult to return to **A** and isatin derivatives, so that more *R* product can be produced through equilibration than at room temperature. The detailed investigation will be carried out in due course.

Having identified the optimal reaction conditions, we next set out to examine the scope and limitations of this reaction using various isatin derivatives **1** with different substituents on the benzene rings; the results are summarized in Table 2. As shown in Table 2, whether electron-withdrawing or -donating group at 5-, 6- or 7-position of the benzene ring of *N*-benzyl isatins **1** were employed, the reactions proceeded smoothly to give **3** in good to excellent yields (up to 99%) along with high enantioselectivities (Table 2, entries 1–7). In the case of products **3j** and **3l**, recrystallization of them could increase *ee* value up to 96% (Table 2, entries 1, 3; it was difficult to recrystallize other products since they are not good crystalline compounds). Unfortunately, for 4-substitued *N*-benzyl isatins, no products were obtained (Table 2, entries 8 and 9), presumably due to the steric hindrance of the 4-substitution. We again tested whether the more sterically congested N-substituent has an effect on enantioselectivity. Isatin **1q** was used in this reaction under identical conditions, but the *ee* value had just been slightly improved up to 88% (Table 2, entry 10). According to the results shown in Table 1, Tr was also an effective substitution, which could give *ee* value as high as Bn. Several *N*-Tr isatin derivatives were examined in this reaction. They gave the corresponding adducts with higher enantioselectivities than Bn, just with a little detriment to yields. The absolute stereochemical assignment of the adduct **3v** has been determined to be *S*, which was based upon a single-crystal X-ray diffraction analysis (Figure 1).[11]

We also tried the MBH reaction of isatin derivatives with methyl vinyl ketone (MVK), the MBH adduct **I** was attained in 57% yield with 94% *ee* catalyzed by TQO in CH_2Cl_2. The major byproduct is compound **II** which is a 1:2 adduct of **1a** and MVK because of high reactivity of MVK. However, after lots of attempts we could not improve both of the yield and the enantioselectivity of adduct **I** or **II** (Scheme 1)

Synthesis of 3,4-disubstituted pyrrolidin-2-one derivatives has been investigated extensively in connection with the design of conformationally restricted analogues of biologi-

Table 2. Asymmetric MBH reaction of *N*-protected isatin derivatives **1** with 1-naphthyl acrylate **2c** catalyzed by TQO.



1 **2c** **3**

Entry[a]	R^1	R^2	Yield [%][b]	*ee* [%][c]	Sign of optical rotation
1	Bn	6-Br	**3j**, 99	88 (96)[d]	–
2	Bn	5-Br	**3k**, 95	88	+
3	Bn	5-F	**3 L**, 99	89 (96)[d]	–
4	Bn	5-Cl	**3m**, 96	87	+
5	Bn	5-Me	**3n**, 82	89	–
6	Bn	7-Br	**3o**, 95	93	–
7	Bn	7-CF_3	**3p**, 87	87	–
8	Bn	4-Cl	–	–	n.d.[e]
9	Bn	4-Br	–	–	n.d.[e]
10	3,5-dimethylbenzyl	5-Cl	**3q**, 99	88	+
11	Tr	5-Cl	**3r**, 89	94	+
12	Tr	5-F	**3s**, 88	91	–
13	Tr	5-Br	**3t**, 90	87	+
14	Tr	5-Me	**3u**, 70	92	+
15	Tr	6-Br	**3v**, 87	94	*S*, +

[a] All reactions were carried out with **1** (0.1 mmol) and **2c** (0.2 mmol) in the presence of TQO in 1.0 mL of solvent. [b] Isolated yields. [c] Determined by chiral HPLC. [d] After being recrystallized once from petroleum ether and CH_2Cl_2. [e] n.d. = not determined.

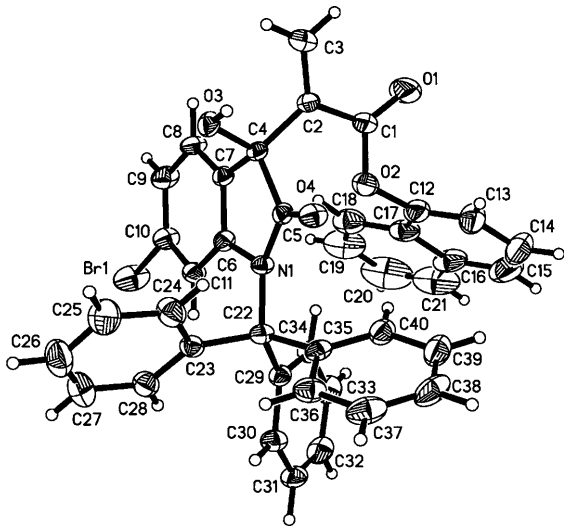
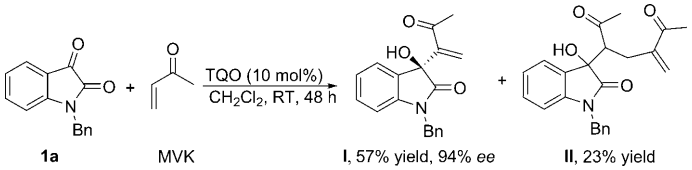
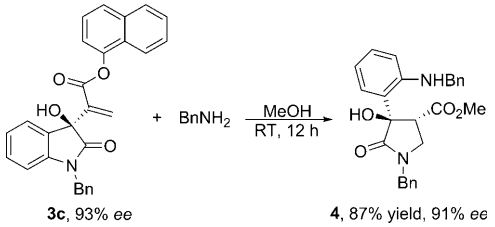


Figure 1. ORTEP drawing of compound **3v**.



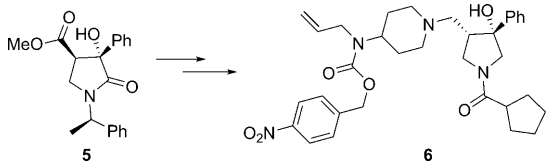
Scheme 1. MBH reaction of *N*-benzyl isatin **1a** with MVK.

cally active amino acids and with the usefulness as intermediates in the synthesis of biologically active nonproteinogenic amino acids.[6c,d] Especially, the synthesis of 3-hydroxypyrrolidin-2-one derivatives has received much attention. From our enantioselective MBH adducts, we could easily obtain chiral 3-aryl-3-hydroxypyrrolidin-2-ones. For example, MBH adduct **3c** with 93% *ee* could react with benzylamine in methanol to give **4** in 87% yield along with 91% *ee* (Scheme 2).[6c,d]



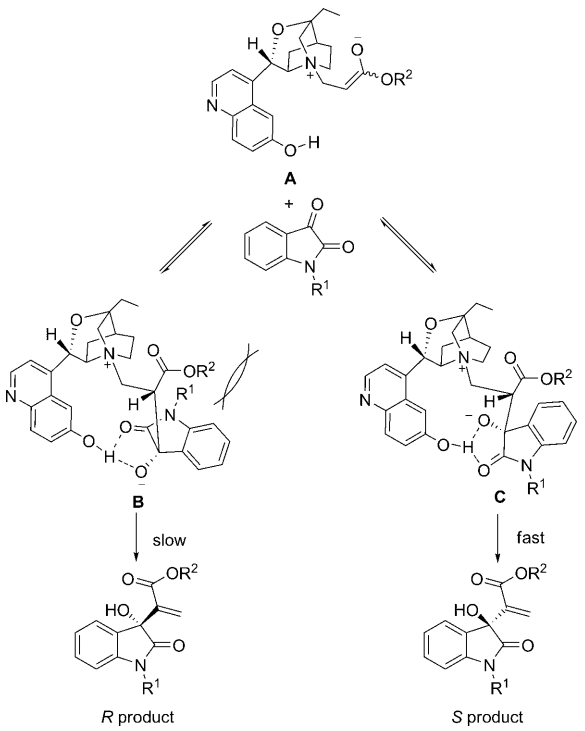
Scheme 2. Synthesis of 3-aryl-3-hydroxypyrrolidin-2-one **4** from the MBH adduct **3c**.

Our product **4** possesses the core structure of 1,3,3,4-tetrasubstituted pyrrolidines, which are the potent CCR5 antagonists and have been recently studied by Ma and co-workers.[12] According to their work, compound **6**, which displayed highly potent and selective inhibition of CCR5-dependant HIV-1 replication, could be easily synthesized starting from 3-aryl-3-hydroxypyrrolidin-2-one **5** which was obtained through three-step synthesis from DABCO-catalyzed MBH reaction of methyl acrylate with ethyl benzoformate (Scheme 3).[12] Our method described above offers a new efficient way to synthesize optically active 1,3,3,4-tetrasubstituted pyrrolidines with an amino group induced on the benzene ring, which could afford diversiform compounds for the evaluation of biological activities.



Scheme 3. Synthesis of 1,3,3,4-tetrasubstituted pyrrolidine **6**.

The observed enantioselectivity may be rationalized via a reaction mechanism depicted in Scheme 4. Based on currently accepted reaction mechanism for MBH reaction,[13] Michael addition of TQO to acrylate forms enolate **A**, which in turn undergoes aldol reaction with the isatin derivative to furnish an equilibrium mixture of several diastereomers. Among them, there would be two intermediates **B** and **C** that are stabilized through hydrogen-bonding between the carbonyl group and the phenolic OH. Taking the repulsion between the ester group and the N-substituents of isatin into account, intermediate **B** suffers from severer



Scheme 4. Proposed mechanism.

steric hindrance than intermediate **C**. Thus, the difference in the reaction rate of subsequent proton transfer and elimination step of **B** and **C** would result in (*S*)-enriched enantioselectivity for the adduct **3v** through equilibration.

In summary, we report for the first time a TQO-catalyzed asymmetric MBH reaction of isatin derivatives with acrylates to afford 3-substituted 3-hydroxy-2-oxindoles in good yields with high enantioselectivities, which demonstrates an efficient synthetic method for the catalytic asymmetric construction of quaternary stereogenic center. This is also the first asymmetric MBH reaction of activated ketones with electron-deficient alkenes. The MBH adducts 3-substituted 3-hydroxy-2-oxindoles could be easily transformed to 3-aryl-3-hydroxypyrrolidin-2-ones with chirality remaining, which are the precursors of promising drug candidates for the treatment of HIV-1 infection. Efforts are in progress to elucidate further mechanistic details of these reactions and to understand their scope and limitations. We are also synthesizing optically active 1,3,3,4-tetrasubstrituted pyrrolidines with different structures and testing their biological activities.

Experimental Section

General methods: ^{1}H NMR spectra were recorded on a 300 or 400 MHz spectrometer in $CDCl_3$ using tetramethylsilane as the internal standard. IR spectra were measured on a spectrometer. Mass spectra were recorded by ESI method, and HRMS was measured on Kratos Analytical Concept mass spectrometer (ESI or MALDI). All reactions were monitored by TLC with silica gel coated plates. Flash Column Chromatography was carried out using 300–400 mesh silica gel at increased pressure.

General procedure for TQO-catalyzed MBH reactions of isatin derivatives 1 and acrylates 2: Isatin derivatives **1** (0.1 mmol), acrylates **2** (0.2 mmol), TQO (0.01 mmol) and solvent (1.0 mL) were added into a Schlenk tube. The reaction mixture was stirred at room temperature for 40 h, then the solvent was removed under reduced pressure and the residue was purified by a flash column chromatography.

Compound **3a**: White solid (42 mg, 97%); m.p. 161–163 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS): δ = 3.78 (s, 1H, OH), 4.86 (d, 1H, J = 15.6 Hz, NCH), 4.95 (d, 1H, J = 15.6 Hz, NCH), 6.71 (d, 1H, J = 7.5 Hz, Ar), 6.74 (s, 1H, =CH), 6.95 (s, 1H, =CH), 6.98 (dd, 1H, J_1 = 2.4, J_2 = 8.7 Hz, Ar), 7.07 (t, 1H, J = 7.8 Hz, Ar), 7.13–7.16 (m, 3H, Ar), 7.21–7.34 (m, 5H, Ar), 7.44–7.47 (m, 2H, Ar), 7.70–7.82 ppm (m, 3H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS): δ = 44.1, 76.2, 109.9, 118.5, 120.7, 123.2, 123.8, 125.7, 126.5, 127.2, 127.4, 127.58, 127.63, 128.6, 129.3, 130.2, 131.4, 133.5, 135.1, 138.8, 143.6, 147.6, 163.2, 176.4 ppm; IR (CH_2Cl_2): $\tilde{\nu}$ = 3352, 3058, 1728, 1701, 1613, 1510, 1488, 1467, 1356, 1315, 1265, 1208, 1157, 1042, 961, 854, 732, 697 cm^{-1}; MS (ESI): *m*/*z* (%): 436.3 $[M+H]^+$ (100); HRMS (MALDI): *m*/*z*: calcd for $C_{28}H_{21}NNaO_4$: 458.1363; found: 458.1363 $[M+Na]^+$; $[\alpha]_D^{20}$ = + 6.6 (*c* = 1.05, $CHCl_3$); HPLC: OD column; λ = 214 nm; eluent: hexane/isopropanol 80:20; flow rate: 0.7 mL min^{-1}; t_{major} = 20.83 min, t_{minor} = 33.40 min; *ee* = 91%.

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Keywords: asymmetric catalysis · Morita–Baylis–Hillman reaction · isatin · organocatalysis · oxindoles

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[11] Crystal data of **3v**: empirical formula: $C_{40}H_{28}BrNO_4$, formula weight: 666.54, crystal size: $0.201\times0.175\times0.069$, crystal color, habit: colorless, prismatic, crystal system: monoclinic, lattice type: primitive, lattice parameters: $a=10.3604(7)$, $b=17.3635(12)$, $c=18.1417(13)$ Å, $\alpha=90$, $\beta=90.230(2)$, $\gamma=90°$, $V=3263.5(4$ Å^3; space group: $P21/n$, $Z=4$, $\rho_{calcd}=1.357\,g\,cm^{-3}$, $F_{000}=1368$, $R1=0.0475$, $wR2=0.0863$. diffractometer: Rigaku AFC7R. CCDC-777629 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.

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