Collective Synthesis of Indole Alkaloids Enabled by Photoredox-Initiated Radical Cascade Reactions

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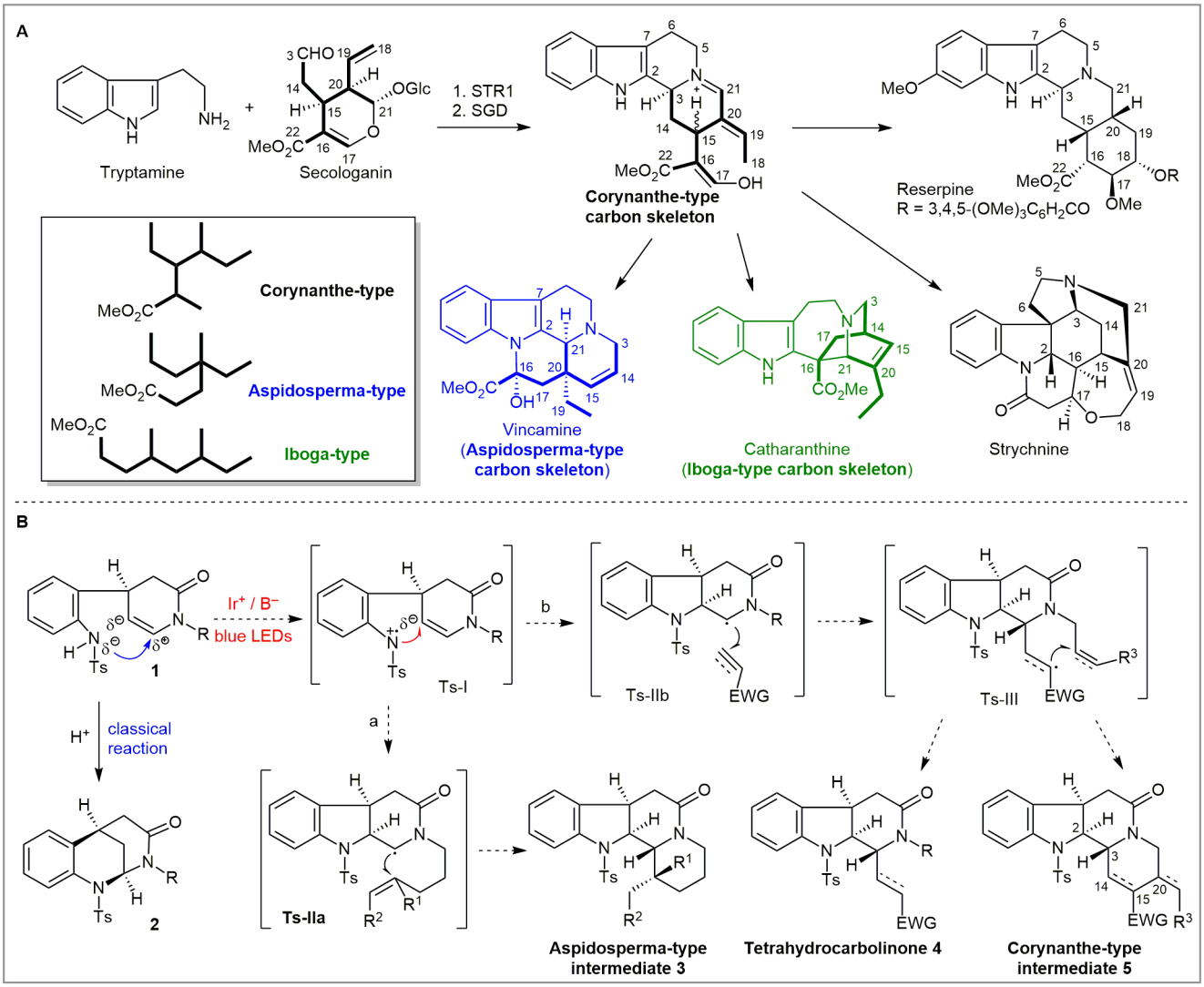
Indole alkaloids represent a large and unique family of natural products that are characterized by complex and diverse structures, as well as an important range of bioactivities. Representative molecules such as vinblastine and reserpine have been used as clinical drugs for decades. These features, combined, have rendered the total synthesis of indole alkaloids a topic of great concern for synthetic chemists, the research of which could be traced back to the historic synthesis of reserpine and strychnine in the 1950s by Woodward and co-workers (*J. Am. Chem. Soc.* **1956**, *78*, 2023 and references therein).

The group of Professor Yong Qin at Sichuan University (P. R. of China) has a long-standing interest in the synthesis of com-

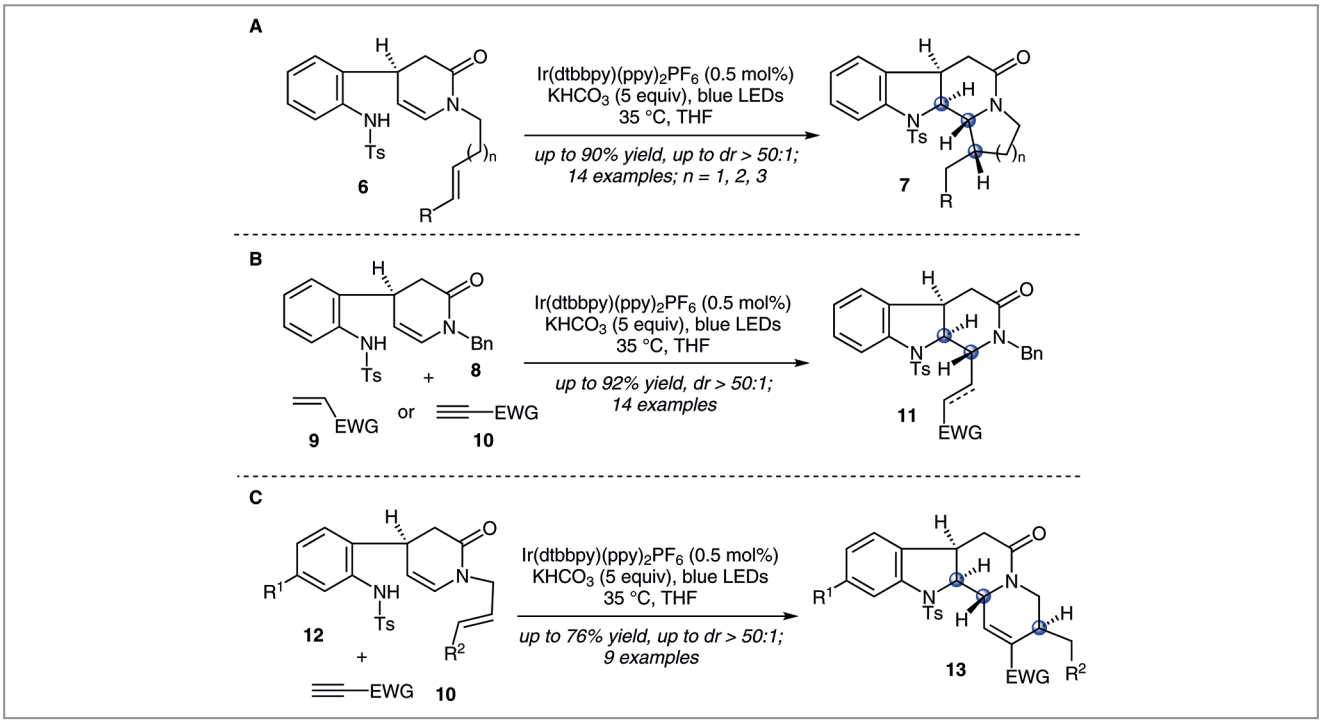


Scheme 1

plex monoterpenoid indole alkaloids. Previously, the group developed a cyclopropanation strategy (*Acc. Chem. Res.* **2011**, *44*, 447), which has proven to be versatile in the synthesis of several intriguing indole alkaloids, such as communesin F, minfiensine, vincorine, lundurine A and fruticosine. Professor Qin explained: "Biogenetically, all monoterpenoid indole alkaloids are derived from tryptamine and secologanin by strictosidine synthase (STR1) and strictosidine glucosidase (SGD) catalyzed condensation (Scheme 1, A). Based on the carbon skeletons of the monoterpenoid units, these alkaloid natural products could be classified into three major types, namely, corynanthe-, aspidosperma-, and iboga-type alkaloids, which were further expanded to over 15 sub-types and more than 3000 known members." He continued: "In the course of our research, we were ambitious enough to pursue a general strategy that would enable the synthesis of all sub-types of indole alkaloids. Obviously, this would require a breakthrough in developing simple, green, catalytic and asymmetric synthetic methods."

By carefully analyzing the structure of a corynanthe-type core, a common biogenetic precursor of indole alkaloid subtypes, the group envisioned that key disconnections at the N–C2, C3–C14 and C15–C20 bonds would lead back to compound **1** (Scheme 1, B). In a classic reaction pathway, the N atom in sulfonamide **1** would add to the α-position of the enamine double bond due to its electrophilicity, forming the tetrahydroquinoline intermediate **2**. "We envisioned that an electron-deficient nitrogen-centered radical (Ts-I; Scheme 1, B) would enable the formation of a C–N bond between the electron-donating aniline nitrogen and the β-carbon of the enamine," said Professor Qin. He continued: "Although this was a big challenge, such a radical could be directly generated via deprotonation and oxidation of a sulfonamide N–H bond, which is superior to the classic homolysis of N–X functionalities. Accordingly, three types of radical cascade reactions (intra-/intra-molecular, intra-/inter-molecular, and intra-/inter-/intra-molecular) were also designed to access the aspidosperma-, tetrahydrocarbolinone-, and corynanthe-type skeletons (**3**, **4**, and **5**, respectively; Scheme 1, B) starting from sulfonamide **1**."

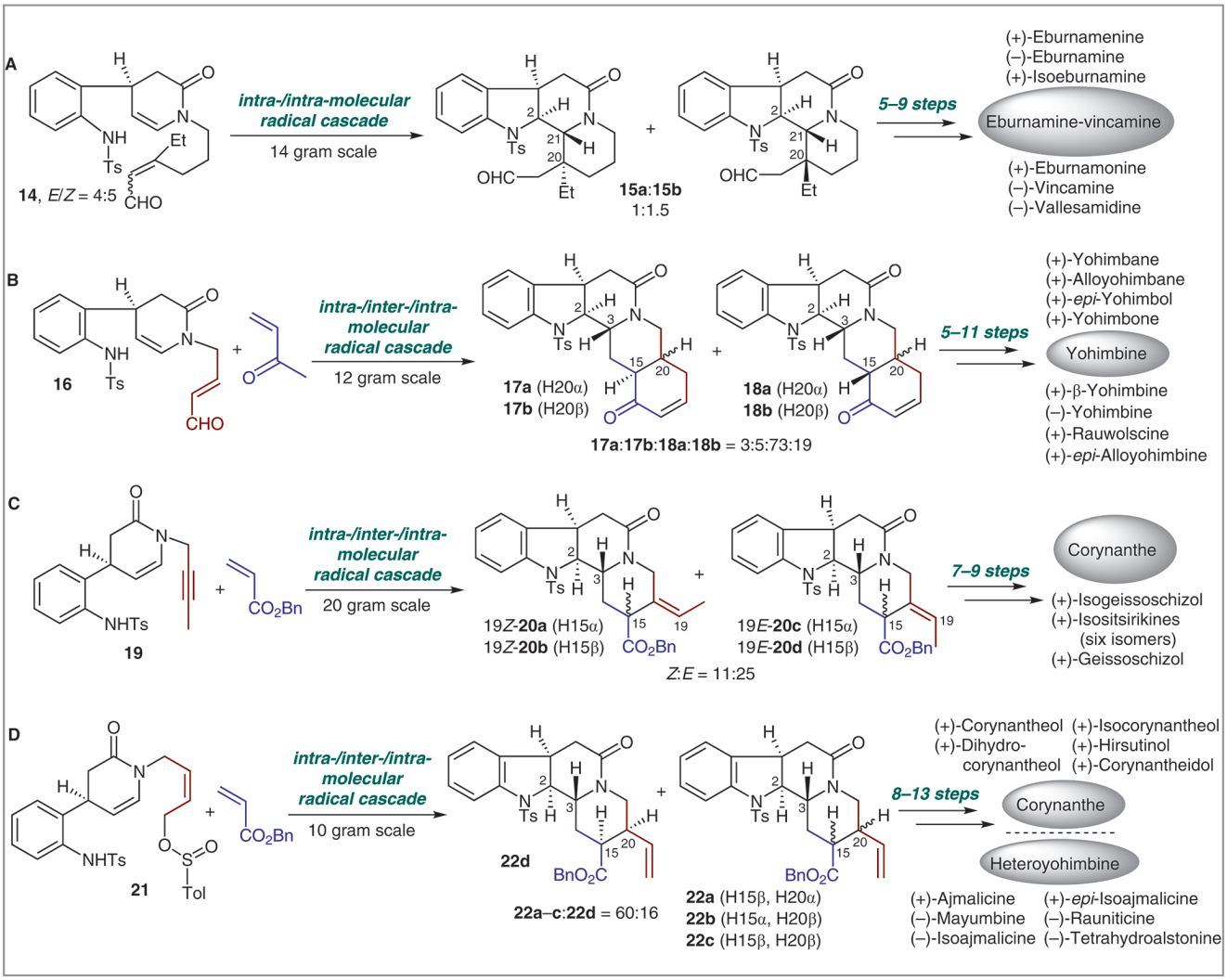
According to their design, the group first examined the generation of a nitrogen-centered radical by direct cleavage of the N–H bond from Ts-protected aniline. Professor Qin said: "Gratifyingly, after extensive experimentation, two PhD students (Xiaobei Wang and Wenfang Qin) detected the formation of an indoline ring when subjecting **1** to the photocatalytic conditions [Ir(dtbbpy)(ppy)$_2$PF$_6$ (0.5 mol%), KHCO$_3$ (5 equiv), THF, blue LEDs]. Inspired by this preliminary result,



Scheme 2

three types of radical cascade reactions were carried out as illustrated in Scheme 2." Treating substrate **6** with the optimized reaction conditions led to the formation of aspidosperma derivatives **7**. Reaction of **8** in the presence of an external radical acceptor (**9** or **10**) yielded tetrahydrocarbolinone derivatives **11**, and an intra-/inter-/intra-molecular cascade occurred using **12** and **10** as substrates to afford tetracyclic corynanthe-type intermediates **13**. All these radical cascade reactions proceeded efficiently to construct multiple C–N and C–C bonds and rapidly establish molecular complexity in moderate to excellent yields. Notably, excellent control of diastereoselectivity of the newly formed stereogenic centers was observed in most of the examples.

Professor Qin remarked: "Having the radical cascade methodology established, we next explored its application to the total synthesis of indole alkaloids (Scheme 3). By careful and precise design of the structure of substrates, our group succeeded in synthesizing 33 indole alkaloids belonging to four sub-types (eburnamine-vincamine, yohimbine, corynanthe, and heteroyohimbine) in 6–14 steps using the radical cascade as a key reaction." He continued: "Of note, all these key radical cascades were performed on decagram scales. While excellent stereoselectivity was observed at positions C2 and C3 (or C21 in aspidosperma-type intermediates 15a/b), generation of stereochemical divergence at distal sites such as C15 and C20 in the products provided us good opportunities to synthesize corresponding naturally differentiated indole alkaloids."



Scheme 3

"To summarize, a target-oriented synthesis program which aimed at a large collection of natural products has prompted us to develop an innovative synthetic method," said Professor Qin. "This photoredox-induced protocol provided mild and direct generation of a nitrogen-centered radical via deprotonation and oxidation of a sulfonamide N–H bond. Subsequent cascade reactions not only reversed the conventional reactivity between two electron-donating amine and enamine groups, but also allowed efficient access to libraries of chiral and multiple-ring-fused tetrahydrocarbolinones." Professor Qin concluded: "Collective synthesis of 33 indole alkaloids has thus been accomplished by employing this simple, mild, and scalable method as a key step. This powerful strategy is expected to facilitate the synthesis of more types of indole alkaloids and associated analogues."

About the authors

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Xiaobei Wang was born in Anhui Province (P. R. of China) and obtained his B.Sc. degree in pharmacy from Sichuan University (P. R. of China) in 2012. In the same year, he joined the group of Professor Yong Qin at Sichuan University to pursue his Ph.D. degree. His research focuses on the total synthesis of complex natural products, especially biologically active indole alkaloids.

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Wenfang Qin was born in Hebei Province (P. R. of China). She received her B.Sc. degree in pharmacy at Chongqing University (P. R. of China) in 2012. In the same year she joined the group of Professor Yong Qin at Chongqing University to conduct her Ph.D. studies. Her research focuses on the total synthesis of natural products and methodology studies.

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Prof. Y. Qin

Yong Qin received his B.Sc. degree from Yunnan University (P. R. of China) in 1989 and his Ph.D. from the Institute of Chemistry, Chinese Academy of Sciences (Beijing, P. R. of China) in 1995. From June 1995 to August 1996, he worked at the Chengdu Institute of Organic Chemistry (P. R. of China) as an Assistant and Associate Professor. From August 1996 to August 2000, he worked with Professor Martin E. Kuehne as a postdoctoral associate at the University of Vermont (USA). Then, he moved to San Diego (USA) and worked as a research scientist at Triad Therapeutics Inc. In 2003, he joined the faculty of West China School of Pharmacy, Sichuan University (P. R. of China) as a full Professor. His research has been focused on the total synthesis of bioactive natural products and medicinal chemistry.

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