Indole Chemistry

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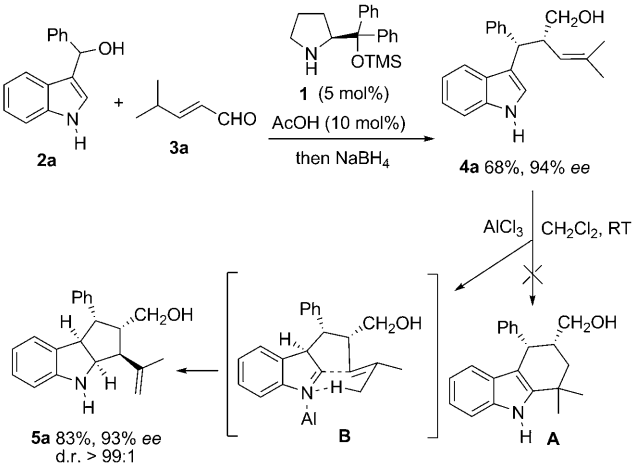
Lewis Acid Catalyzed Intramolecular Direct Ene Reaction of Indoles**

*Bo Han, You-Cai Xiao, Yuan Yao, and Ying-Chun Chen**

Synthetic modifications on indole skeletons have provoked increasing interest because the related heterocyclic systems are present in numerous alkaloid products, pharmaceuticals, and agrochemicals.[1] Indole heterocycles, which basically consist of a benzo[*b*]pyrrole framework, are considered electron-rich compounds that exhibit substantial reactivity, especially at the C3-position.[2] Not surprisingly, the majority of studies in this field have been focused on the Friedel–Crafts reaction of indoles with a range of electrophiles.[3] Indeed, even C3-substituted indoles demonstrate high nucleophilicity;[4] C3-selective reactions have been realized by means of electrophilic compounds and subsequent tandem addition to the newly formed imine group. This processes lead to the construction of fused indolines having C3-quaternary stereocenters. In addition, C3-substituted indoles also show reactivity at the C2-position,[5] and the most well-established reaction is the Pictet–Spengler reaction.[6] On the other hand, the heteroaromatic indolyl structure contains an enamine functionality, which is likely to isomerize to an electrophilic imine (or iminium) group through proton transfer under the proper reaction conditions (such as by the activation of Brønsted or Lewis acids).[7] As a consequence, a chemoselective, direct nucleophilic C2-functionalization pathway could be developed for the synthesis of indoline compounds, as proposed in Equation (1; Nu = nucleophile). Nevertheless, such a synthetic approach has not yet been addressed.

Recently, our research group[8] has reported an α-regio- and stereoselective Michael addition of γ,γ-disubstituted α,β-unsaturated aldehydes to nitroolefins through dienamine catalysis.[9] We further found that this activation mode was quite successful in the direct asymmetric alkylation reaction of 3-indolylmethanols[10] and γ,γ-disubstituted α,β-unsaturated aldehydes. As shown in Scheme 1, under the catalysis of



Scheme 1. Organocatalytic asymmetric alkylation and subsequent discovery of Lewis acid catalyzed intramolecular imino-ene reaction of indole. TMS = trimethylsilyl.

α,α-diphenylprolinol *O*-TMS ether **1** (5 mol%) and AcOH (10 mol%), the exclusive α-regioselective alkylation product **4a** could be smoothly isolated in a diastereomerically pure form from 3-indolylphenylmethanol **2a** and 4-methyl-2-pentenal **3a** after reduction with $NaBH_4$, and the reaction also gave excellent enantioselectivity.[11] In an attempt to conduct Friedel–Crafts annulation of **4a** under the catalysis of a Lewis acid such as $AlCl_3$ (1.0 equiv), we discovered that an unexpected and highly substituted cyclopentyl[*b*]indoline[12] compound **5a** could be cleanly obtained with complete diastereocontrol within 30 minutes,[13,14] while the Friedel–Crafts product **A** was not detected (Scheme 1).[15] We recognized that an unprecedented and unique intramolecular imino-ene reaction of the indole heterocycle had occurred—probably through $AlCl_3$-promoted enamine–imine isomerization and a subsequent ene cyclization (Scheme 1; intermediate **B**). The efficient participation of the inactivated imine in the relatively less explored imino-ene-type reaction was an unusual result.[16]

To gain some insight into the reaction pathway, we conducted isotopic labeling experiments. Compound **4a** was treated with NaH and subsequently quenched with D_2O and afforded deuterated product **4a′** (Scheme 2). Then, the $AlCl_3$-catalzyed imino-ene reaction of **4a′** was performed. Pleasingly, significant deuteration (61%) was observed at the 3-position of indoline **5a′**; this result verified that enamine–

[*] Dr. B. Han, Y.-C. Xiao, Y. Yao, Prof. Dr. Y.-C. Chen
Key laboratory of Drug Targeting and Drug Delivery System
of the Education Ministry, Department of Medicinal Chemistry
West China School of Pharmacy, Sichuan University
Chengdu, 610041 (China)
Fax: (+86) 288-550-2609
E-mail: ycchenhuaxi@yahoo.com.cn
Prof. Dr. Y.-C. Chen
State Key Laboratory of Biotherapy, West China Hospital
Sichuan University, Chengdu, 610041 (China)

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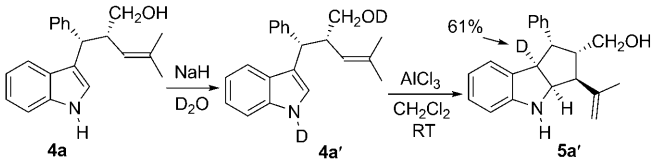
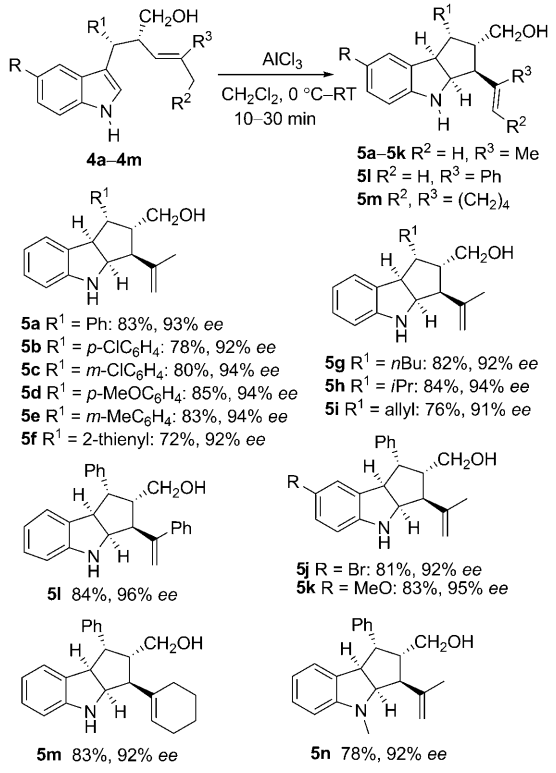


Scheme 2. Isotopic labeling experiments.

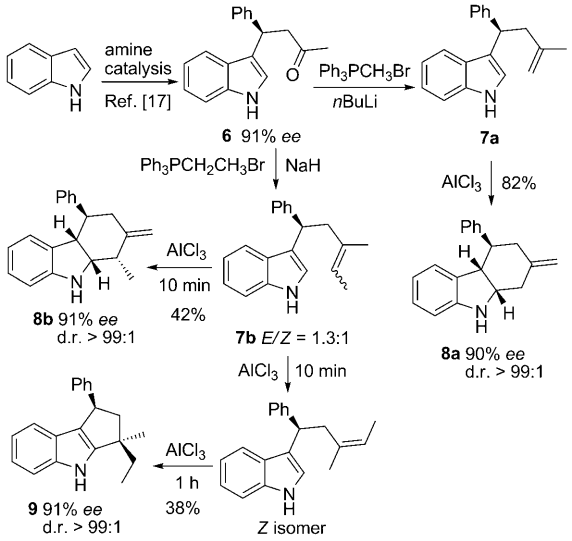
imine isomerization should occur through proton transfer in the presence of $AlCl_3$.[7]

Thus, we explored an array of 3-indolylmethanols **2** in the reaction with γ,γ-disubstituted α,β-unsaturated aldehydes **3** under the catalysis of chiral secondary amine **1**, which successfully provided different types of olefinic indole precursors **4**, generally with excellent enantioselectivities (see the Supporting Information).[11] Notably, the 3-indolylmethanols **2**, bearing an alkyl substituent at the benzylic position, could be smoothly utilized in this dienamine-catalyzed alkylation procedure—the use of these substrates has not been established under other catalytic conditions.[10] As summarized in Scheme 3, all the indole substrates **4a**–**4m** were efficiently converted into the desired cyclopentyl[*b*]indoline products **5a**–**5m** with retained configuration and in moderate to high yields of the corresponding isolated products, usually in less than half an hour. In general, the tested reactions led to the formation of the single diastereomer. It was noteworthy that an allylic group at the benzylic position did not affect the expected annulation reaction, and the ene reaction selectively occurred at the trisubstituted alkene group (product **5i**). Interestingly, the *N*-methyl indole precursor could be smoothly converted into the imino-ene product in a similar way, as shown in Scheme 3, product **5n**.



Scheme 3. Substrate scope in the synthesis of cyclopentyl[*b*]indolines through intramolecular imino-ene reactions.

Because a number of catalytic asymmetric reactions for the synthesis of C3-functionalized chiral indole derivatives have been well-established over the past years,[3] more enantioenriched indole precursors that might be utilized in the Lewis acid catalyzed imino-ene reaction could be accessed. For example, the asymmetric C3-selective Friedel–Crafts reaction of indole with benzylideneacetone was easily conducted to give chiral intermediate **6**,[17] which could be transformed into alkene precursors through the traditional Wittig reaction. To our delight, the imino-ene reaction of alkene **7a** with 1,1-disubstituted pattern proceeded smoothly under $AlCl_3$ catalysis, thus affording cyclohexyl[*b*]indoline (**8a**), bearing an *exo*-methylene group, in outstanding diastereoselectivity (Scheme 4). Although an *E*/*Z* mixture was

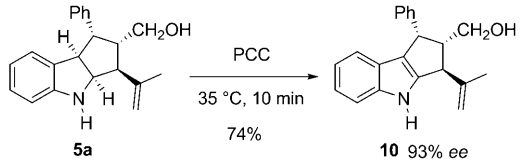


Scheme 4. Synthesis of enantioenriched cyclohexyl[*b*]indolines.

obtained for alkene **7b**, it was pleasing to observe that the *E* isomer could be preferably and chemoselectively converted into the imino-ene product **8b** in less than 10 minutes, and with remarkable diastereocontrol. In contrast, the *Z* isomer remained almost unchanged, while the transformation could be continued to deliver Friedel–Crafts-type product **9** after a longer reaction time, also with complete diastereoselectivity.

As shown in Scheme 5, the indoline **5a** could be readily and chemoselectively oxidized into indole derivative **10** under mild conditions, even without affecting the primary alcohol group. Thus, both fused indolines and indoles could be efficiently accessed.

In conclusion, we have discovered a highly efficient, direct, and diastereoselective intramolecular imino-ene reaction of indoles bearing a tethered olefinic functionality. This novel reaction proceeded through a key Lewis acid catalyzed enamine–imine isomerization, which followed the Lewis acid mediated ene cyclization. The olefinic indole precursors could



Scheme 5. Synthesis of fused indoles. PCC = pyridinium chlorochromate.

be readily prepared by means of well-established asymmetric catalytic procedures. A range of highly enantioenriched and versatile cyclopentyl[*b*]indolines and cyclohexyl[*b*]indolines has been prepared with remarkable efficiency. We hope that the Lewis acid catalyzed enamine–imine isomerization of indoles will be helpful for the development of a direct nucleophilic C2-selective functionalization pathway for indole chemistry. Studies aimed at further exploration of the synthetic potential of this reaction are currently under way.

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[14] The absolute structure of **5a** was confirmed by X-ray crystallographic analysis after derivatization (*S*-10-camphorsulfonate). CCDC 793950 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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