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Organocatalytic Michael Addition of Indoles to Isatylidene-3-acetaldehydes: Application to the Formal Total Synthesis of (−)-Chimonanthine

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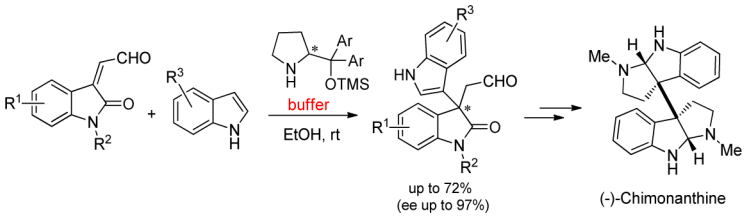
ABSTRACT



A novel strategy for the enantioselective synthesis of 3,3′-disubstituted oxindoles by the organocatalytic Michael addition of indoles to isatylidene-3-acetaldehydes was developed, which can be used for the formal total synthesis of (−)-chimonanthine and the core structure construction of (+)-gliocladin C.

3,3′-Disubstituted oxindoles are frequently found in many biologically active natural products and widely utilized as building blocks for alkaloid synthesis.[1] In recent decades, much effort has been devoted to the catalytic asymmetric construction of oxindole framework with chiral C3-quaternary centers, including (a) direct asymmetric functionalization of 3-substituted oxindoles;[2] (b) enantioselective intramolecular Heck reaction[3] and arylation reaction[4]; (c) asymmetric rearrangement of indolyl acetates and carbonates;[5] (d) enantioselective substitution of 3-halo-3′-substituted oxindoles;[6] and (e) cycloaddition of methyleneindolinones.[7] However, to

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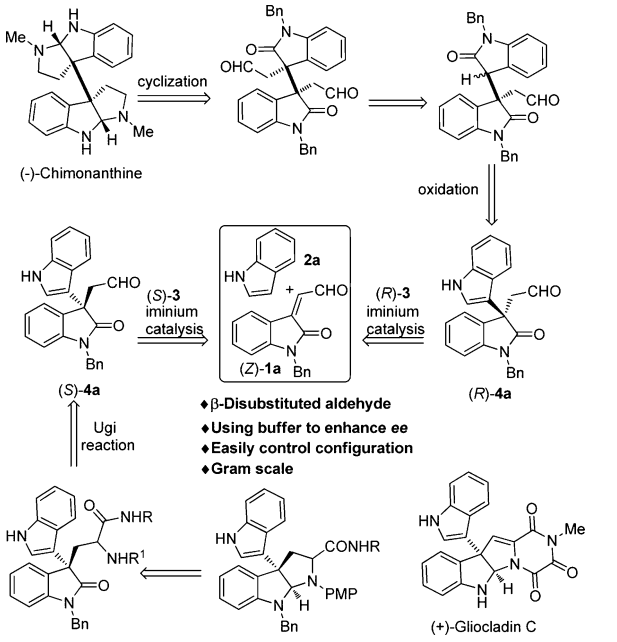
our surprise, as one of the readily available oxindole derivatives, isatylidene-3-acetaldehydes have not been used to construct optically active oxindoles with quaternary stereocenters untill very recently.[7k]

3a,3a′-Bispyrrolidino[2,3-*b*]indolines and C3-(3′-indolyl)-hexahydropyrroloindole are two important substructures present in a significant subset of natural alkaloids.[8] How to enantioselectively construct both of them has been a longstanding challenge in organic synthesis and attracted much attention over recent years. To date, only a few groups have achieved total synthesis of these alkaloids. For the synthesis of 3a,3a′-bispyrrolidino[2,3-*b*]indoline alkaloids, Overman et al. enantioselectively constructed these structures by either diastereoselective dialkylation or double Heck cyclization using a chiral auxiliary strategy.[9] Movassaghi et al. took advantage of a Co-promoted reductive homocoupling of L-tryptophan derived 3-bromohexahydropyrroloindoles and succeeded in completing the enantioselective total synthesis of a series of 3a,3a′-bispyrrolidino[2,3-*b*]-indoline alkaloids.[10] Sodeoka et al. finished the total synthesis of a related natural product, (+)-chaetocin, using a similar homodimerization strategy.[11] Recently, Gong et al. described a novel chiral phosphoric acid catalyzed substitution of 3-hydroxyoxindoles to complete the enantioselective total synthesis of (+)-folicanthine.[12] Very recently, Kanai and Matsunaga established an elegant Mn^{2+}/Schiff base and $Mg(OAc)_2$/benzoic acid catalyst system to construct these alkaloids by sequential Michael additions of *N*-Boc-protected bisoxindole to nitroethylene.[13] For the synthesis of C3-(3′-indolyl)hexahydropyrroloindole alkaloids, the groups of Overman,[14a,b] Stephenson,[14c] and Movassaghi[14d] have developed several methodologies to enantioselectively construct the C3-(3′-indolyl)hexahydropyrroloindole structures and achieved the total synthesis of (+)-gliocladin C and several other hexahydropyrroloindole alkaloids. Besides, Trost et al. also demonstrated an efficient Pd-catalyzed asymmetric addition of oxindoles to allenes for the synthesis of the core structure of the (+)-gliocladin C.[14e]

Despite these notable advances, to the best of our knowledge, there is no report about the synthesis of these two substructures from the same starting materials. We

Scheme 1. Retrosynthetic Analysis of (−)-Chimonanthine and (+)-Gliocladin C



envisioned that both (−)-chimonanthine with the 3a,3a′-bispyrrolidino[2,3-*b*]indoline structure and (+)-gliocladin C with the C3-(3′-indolyl)hexahydropyrroloindole structure might be prepared from two enantiomers (*R*)-**4a** and (*S*)-**4a**, which are obtained from the same starting materials indoles and isatylidene-3-acetaldehydes with the concept of iminium catalysis (Scheme 1).[15] Although the amine-catalyzed asymmetric Michael additions to β-monosubstituted α,β-unsaturated aldehydes have been well developed, the conjugate additions to β-disubstituted unsaturated aldehydes leading to quaternary carbon stereocenters are scarcely explored,[16] due to the fact that the steric effect would lead to the 1,2-addition as the major reaction rather than the 1,4-conjugate addition. Herein, we report our effort on the enantioselective organocatalytic Michael addition to isatylidene-3-acetaldehydes, the readily available β-disubstituted α,β-unsaturated aldehydes from isatins,[17] to construct 3,3′-disubstituted oxindoles bearing all-carbon quaternary stereocenters.[18] Furthermore, the synthetic

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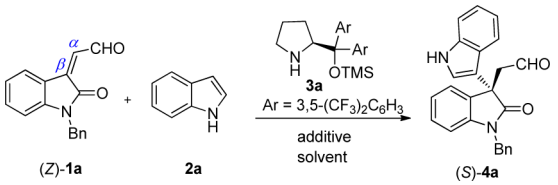
utility of this transformation is well demonstrated by the formal total synthesis of (−)-chimonanthine and the core structure construction of (+)-gliocladin C.

Table 1. Optimization of the Reaction Conditions[a]



(Z)-**1a** **2a** (S)-**4a**

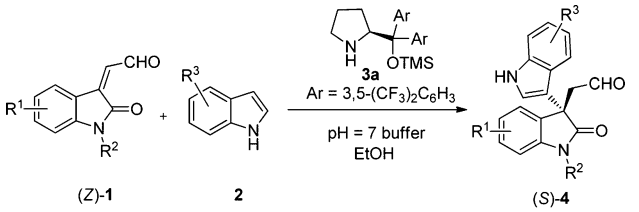
entry	additive	solvent	t (h)	yield (%)	ee (%)
1	$PhCO_2H$	EtOH	5	72	63
2	–	EtOH	40	60	80
3	–	toluene	30	40	61
4	–	CH_2Cl_2	30	45	59
5	–	*i*-PrOH	30	55	76
6[b]	H_2O	EtOH	40	58	82
7	$PhCO_2Na$	EtOH	3	15	83
8[c]	buffer	EtOH	40	55	87
9[d]	buffer	EtOH	40	63	84
10[e]	buffer	EtOH	35	60	91

[a] Reaction conditions: **1a** (1.0 equiv), **2a** (2.0 equiv), 20 mol % catalyst, 20 mol % additive, with solvent indicated 0.1 M at room temperature. [b] 5.0 equiv H_2O were added. [c] pH = 7 buffer (5.0 equiv) was added; see Supporting Information for details. [d] pH = 7 buffer (2.5 equiv) was added. [e] 40 mol % catalyst and pH = 7 buffer (5.0 equiv) were added.

In the initial study, to our delight, the Michael addition of indole **2a** to isatylidene-3-acetaldehyde (*Z*)-**1a** did give the desired product **4a** with moderate enantioselectivity in the presence of Jørgensen–Hayashi catalyst **3a** and benzoic acid (Table 1, entry 1). A series of other Jørgensen–Hayashi type catalysts were also screened.[19] Gratifyingly, the reaction proceeded smoothly to afford the desired product in 80% ee without the additive benzoic acid (Table 1, entry 2). No improvement in enantioselectivity was observed in the other tested solvents such as toluene, CH_2Cl_2, and *i*-PrOH (Table 1, entries 3–5). The addition of 5.0 equiv of water brought little benefit to this reaction (Table 1, entry 6). When sodium benzoate was used as an additive, the enantioselectivity exhibited a small increase but only a 15% yield was obtained (Table 1, entry 7). Further screening reaction conditions revealed that the addition of neutral buffer could give a better enantioselectivity up to 87% ee (Table 1, entry 8). To the best of our knowledge, this is the first example using buffer to enhance the enantioselectivity in the amine-catalyzed Michael addition. Reducing the equivalents of buffer from 5.0 to 2.5 equiv resulted in a small decrease in the enantioselectivity (Table 1, entry 9). Improvement of the catalyst loading to 40 mol % gave product **4a** in 60% yield with the highest enantiomeric excess (91% ee, Table 1, entry10).

(19) For detailed catalyst screening and optimization of the reaction conditions, see Supporting Information.

Table 2. Substrate Scope of Isatylidene-3-acetaldehyde and Indole[a]



(Z)-**1** **2** (S)-**4**

entry	**1**; R^1, R^2	**2**; R^3	t (h)	**4**, yield (%)	ee (%)
1	**1a** H, Bn	**2a** H	35	**4a** 60	91
2	**1a** H, Bn	**2b** 5-F	40	**4b** 60	96
3	**1a** H, Bn	**2c** 5-Cl	40	**4c** 55	93
4	**1a** H, Bn	**2d** 5-Br	30	**4d** 72	94
5	**1a** H, Bn	**2e** 5-Me	40	**4e** 63	91
6	**1a** H, Bn	**2f** 6-F	40	**4f** 52	97
7	**1a** H, Bn	**2g** 6-Cl	40	**4g** 52	93
8	**1a** H, Bn	**2h** 6-Br	40	**4h** 60	96
9	**1a** H, Bn	**2i** 6-CO_2Me	40	**4i** 58	91
10	**1a** H, Bn	**2j** 6-Me	40	**4j** 54	86
11	**1a** H, Bn	**2k** 7-Cl	50	**4k** 53	92
12	**1a** H, Bn	**2l** 7-Br	40	**4l** 52	94
13	**1b** 5-Me, Bn	**2a** H	60	**4m** 67	88
14	**1c** 5-MeO, Bn	**2a** H	48	**4n** 53	90
15	**1b** 5-Me, Bn	**2d** 5-Br	60	**4o** 65	95
16	**1d** 5-F, Bn	**2d** 5-Br	40	**4p** 34	96
17	**1e** H, Me	**2d** 5-Br	45	**4q** 54	95

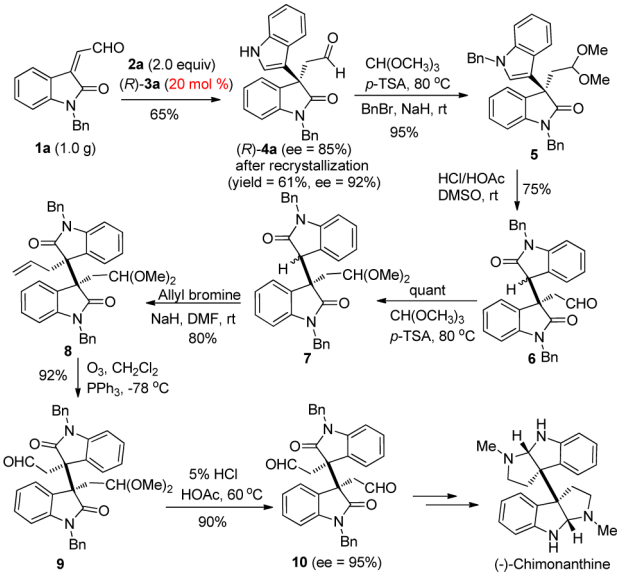
[a] Reaction conditions: **1** (0.12 mmol, 1.0 equiv), **2** (0.24 mmol, 2.0 equiv), catalyst **3a** (40 mol %), pH = 7 buffer (5.0 equiv, 12 μL), EtOH (1.2 mL), at room temperature.

With the optimal reaction conditions in hand, we investigated the reaction scope by variation of two substrate components. Generally, both electron-withdrawing and -donating groups on the indole moiety were tolerated, affording the corresponding products with >90% ee in most cases (Table 2, entries 1–12). The substrates with electron-withdrawing groups gave relatively higher ee's than those bearing electron-donating groups. The substituent effect on the isatylidene-3-acetaldehyde moiety was also investigated, and high ee values were obtained (Table 2, entries 13–16). The absolute configuration of product **4o** was determined to be an *S*-configuration by single crystal X-ray analysis.[20] The *N*-Me protected substrate **1e** was also well suited for this transformation (Table 2, entry 17).

The synthetic utility of this reaction was showcased by applying it to the catalytic enantioselective formal total synthesis of (−)-chimonanthine (Scheme 2) and the core structure of (+)-gliocladin C (Scheme 3). The enantioselective Michael addition with a gram scale of **1a** and 20 mol % catalyst (*R*)-**3a** gave (*R*)-**4a** in 65% yield and 85% ee (92% ee from the mother liquid of recrystallization process) in 60 h. Protection of the aldehyde and further alkylation furnished compound **5** in 95% yield. Subsequent oxidation by

(20) See Supporting Information for details.

Scheme 2. Formal Total Synthesis of (−)-Chimonanthine



DMSO/HCl gave rise to the compound **6** in 75% overall yield.[21] After further protection of aldehyde and allylation of the vicinal quaternary stereogenic centers, compound **8** was obtained in 80% yield as the only isomer. Ozonolysis of **8** in CH_2Cl_2 and subsequent deprotection afforded product **10** in 47% overall yield from oxindole **4a** in 7 steps, from which (−)-chimonanthine could be then synthesized using the procedure described by Overman.[9a]

Interestingly, compound **11** could be easily prepared in high yield (Scheme 3) by a three-component Ugi reaction of (*S*)-**4a**, *tert*-butyl isocyanide, and 4-methoxyaniline under the catalysis of phenyl phosphinic acid, which was developed by List.[22] After treatment with DIBAL-H, a cyclization compound **12** could be isolated in 56% yield. Alternatively, protection of compound **11** by BSTFA (bis(trimethylsilyl)trifluoroacetamide) and subsequent reduction by DIBAL-H afforded a *N*-TMS protected compound **14** in 82% overall yield in two steps. The total synthesis of (+)-gliocladin C is then realized from compound **12** or **14** following the route explored by Stephenson.[14c]

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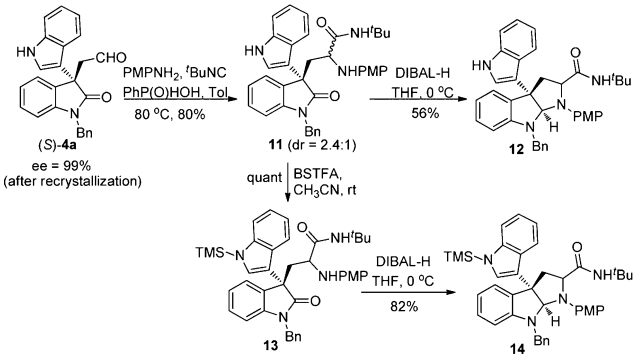
Scheme 3. Synthesis of Core Structure of (+)-Gliocladin C



In summary, we have developed the first example of the organocatalytic asymmetric conjugate addition of indole to isatylidene-3-acetaldehyde, which provides a facile access to oxindoles bearing all-carbon quaternary stereocenters at the 3-position with high enantioselectivity. This transformation is easily scaled up to gram scale. The method can be used for the enantioselective formal total synthesis of (−)-chimonanthine and the core structure construction of (+)-gliocladin C. In addition, it is also interesting to find that the buffer can enhance the enantioselectivity, which may bring new applications to other amine-catalyzed reactions. Further studies including investigation of other asymmetric transformations of isatylidene-3-acetaldehyde are being carried out in this laboratory and will be reported in due course.

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Supporting Information Available. Typical experimental procedure and characterization for all products, and X-ray data of **4o** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.