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# Enantioselective [4+2] Cycloadditions of 2-Vinyl-1*H*-indoles with 3-Nitro-2*H*-chromenes Catalyzed by a $Zn(OTf)_2$/Bis(oxazoline) Complex: An Efficient Approach to Fused Heterocycles with a Quaternary Stereocenter

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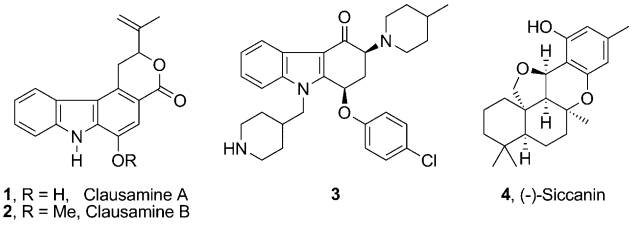
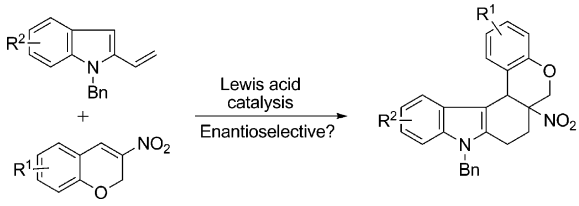
Highly functionalized fused heterocycles are of great significance, with prevalence in many natural alkaloids and bioactive compounds.[1] In particular, diversely substituted carbazoles and tetrahydrocarbazoles (THCs) have become prime targets for drug development.[2] As shown in Scheme 1, clausamine A and B are typical carbazole alkaloids isolated from *Clausena anisata* (Rutaceae) collected in Thailand.[2d] Pharmacological screening identified substituted tetrahydrocarbazole **3** as a new NPY-1 antagonist.[2e] Consequently, these compounds represent particularly appealing targets for synthetic efforts.[3] In this regard, Bandini and Eichholzer reported an elegant allylic alkylation of indoles in the presence of a gold complex, providing an efficient synthesis of 1-vinyl- and 4-vinyl-THCs in a highly enantioselective manner.[3f] Furthermore, You and co-workers described an olefin cross metathesis (CM)/intramolecular asymmetric Friedel–Crafts alkylation sequence, which offered a powerful platform to construct enantioenriched tetrahydropyrano[3,4-b]indoles (THPIs) and tetrahydro-β-carbolines (THBCs).[3g]




Scheme 1. Representative biologically active carbazole, tetrahydrocarbazole, and chroman derivatives.

Chromans are another important type of heterocycles that exhibit remarkable biological activities.[4,5] For example, (−)-siccanin (**4**), isolated from the culture broth of *Helemin-thosposium siccans*, was found to possess antifungal activity against the pathogenic fungi *Trichophyton interdigitale*, *Trichophyton asteroids*, *Mycosporum*, and *Epidermophyton* (Scheme 1).[6] Because of the interesting biological profiles of tetrahydrocarbazole and chroman derivatives, we envisaged that combinatorial assembly of these two "privileged" structural motifs into one molecule in an enantioselective manner would lead to a new type of fused heterocycle for drug discovery.

During the past decades, asymmetric [4+2] cycloaddition reactions have been widely applied for the construction of diversely functionalized complex molecules, with up to four stereogenic centers created in a single step.[7,8] Among the different reaction components of this methodology, vinylindoles have recently been actively investigated for the enantioselective synthesis of biologically interesting polycyclic indole derivatives.[9,10] For example, the MacMillan group reported an enantioselective total synthesis of the *Strychnos* alkaloid (+)-minfiensine based on an organocatalytic Diels–Alder/amine cyclization sequence from 2-vinylindole.[10a] Meanwhile, Ricci and co-workers disclosed an asymmetric Diels–Alder reaction to afford a variety of enantiomerically pure tetrahydrocarbazoles.[10b,c] In the context of our ongoing interest in the synthesis of biological important carbon- and heterocycles,[11] we have also developed several examples of enantioselective cycloaddition reactions of 2-vinylindoles with nitroolefins[12a] and enals.[12b] Herein, we further advance the use of 2-vinylindoles[12c,d] to develop a chiral Lewis acid complex-catalyzed enantioselective [4+2] cycloaddition with 3-nitro-2*H*-chromenes [Equation (1)].[13,14]

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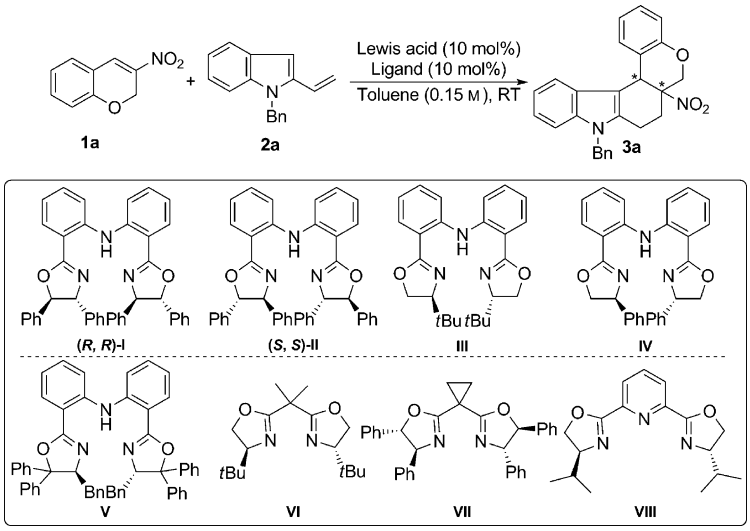
This protocol provides an efficient and convenient approach to fused heterocycles bearing a quaternary stereocenter[15] with excellent reaction efficiency (up to 94% yield), high enantioselectivities (up to 96% *ee*), and great diastereoselectivities (>95:5 d.r.).

At the outset of the studies, 3-nitro-2*H*-chromene **1a** and 1-benzyl-2-vinyl-1*H*-indole **2a** were chosen as model substrates for this asymmetric [4+2] cycloaddition reaction. A variety of Lewis acids and the chiral ligands were investigated, and the representative results are summarized in Table 1. In the presence of chiral ligand **I**, the screening of metal catalysts demonstrated that $Zn(OTf)_2$ (OTf = $CF_3SO_3$)was the best choice (Table 1, entry 1). $ZnCl_2$ and $Cu(OTf)_2$ led to moderate yields and low enantioselectivities (Table 1, entries 2 and 3). $In(OTf)_3$ gave reversed enantioselectivity, while other rare-earth triflates gave no enantioselectivities (Table 1, entries 4 and 5–7). When $Mg^{II}$ and $Ag^{I}$ triflates were used, no desired product was observed (Table 1, entries 8 and 9). To improve the enantioselectivity of this process, we further examined chiral ligands.[16] The tabulated results showed that tridentate bis(oxazoline) ligand **I** was the most promising ligand, and it was found to be more active than ligands **III**–**V** (Table 1, entry 1 vs. entries 11–13). Ligand **II**, which is otherwise identical to ligand **I** but has the opposite configuration, gave comparable results (Table 1, entry 10). Other $C_2$-symmetric bis(oxazoline) ligands **VI**–**VIII** had detrimental effects on the enantioselectivity, albeit with good yields (Table 1, entries 14–16).

Table 1. Effects of various metal sources and chiral ligands.[a]




| Entry | Lewis acid | Ligand | *t* [h] | Yield[b] [%] | *ee*[c] [%] | d.r.[c] |
|---|---|---|---|---|---|---|
| 1 | $Zn(OTf)_2$ | **I** | 23 | 88 | 89 | >95:5 |
| 2 | $ZnCl_2$ | **I** | 108 | 62 | 7 | >95:5 |
| 3 | $Cu(OTf)_2$ | **I** | 58 | 79 | 13 | >95:5 |
| 4 | $In(OTf)_3$ | **I** | 21 | 80 | −5 | >95:5 |
| 5 | $Sc(OTf)_3$ | **I** | 19 | 80 | 0 | >95:5 |
| 6 | $Sm(OTf)_3$ | **I** | 13 | 95 | 0 | >95:5 |
| 7 | $La(OTf)_3$ | **I** | 41 | 91 | 0 | >95:5 |
| 8 | $Mg(OTf)_2$ | **I** | 130 | <5 | – | – |
| 9 | AgOTf | **I** | 130 | <5 | – | – |
| 10 | $Zn(OTf)_2$ | **II** | 26 | 87 | −86 | >95:5 |
| 11 | $Zn(OTf)_2$ | **III** | 48 | 93 | −71 | >95:5 |
| 12 | $Zn(OTf)_2$ | **IV** | 28 | 94 | −80 | >95:5 |
| 13 | $Zn(OTf)_2$ | **V** | 40 | 94 | −63 | >95:5 |
| 14 | $Zn(OTf)_2$ | **VI** | 45 | 74 | −5 | >95:5 |
| 15 | $Zn(OTf)_2$ | **VII** | 64 | 93 | 7 | >95:5 |
| 16 | $Zn(OTf)_2$ | **VIII** | 64 | 83 | −4 | >95:5 |

[a] Conditions: **1a** (0.30 mmol), **2a** (0.45 mmol), Lewis acid (10 mol%), ligand (10 mol%), toluene (2.0 mL). [b] Yield of isolated product after chromatography. [c] Determined by HPLC analysis on a chiral stationary phase.

With the optimal chiral $Zn(OTf)_2$/**I** complex identified, we continued to examine the reaction media and other parameters to further improve the chemical yield and stereoselectivity. It was found that the reactions in toluene and xylenes gave almost identical results (Table 2, entries 1 and 2). The use of halogenated solvents resulted in a substantial decrease in enantioselectivities, although high diastereoselectivities were obtained (Table 2, entries 3 and 4). Notably, the reaction could also proceed efficiently in ethereal solvents, such as $Et_2O$, MeO*t*Bu, PhOMe, and 1,4-dioxane, and generally good results were achieved, except for in THF (Table 2, entries 7–10 vs. entry 6). Variation of the ratio of metal to ligand **I** revealed that a 1:1.1 ratio of $Zn(OTf)_2$ to **I** increased the *ee* from 89 to 92% (Table 2, entry 11 vs. 1). Optimizations of the concentration did not improve the reaction efficiency. The desired cycloaddition reaction also worked well even with 5 mol% catalyst loading, although a slight decrease in enantioselectivity was found for these conditions (Table 2, entry 16). Finally, we determined that the use of 10 mol% $Zn(OTf)_2$ and 11 mol% **I** in toluene (2.0 mL) at room temperature were the optimal reaction conditions for this asymmetric [4+2] cycloaddition reaction (Table 2, entry 11).

Having established the optimal reaction conditions, we next explored the scope of this asymmetric [4+2] cycloaddition reaction. As highlighted in Table 3, a wide range of 3-nitro-2*H*-chromenes with electron-donating and -withdraw-

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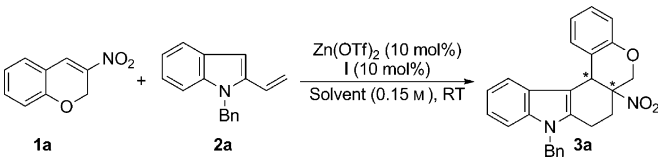
Table 2. Reaction conditions optimization.[a]




| Entry | Solvent | *t* [h] | Yield[b] [%] | *ee*[c] [%] | d.r.[c] |
|---|---|---|---|---|---|
| 1 | toluene | 23 | 88 | 89 | >95:5 |
| 2 | xylenes | 22 | 87 | 89 | >95:5 |
| 3 | $CH_2Cl_2$ | 33 | 87 | 72 | >95:5 |
| 4 | $ClCH_2CH_2Cl$ | 41 | 76 | 50 | >95:5 |
| 5 | $CH_3CN$ | 26 | 88 | 26 | >95:5 |
| 6 | THF | 136 | 63 | 50 | >95:5 |
| 7 | $Et_2O$ | 45 | 76 | 88 | >95:5 |
| 8 | MeO*t*Bu | 36 | 76 | 78 | >95:5 |
| 9 | PhOMe | 18 | 88 | 77 | >95:5 |
| 10 | 1,4-dioxane | 23 | 75 | 86 | >95:5 |
| 11[d] | toluene | 20 | 92 | 92 | >95:5 |
| 12[e] | toluene | 21 | 90 | 92 | >95:5 |
| 13[d,f] | toluene | 22 | 93 | 90 | >95:5 |
| 14[d,g] | toluene | 17 | 91 | 87 | >95:5 |
| 15[d,h] | toluene | 18 | 93 | 88 | >95:5 |
| 16[i] | toluene | 24 | 90 | 89 | >95:5 |

[a] Conditions: **1a** (0.30 mmol), **2a** (0.45 mmol), $Zn(OTf)_2$ (10 mol%), **I** (10 mol%), solvent (2.0 mL). [b] Yield of isolated product after chromatography. [c] Determined by HPLC analysis on a chiral stationary phase. [d] $Zn(OTf)_2$/**I** = 1:1.1. [e] $Zn(OTf)_2$/**I** = 1:1.2. [f] Toluene (3.0 mL) was used. [g] Toluene (1.5 mL) was used. [h] Toluene (1.0 mL) was used. [i] $Zn(OTf)_2$ (5 mol%), **I** (5.5 mol%) were used.

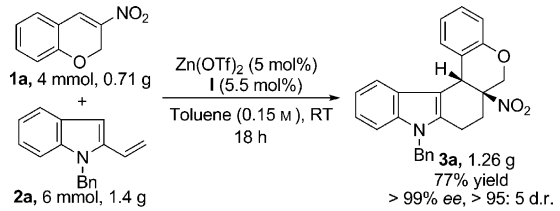
Table 3. Asymmetric [4+2] cycloaddition reaction of 3-nitro-2*H*-chromene **1** with 1-benzyl-2-vinyl-1*H*-indole **2** catalyzed by $Zn(OTf)_2$-**I** complex[a]


| Entry | $R^1$ | $R^2$ | Yield[b] [%] | *ee*[c] [%] | d.r.[c] |
|---|---|---|---|---|---|
| 1 | H (**1a**) | H (**2a**) | 92 (**3a**) | 92 | >95:5 |
| 2 | 6-F (**1b**) | H | 90 (**3b**) | 89 | >95:5 |
| 3 | 6-Cl (**1c**) | H | 91 (**3c**) | 86 | >95:5 |
| 4 | 6-Br (**1d**) | H | 90 (**3d**) | 86 | >95:5 |
| 5 | 6-Me (**1e**) | H | 91 (**3e**) | 94 | >95:5 |
| 6 | 6-MeO (**1f**) | H | 93 (**3f**) | 96 | >95:5 |
| 7 | 7-MeO (**1g**) | H | 91 (**3g**) | 75 | >95:5 |
| 8[d] | 8-MeO (**1h**) | H | 82 (**3h**) | 92 | >95:5 |
| 9 | 6,8-$Br_2$ (**1i**) | H | 94 (**3i**) | 90 | >95:5 |
| 10 | 2-naphthyl (**1j**) | H | 91 (**3j**) (63)[d] | 70 (>99)[d] | >95:5 |
| 11 |  (**1k**) | H | 67 (**3k**) | 24 | >95:5 |
| 12 | H | 5-F (**2b**) | 93 (**3l**) (65)[d] | 78 (>99)[d] | >95:5 |
| 13 | H | 5-Cl (**2c**) | 93 (**3m**) | 78 | >95:5 |
| 14 | H | 5-Me (**2d**) | 92 (**3n**) | 92 | >95:5 |
| 15 | H | 5-MeO (**2e**) | 91 (**3o**) | 94 | >95:5 |

[a] Conditions: **1** (0.30 mmol), **2** (0.45 mmol), $Zn(OTf)_2$ (10 mol%), **I** (11 mol%), toluene (2.0 mL). [b] Yield of isolated product after chromatography. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The result was based on direct filtration of the reaction mixture.

ing groups at 6-, 7-, and 8-positions reacted well with 1-benzyl-2-vinyl-1*H*-indole **2a**, giving the corresponding products in generally good yields (82–94%) with high stereoselectivities (86–96% *ee*, >95:5 d.r.). The reaction with disubstituted 3-nitro-2*H*-chromenes, such as **1i**, also exhibited high efficiency and stereoselectivity (94% yield, 90% *ee*, >95:5 d.r.) (Table 3, entry 9). Moreover, 2-naphthyl-substituted 3-nitro-2*H*-chromene **1j** could efficiently participate in the cycloaddition reaction to afford the desired product **3j** in 91% yield with 70% *ee* and >95:5 d.r. (Table 3, entry 10). Interestingly, simple filtration gave the cyclized product **3j** in acceptable yield (63%) with more than 99% *ee* when the reaction was completed. For the less reactive 5-nitro-3,4-dihydro-2*H*-pyran **1k**,[17] the cycloaddition reaction also occurred efficiently with excellent d.r. (>95:5), albeit with low *ee* (Table 3, entry 11). Then, the generality of the reaction was further probed by variation of 2-vinylindole partner with 3-nitro-2*H*-chromene **1a**. Substrates with electron-rich substituents on the indole ring (**2d** and **2e)** proved to be more effective than the electron-poor ones (**2b** and **2c**; Table 3, entries 14–15 vs. 12–13).

To demonstrate the synthetic utility of the current methodology, we performed the reaction of 3-nitro-2*H*-chromene **1a** with 1-benzyl-2-vinyl-1*H*-indole **2a** on a gram scale with 5 mol% catalyst (Scheme 2). To our delight, the desired fused heterocycle derivative **3a** could be isolated in 77% yield with >99% *ee* and >95:5 d.r. by simple filtration of the reaction mixture.




Scheme 2. Gram-scale preparation of **3a**.

Finally, the absolute stereochemistry of **3i** was elucidated by X-ray crystallographic analysis.[18] To account for the stereochemical course of this reaction, a possible transition state was shown in Figure 1. According to Du and Xu's activation model[19] of reactions catalyzed by metal bis(oxazoline) complexes, we proposed a bifunctional activation form, wherein zinc(II) acted as a Lewis acid to activate the nitro moiety of 3-nitro-2*H*-chromene, while the NH group of ligand **I** worked as a donor for the NH···π (2-vinylindole) interaction.[20] Such an *endo*-selective cycloaddition process provided the corresponding product with (7*S*,8*R*) configuration exclusively.

In conclusion, we have developed a practical and convenient catalytic asymmetric [4+2] cycloaddition of 3-nitro-2*H*-chromenes to 1-benzyl-2-vinyl-1*H*-indoles in the presence of chiral $Zn(OTf)_2$/bis(oxazoline) complex. High reaction efficiency (up to 94% yield) and excellent stereoselectivities (up to 96% *ee*, >95:5 d.r.) have been obtained for a variety

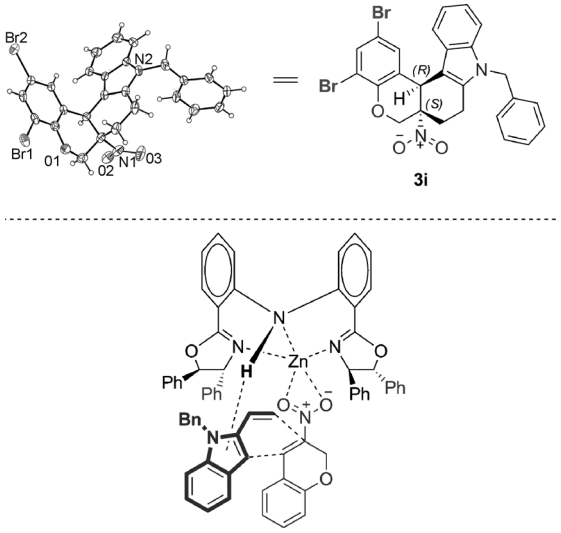



Figure 1. X-ray crystal structure of **3i** and the proposed transition state for the asymmetric [4+2] cycloaddition reaction.

of biologically important fused heterocycles bearing a quaternary stereocenter. Further efforts will focus on the applications of this asymmetric transformation, and the studies are currently in progress.

## Experimental Section

General procedure: The metal catalyst $Zn(OTf)_2$ (10 mol%) and chiral ligand **I** (11 mol%) were stirred in toluene (2.0 mL) at room temperature for 30 min in a 10 mL Schlenk tube. 3-Nitro-2*H*-chromene **1** (0.30 mmol) was then added. After 20 min, 1-benzyl-2-vinyl-1*H*-indole **2** (0.45 mmol) was added quickly. The reaction mixture was stirring until the completion of the reaction as determined by TLC. Then the reaction mixture was purified directly by flash column chromatography on silica gel (petroleum ether/acetone (65:1 to 60:1)) to give the corresponding product as a solid.

## Acknowledgements

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**Keywords:** cycloaddition · enantioselectivity · heterocycles · indoles · Lewis acid catalysis

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