Alkaloid Synthesis

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Enantioselective Palladium-Catalyzed Decarboxylative Allylation of Carbazolones: Total Synthesis of (−)-Aspidospermidine and (+)-Kopsihainanine A**

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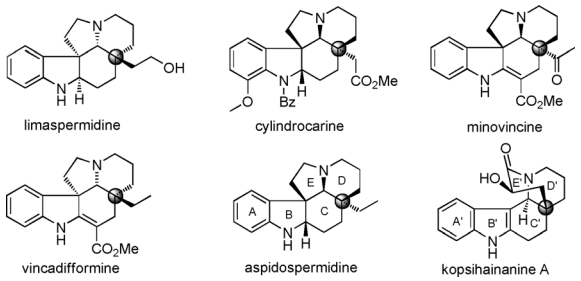
The *Aspidosperma* alkaloids represent the largest family of monoterpenoid indole alkaloids, with more than 250 members isolated from various biological sources.[1] Because of their structural and stereochemical complexity, their central biosynthetic role in plants, and their interesting biological activity, *Aspidosperma* alkaloids have attracted attention from the synthetic community for over 40 years and have remained a focus of extensive research activity to the present day.[2] Aspidospermidine (Scheme 1), the archetypal member, is among the most highly sought *Aspidosperma* alkaloid targets. Because it comprises the basic skeletal features of this family of natural products, particularly the complex and characteristic pentacyclic ABCDE framework, it has been the primary target of most syntheses toward *Aspidosperma* alkaloids and has served as the ideal proving ground for the development of new synthetic methods and strategies.[3,4] Since the 1960s,[3a] aspidospermidine has been synthesized by over 40 research groups in racemic[3] and nonracemic[4] forms. The majority of these syntheses follow one of the following three synthetic strategies: 1) the Fischer indole approach used by Stork and co-workers,[3a] 2) the indoloquinolizidine rearrangement approach used by Harley-Mason and co-workers,[3c] and 3) E-ring-closing approach.[3p] Despite the numerous successful syntheses of aspidospermidine, there are only few reports on the employment of catalytic asymmetric strategies.[4f,l] In 2002, Rawal and co-workers reported an elegant catalytic enantioselective total synthesis of (+)-aspidospermidine. In this approach, a highly enantioselective Diels–Alder reaction between 1-amino-3-siloxydiene and 2-ethylacrolein catalyzed by the chiral Cr^{III}–salen complex developed by Jacobsen was exploited to form the C ring, which bears a quaternary carbon center at C4, and subsequently the DABE ring system was formed sequentially (the E-ring-closing approach).[4f] Recently, MacMillan and co-workers described an impressive organocatalytic asymmetric total synthesis of (+)-aspidospermidine based on a cascade Diels–Alder/cyclization sequence.[4l] The development of a general, efficient, and conceptually new strategy for the catalytic enantioselective total synthesis of aspidospermidine still remains important and challenging.



Scheme 1. Selected *Aspidosperma* and *Kopsia* alkaloids. The core structure of these alkaloids is the piperidine-fused hydrocarbazole ring system.

We sought to develop a general catalytic asymmetric strategy for the synthesis of aspidospermidine and related natural products in a concise and divergent manner. In this regard, we selected kopsihainanine A, a member of the *Kopsia* alkaloid family, which has not been synthesized in asymmetric form, as our second target to demonstrate the feasibility of our strategy. Structurally, aspidospermidine and kopsihainanine A contain a common functionalized tetracyclic framework that features a hydrocarbazole core with a crucial all-carbon quaternary stereogenic center (Scheme 1). In addition to the formation of this all-carbon quaternary stereogenic center, another key challenge for the divergent asymmetric synthesis is the *cis*-fused C/D ring in aspidospermidine and several other members of the family of *Aspidosperma* alkaloids (such as limaspermidine, cylindrocarine, minovincine, and vincadifformine), whereas the C′/D′ ring in kopsihainanine A is *trans*-fused (Scheme 1).

To achieve our challenging goal, we developed a diversity-oriented retrosynthetic analysis (Scheme 2). We planned to form both the *cis*-fused C/D ring in aspidospermidine and the *trans*-fused C′/D′ ring in kopsihainanine A from the common

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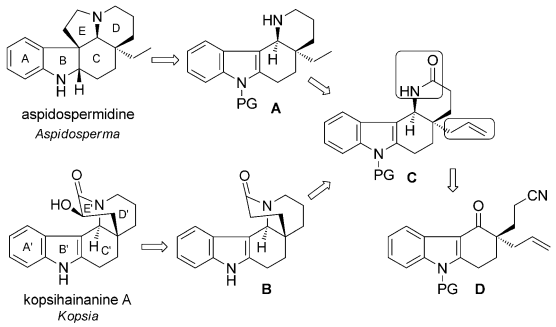
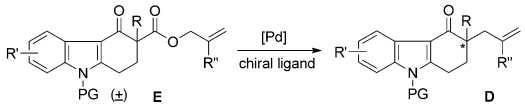


Scheme 2. Diversity-oriented retrosynthetic analysis.

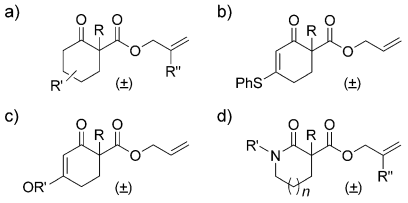
chiral tetracyclic intermediate **C**. This intermediate is also potentially useful for the synthesis of other *Aspidosperma* alkaloids, such as limaspermidine and minovincine (Scheme 1), which can be obtained through diverse transformations at the allyl and amide groups. Intermediate **C** would be assembled diastereoselectively and enantioselectively from the highly functionalized carbazolone **D** through hydrolysis of the nitrile group followed by selective reduction and a highly *cis*-selective cyclization. The key feature of this approach is the catalytic enantioselective decarboxylative allylic alkylation of the highly functionalized carbazolone **D**, which features an α-quaternary carbon center [Eq. (1)]. After the development of this reaction, we applied the methodology to the divergent asymmetric synthesis of natural products. Both, *Aspidosperma* alkaloid (−)-aspidospermidine and *Kopsia* alkaloid (+)-kopsihainanine A were synthesized concisely in a catalytic enantioselective fashion, and the absolute configuration of the latter was unambiguously confirmed.



(1)

Recently, transition-metal-catalyzed asymmetric decarboxylative allylation has emerged as a powerful transformation in organic synthesis,[5–7] chiefly because of the pioneering efforts of the groups of Stoltz,[6a,b] Tunge,[6f] Trost,[6h–i] Nakamura,[6l] Murakami,[6m] You,[6t] and others.[6n–u] While a series of different types of substrates, including cyclic ketones, vinylogous thioesters, and lactams (Scheme 3), have been employed successfully in this transformation, there is no report on the catalytic enantioselective decarboxylative allylic alkylation of heterocyclic carbazolones.

Our work in this field is based on the recognition of heterocyclic carbazolones,[8] such as **E**, as a valuable class of substrates for the Pd-catalyzed enantioselective decarboxylative allylic alkylation [Eq. (1)], thus providing the chiral α-allylated carbazolone **D** with the key quaternary carbon center, a motif that is common in natural products and medicinal chemistry. The catalytic asymmetric formation of chiral all-carbon quaternary centers is one of the most challenging and dynamic research areas in modern organic synthesis.[9] To the best of our knowledge, there is no catalytic method available for the asymmetric synthesis of this class of

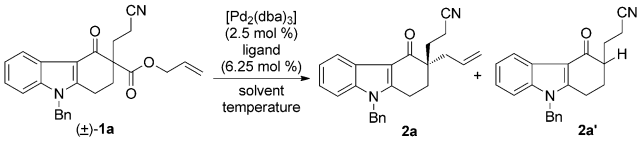


Scheme 3. Selected substrates for the decarboxylative allylation. a) Stoltz, Ref. [6b]; b) Trost, Ref. [6i]; c) Trost, Ref. [6i]; d) Stoltz, Ref. [6e].

target molecules. Unlike the decarboxylative allylic alkylation with simple cyclic ketones,[6b] the decarboxylative allylic alkylation with carbazolones is more challenging than it appears at first glance because of the well-known nucleophilicity at C3 of indoles[10] and its influence on the proposed decarboxylative allylic alkylation reaction. We reasoned that by combining a source of Pd^0 with an adequately chosen chiral ligand, this reaction would be possible.

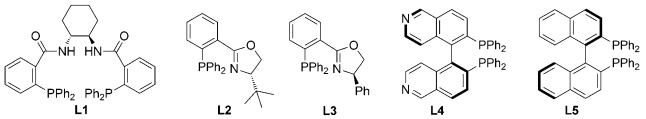
To explore the feasibility of the proposed synthetic strategy, we began our study of the Pd-catalyzed decarboxylative allylic alkylation of carbazolones with substrate **1a** (Table 1). Formation of the C3 allylation product was not observed, however, the unexpected decarboxylative protonation product **2a′** was obtained. Interestingly, when Trost's ligand **L1**, which is known to be effective in decarboxylative allylation reactions of allyl-β-keto esters,[6f,i] was used as the chiral ligand, the expected product **2a** was not obtained. In contrast, the decarboxylative protonation product **2a′** was obtained solely (Table 1, entry 1). During the examination of

Table 1: Optimization of reaction conditions.[a]



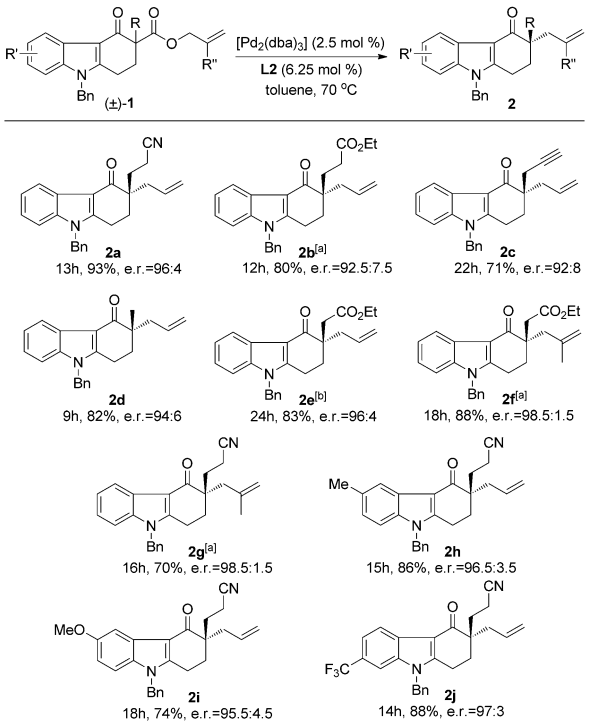
Entry	L	Solvent	*T* [°C]	**2a**:**2a′**	Yield of **2a** [%][b]	e.r. of **2a**[c]
1	**L1**	toluene	70	0:100	0	–
2	**L2**	**toluene**	**70**	**19:1**	**93**	**96:4**
3	**L3**	toluene	70	6:1	75	13:87
4	**L4**	toluene	70	6:1	80	30:70
5	**L5**	toluene	70	3:1	66	61:39
6	**L2**	THF	70	1.6:1	51	94.5:5.5
7	**L2**	*m*-xylene	70	3.4:1	64	96.5:3.5
8	**L2**	benzene	70	4.6:1	74	88:12
9	**L2**	toluene	55	1.7:1	57	94:6
10	**L2**	toluene	80	2.7:1	67	95.5:4.5

[a] Reaction conditions: **1a** (100 mg, 0.24 mmol) in solvent (7.5 mL). [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase (Chiralpak AD-H). Entry in bold marks optimized reaction conditions. dba = *trans*,*trans*-dibenzylideneacetone.



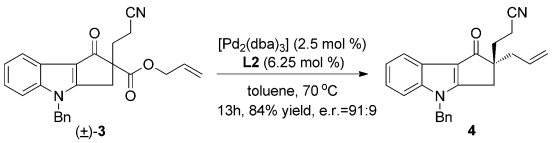
other chiral ligands, we found that chiral ligands have a crucial effect on the results of the decarboxylative process (Table 1, entries 1–5). Among them, the chelating P/N ligands **L2** and **L3** (phosphinooxazolines (PHOX)), which were developed by Pfaltz, Helmchen, and Williams,[11] and used by Stoltz[6a] in the decarboxylative allylic alkylation of cyclic ketones, gave the desired product **2a** in moderate to good results. The solvents and temperatures also had effects on the result of the reaction (Table 1, entries 6–10). Finally, the desired allylation product **2a** was obtained in 93% yield with e.r. = 96:4 using ligand **L2** in toluene at 70°C (Table 1, entry 2).

With the optimized reaction conditions in hand, we investigated the scope of this asymmetric allylic alkylation. A variety of carbazolone substrates were converted smoothly into the desired products in good yields with high enantioselectivity (e.r. = 92:8–98.5:1.5; Scheme 4). The reaction is



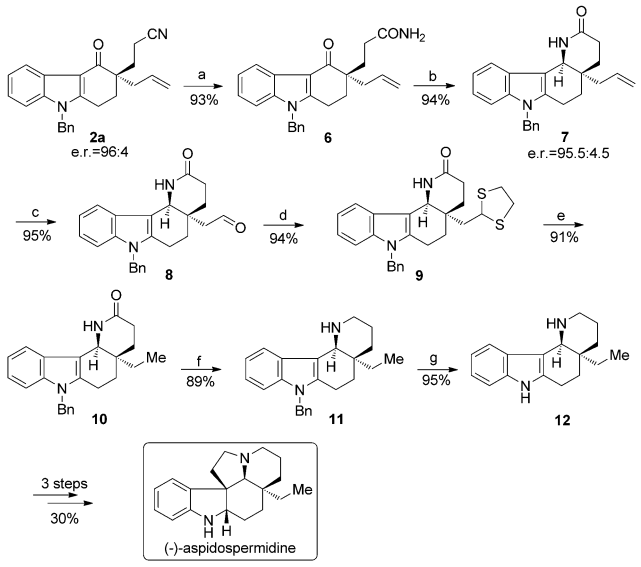
Scheme 4. Pd-catalyzed enantioselective decarboxylative allylic alkylation. [a] $[Pd_2(dba)_3]$ (3.5 mol%), **L2** (8.75 mol%). [b] At 55°C.

highly tolerant toward a wide range of functionalities (e.g., CH_2CH_2CN, $CH_2CH_2CO_2Et$, $CH_2C{\equiv}H$, CH_2CO_2Et and CH_3). The presence of a 1,6-enyne moiety in compound **2c** is of particular interest because of the rich chemistry of 1,6-enynes.[12] Substituted allyl groups can also be incorporated, leading to products **2f** and **2g** in good yields and high enantioselectivity (e.r. = 98.5:1.5). Moreover, substrates with different substituents, including CH_3, OCH_3, and CF_3 groups on the benzene ring, also afforded the desired products **2h**–**2j** in good yields and high enantioselectivity (e.r. > 95:5). On the other hand, the Pd-catalyzed asymmetric allylic alkylation of compound **3** also proceeded successfully to provide the corresponding product **4** in good yield and enantioselectivity [Eq. (2)]. The absolute configurations of the allylation products were assigned on the basis of X-ray crystal-structure analysis of product **2e** (Flack parameter = 0.1(3)).[13] Compound **2b** was quantitatively transformed into the chiral polycyclic product **5** through a tandem sequence of the selective reduction of the ketone moiety and a cyclization[14] without loss of the enantiomeric purity.[15]



(2)

Having developed this key asymmetric decarboxylative allylation reaction, we turned our attention to the divergent asymmetric natural product synthesis. Firstly, we developed a concise enantioselective synthesis of *Aspidosperma* alkaloid (−)-aspidospermidine (Scheme 5). Mild hydrolysis of the nitrile group of intermediate **2a** gave chiral amide **6**, which was then transformed into the tetracyclic intermediate **7** in excellent yield without loss of enantiomeric purity through the chemoselective reduction of the ketone group followed by diastereoselective cyclization.[14] Following the oxidation to **8**, the angular ethyl side chain was introduced by mercaptalation and subsequent hydrogenation with Raney nickel to give **10**. Reduction of the amide group with LAH and subsequent N-debenzylation with Na/NH_3 resulted in the formation of the enantiopure tetracyclic intermediate **12** in 85% yield over two steps. Following the procedure developed by Toczko and Heathcock,[3o] compound **12** was transformed into (−)-aspidospermidine, which was obtained in 30% yield over three steps. All spectroscopic and optical data of the synthetic

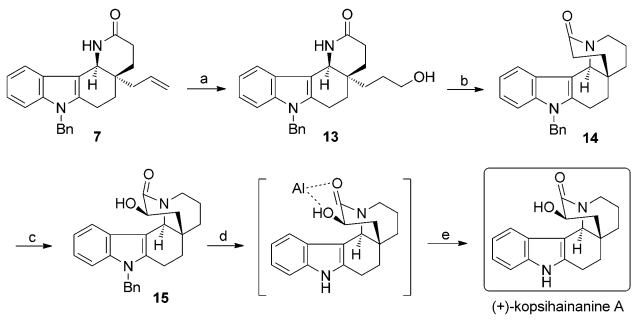


Scheme 5. Catalytic enantioselective total synthesis of (−)-aspidospermidine. Reaction conditions: a) HCO_2H, RT; b) $LiAlH_4$, THF, −20°C, then HCl (2 M); c) $K_2OsO_4{\cdot}2H_2O$, NMO, THF/H_2O (1:1), then $NaIO_4$; d) 1,2-ethanedithiol, $BF_3{\cdot}Et_2O$, CH_2Cl_2; e) Raney nickel, H_2, EtOH, 60°C; f) $LiAlH_4$, Et_2O, reflux; g) Na/NH_3, THF, −78°C. NMO = *N*-methylmorpholine-*N*-oxide.

(−)-aspidospermidine were in accordance with those reported previously.[4k]

The present work also comprises catalytic asymmetric formal syntheses of (+)-quebrachamine[3g] and (−)-vincadifformine,[4l] as they can be obtained in two steps from the tetracyclic intermediate **12** and the synthetic (−)-aspidospermidine, respectively, by established methods.

We further extended our strategy to the enantioselective total synthesis of kopsihainanine A (Scheme 6), which was recently isolated by Gao and co-workers[16] from the leaves and stems of a Chinese medicinal plant, *Kopsia hainanensis*.[17] Subsequently, She, Xie, and co-workers reported the synthesis of racemic kopsihainanine A.[14] To date, no asymmetric total synthesis of kopsihainanine A has been reported.



Scheme 6. Catalytic enantioselective total synthesis of (+)-kopsihainanine A and confirmation of its absolute configuration. Reaction conditions: a) BH_3·THF, −20 °C, then $NaBO_3$, RT; b) MsCl, Et_3N, CH_2Cl_2, 0 °C, then NaH, DMF, 0 °C→RT; c) LDA, Na_2SO_3, O_2, 0 °C→RT; d) $AlCl_3$, toluene; e) saturated aqueous solution of Rochelle salt, RT, overnight. DMF = *N*,*N*-dimethylformamide, LDA = lithium diisopropylamide, Ms = methanesulfonyl.

We obtained chiral compound **15** through a three-step transformation of key intermediate **7**. Following the procedure developed by She, Xie, and co-workers,[14] treatment of **15** with $AlCl_3$ in anisole at 100 °C supposedly gave the target molecule kopsihainanine A. Interestingly, this synthetic molecule was insoluble in $CHCl_3$, whereas the natural kopsihainanine A that was isolated by Gao and co-workers was soluble in $CHCl_3$.[17] Furthermore, we noticed that the molecule previously synthesized by She, Xie, and co-workers was also insoluble in $CHCl_3$.[14] To uncover the reason behind this rather puzzling result, we also synthesized the target molecule of She, Xie, and co-workers. Our results were in accordance with their report[14] that this synthetic racemic molecule was indeed insoluble in $CHCl_3$, but soluble in DMSO. After extensive analysis and investigations, we reasoned that the synthetic molecules are not kopsihainanine A, but instead its aluminium complex. To our delight, the treatment of these synthetic compounds with Rochelle salt gave (+)-kopsihainanine A and (±)-kopsihainanine A, which were both soluble in $CHCl_3$. All spectroscopic data (^{1}H NMR and ^{13}C NMR) were in accordance with Gao's report.[17] By comparing the optical rotation of the synthetic molecule with natural kopsihainanine A, the absolute configuration of the latter was unambiguously confirmed. Finally, we accomplished the first catalytic enantioselective total synthesis of natural (+)-kopsihainanine A.

In summary, we have demonstrated the feasibility of divergent total syntheses of both *Aspidosperma* and *Kopsia* alkaloids in combination with transition-metal asymmetric catalysis. Specifically, we have developed the first Pd-catalyzed chemo- and enantioselective decarboxylative allylic alkylation of carbazolone enolates, leading to highly functionalized chiral carbazolones that feature an α-quaternary carbon center, which are found in numerous natural products and pharmacologically active compounds, in good yields with high enantioselectivity (e.r. of up to 98.5:1.5). With this protocol, a concise catalytic enantioselective synthesis of (−)-aspidospermidine was accomplished. A catalytic asymmetric strategy for the synthesis of *Aspidosperma* alkaloids has also been established. Secondly, the catalytic enantioselective total synthesis of *Kopsia* alkaloid kopsihainanine A was achieved successfully from a common intermediate, and its absolute configuration was unambiguously confirmed. Further application of this methodology to the asymmetric synthesis of other members of *Aspidosperma* alkaloids and investigation of new catalytic asymmetric reactions involving carbazolones are currently under way in our research group.

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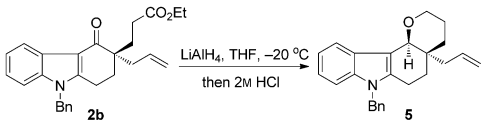

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