Natural Product Synthesis

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Iridium-Catalyzed Enantioselective Indole Cyclization: Application to the Total Synthesis and Absolute Stereochemical Assignment of (−)-Aspidophylline A

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Dedicated to Professor Yoshito Kishi

Abstract: *The first enantioselective total synthesis of (−)-aspidophylline A, including assignment of its absolute configuration has been accomplished. A key element of the synthesis is a highly enantioselective indole allylic alkylation/iminium cyclization cascade which was developed by employing a combination of Lewis acid activation and an iridium/ligand catalyst. This strategy relies on the direct use of 2,3-disubstituted indoles with secondary allylic alcohols appended at C2 and heteronucleophiles appended at C3, indoles which are easily prepared from simple starting materials under C−H activation conditions.*

Recently, members of the biologically active akuammiline family of monoterpene indole alkaloids (Figure 1) have emerged as high-profile targets for total synthesis and medicinal chemistry studies.[1] On one hand, many of these alkaloids exhibit a broad range of important biological activities varying from anticancer, antibacterial, anti-inflammatory, and antitussive to antimalarial activity. And on the other hand, they have many synthetic challenges, such as complex stereogenic centers, a labile aminal moiety, and a strained ring system within their intricate polycyclic caged structure. One of the notable akuammiline alkaloids is (−)-aspidophylline A [(−)-**2**],[2] which was isolated from Malayan *Kopsia singapurensis* by Kam and co-workers in 2007 and was found to reverse drug resistance in drug-resistant KB cells. Structurally, this pentacyclic alkaloid includes a tricyclic furoindoline motif, a densely substituted cyclohexyl ring bearing five contiguous stereogenic centers and a bridged [3,3,1] bicycle.

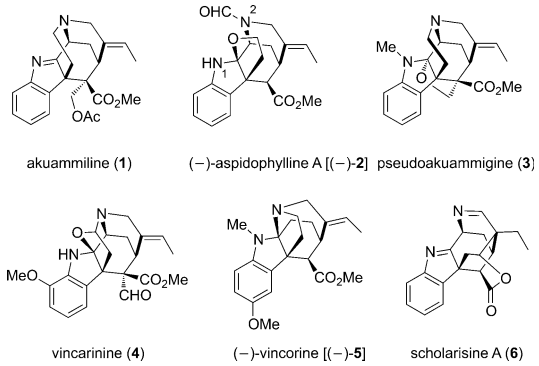

Figure 1. Representative akuammiline alkaloids.

The intriguing structure and important bioactivity renders (−)-**2** a privileged synthetic target. A number of research groups have undertaken the synthesis of **2**. In 2011, the group of Garg reported an inaugural synthesis[3] of (±)-aspidophylline A [(±)-**2**], and a Fischer indolization[4] was adopted to construct the pentacyclic framework of the natural product. Later, the groups of Ma[5] and Zhu[6] coincidently published their racemic total syntheses in 2014. The group of Ma utilized an intramolecular oxidative coupling[7] to create the tetracyclic furoindoline motif of the natural product, whereas the group of Zhu employed a desymmetrization approach to the dihydrocarbazole and an oxidative azidoalkoxylation reaction[8] to install N2 of the alkaloid's scaffold and furoindoline moiety. Besides (−)-**2**,[9] the total synthesis of other members of akuammiline alkaloids such as (−)-vincorine [(−)-**5**],[10] scholarisine A (**6**),[11] and picrinine[12] have recently been reported.[13] Without a doubt, all the above syntheses in the literature are acclaimed for the innovation in their strategies. However, efforts toward the catalytic asymmetric strategies for akuammiline alkaloids have been sparse. To our knowledge, except for the recent organocatalytic Diels–Alder cascade cyclization, reported by MacMillan and co-workers,[14] in the elegant synthesis of (−)-**5**,[10c] there is no other highly efficient enantioselective cyclization reaction employed in the total synthesis of akuammiline alkaloids. To this end, we embarked on the total synthesis of (−)-**2** by taking advantage of a transition-metal-catalyzed asymmetric cyclization, which has yet to be exploited in the total synthesis of the akuammiline alkaloids,[15] with the hope of developing a general synthetic strategy applicable to the other congeners and confirming the absolute stereochemistry of (−)-**2**.

As outlined in Scheme 1, we envisioned a general strategy for (−)-**2** and other akuammiline alkaloids in which the final ring might be forged by cyclizations between the vinyl iodide **8** and α,β-unsaturated ester **7** at C3 and C15, respectively.[16] The ester **7** is a common akuammiline core and might arise from the ketone precursor **9**, coined herein as the akuammi-

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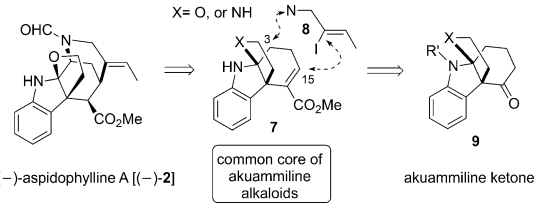
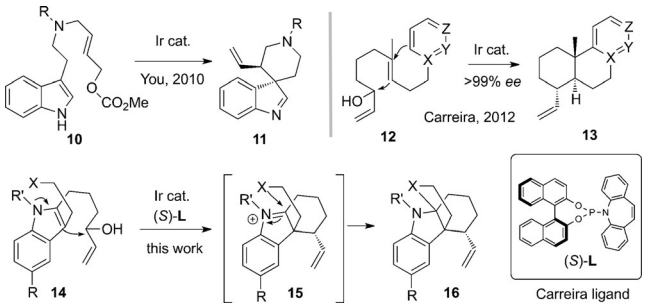


Scheme 1. Retrosynthetic approach to akuammiline alkaloid (−)-aspidophylline A [(−)-**2**].

line ketone, which in turn would be our target for the development of a catalytic enantioselective cascade cyclization.

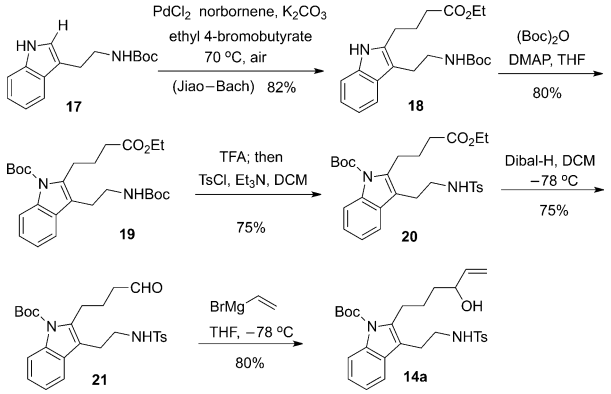
Transition-metal-catalyzed asymmetric allylic substitution reactions are among the most significant and reliable methods in organic synthesis.[17] Recently, investigations of indoles as nucleophiles undergoing allylic alkylation reactions catalyzed by transition metals, such as Mo,[18] Pd,[19] Au,[20] Ru,[21] and Ir,[22] to furnish motifs of polycyclic products, have progressed rapidly.[23] For example, You et al. reported an intramolecular allylic dearomatization of the indole **10**, having a linear C3-substituted allylic carbonate, thus giving the spiro-polycyclic scaffold **11** (Scheme 2).[22b] However, the thus generated



Scheme 2. The iridium-catalyzed asymmetric synthesis of polycyclic frameworks.

scaffold differs from the natural architectures of the most monoterpene indole alkaloids, and thus constitutes a major impediment to the application of this ingenious method in total synthesis. To this end, designing a novel target-orientated strategy is in great demand. Inspired by the iridium-catalyzed enantioselective polyene cyclization **12**→**13**, recently reported by Carreira and co-workers,[24] we speculated that the Carreira catalysis system[25] could be applied to the functionalized indole **14** having a secondary allylic alcohol appended to C2 and a heteronucleophiles appended to C3. In this way, a novel asymmetric and catalytic cascade sequence of indole allylic alkylation/iminium cyclization would serve to construct the tetracyclic architecture of the akuammiline ketone (**16**), having two contiguous quaternary stereogenic centers, in one step (Scheme 2).

Our synthesis started with the preparation of the functionalized 2,3-disubstituted indole **14** from the commercial material **17** (Scheme 3). Given the limited availability of the synthetic routes toward 2-alkylindoles,[26a] in particular, for the substrate having a protecting-group-free N1 or one that



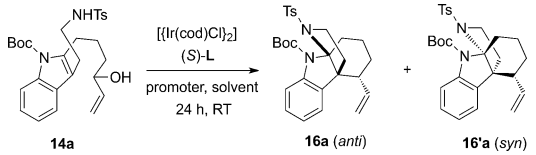
Scheme 3. General preparation of the 2,3-disubstituted indoles **14**. Boc = *tert*-butoxycarbonyl, DCM = dichloromethane, Dibal-H = diisobutylaluminum hydride, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, TFA = trifluoroacetic acid, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.

has another reactive NH group appended to C3 (e.g., **17**), a direct approach is unprecedented. Pleasingly, after many experiments, we found that a direct palladium-catalyzed 2-alkylation reaction of the N1H-indole, thus invoking a norbornene-mediated C–H activation cascade,[26] a new protocol reported by Jiao and Bach, could be successfully applied to **17** and yielded the 2-substituted ethyl butyrate **18** in 82% yield. The compound **18** was advanced to the secondary allylic alcohol **14a** by using the standard procedures outlined in Scheme 3.

With the routes to 2,3-disubstituted indoles (**14**) established,[27] we began to study the iridium-catalyzed indole cyclization by evaluating the reaction of **14a** as a test substrate under the reaction conditions similar to those employed by Carreira and co-workers for polyene cyclization (Table 1). By fixing dichloroethane as the solvent, exposure of **14a** to [{Ir(cod)Cl}$_2$] and the ligand (*S*)-**L** in the presence of TFA, as a promoter, afforded the tetracyclic products **16a** and **16′a** with excellent *ee* values (93 and 93%, repectively), albeit in 38% combined yield and a moderate 1:5 d.r. (entry 1). Although other Brønsted acids (entries 2 and 3) did not noticeably enhance the yields, encouragingly, an excellent 97% *ee* was obtained for both diastereoisomers in the case of di-*n*-butylphosphoric acid (entry 3). We next turned our attention to Lewis acids in the same solvent. We observed that the use of 10 mol% Bi(OTf)$_3$ improved conversion after 24 hours at ambient temperature, thus leading to a combined yield of 58%, although the enantioselectivity was not satisfactory. Further screening of other Lewis acids such as In(OTf)$_3$, Yb(OTf)$_3$, Sc(OTf)$_3$, and Zn(OTf)$_2$, revealed that Zn(OTf)$_2$ afforded the best enantioselectivity with greater than 99.5% *ee* for two diastereoisomers (entry 9), and Sc(OTf)$_3$ gave the highest conversion, but with a lower *ee* value (entry 7). After a survey of solvents, Zn(OTf)$_2$ in toluene was found to provide excellent *ee* values and the highest d.r. value (1:10), although the yield was lower (entry 11). Finally, Zn(OTf)$_2$ with dichloroethane was selected as the optimum reaction conditions.

With optimized reaction conditions in hand, we set out to explore the scope of the cyclization. As shown in Table 2, the

Table 1: Optimization of the iridium-catalyzed indole cyclization reaction.[a]

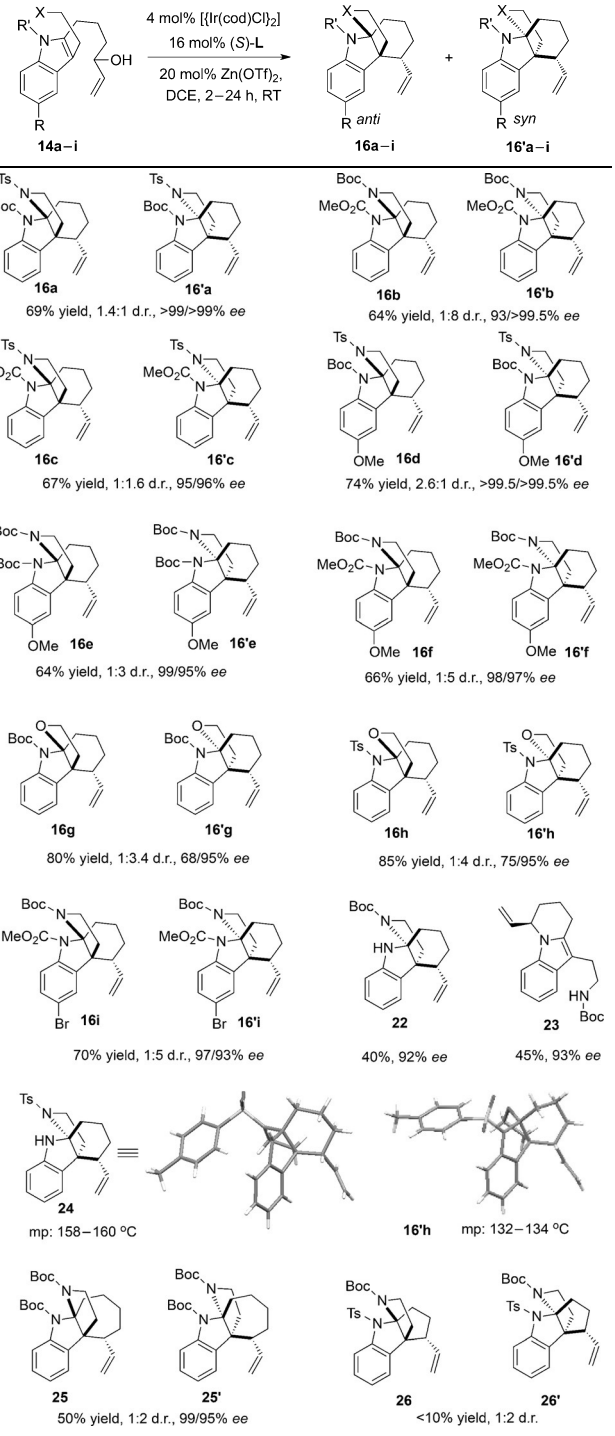


14a **16a** (*anti*) **16'a** (*syn*)

Entry	Promoter (mol%)	Solvent	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]
1	TFA (20)	$(CH_2Cl)_2$	38	1:5	93, 93
2	TfOH (20)	$(CH_2Cl)_2$	54	1:1.7	46, 18
3	$P(O)(OBu)_2OH$ (50)	$(CH_2Cl)_2$	23	1:5	97, 97
4	$Bi(OTf)_3$ (10)	$(CH_2Cl)_2$	58	1:2	75, 25
5	$In(OTf)_3$ (10)	$(CH_2Cl)_2$	56	1:2	82, 30
6	$Yb(OTf)_3$ (10)	$(CH_2Cl)_2$	43	1:0.8	97, 78
7	$Sc(OTf)_3$ (10)	$(CH_2Cl)_2$	88	1:1.1	86, 25
8	$Zn(OTf)_2$ (10)	$(CH_2Cl)_2$	65	1:0.7	>99.5, >99.5
9	$Zn(OTf)_2$ (20)	$(CH_2Cl)_2$	69	1:0.7	>99.5, >99.5
10	$Zn(OTf)_2$ (50)	$(CH_2Cl)_2$	65	1:0.7	>99.5, 96
11	$Zn(OTf)_2$ (20)	toluene	47	1:10	94, 98
12	$Zn(OTf)_2$ (20)	DMF	n.r.	–	–
13	$Zn(OTf)_2$ (20)	THF	28	1:1.7	94, 81

[a] Reaction conditions: **14a** (0.1 mmol, 1.0 equiv), [{Ir(cod)Cl}$_2$] (4 mol%), (*S*)-**L** (16 mol%), promoter, solvent (3.0 mL), RT, 24 h. [b] Yield of **16a** plus **16'a** after purification by chromatography. [c] Ratio measured by ^{1}H NMR analysis. [d] Enantiomeric excess determined by chiral-phase HPLC analysis. Values given are those for the *anti* and *syn* isomers, respectively. cod = 1,5-cyclooctadiene, DMF = *N*,*N*-dimethylformamide.

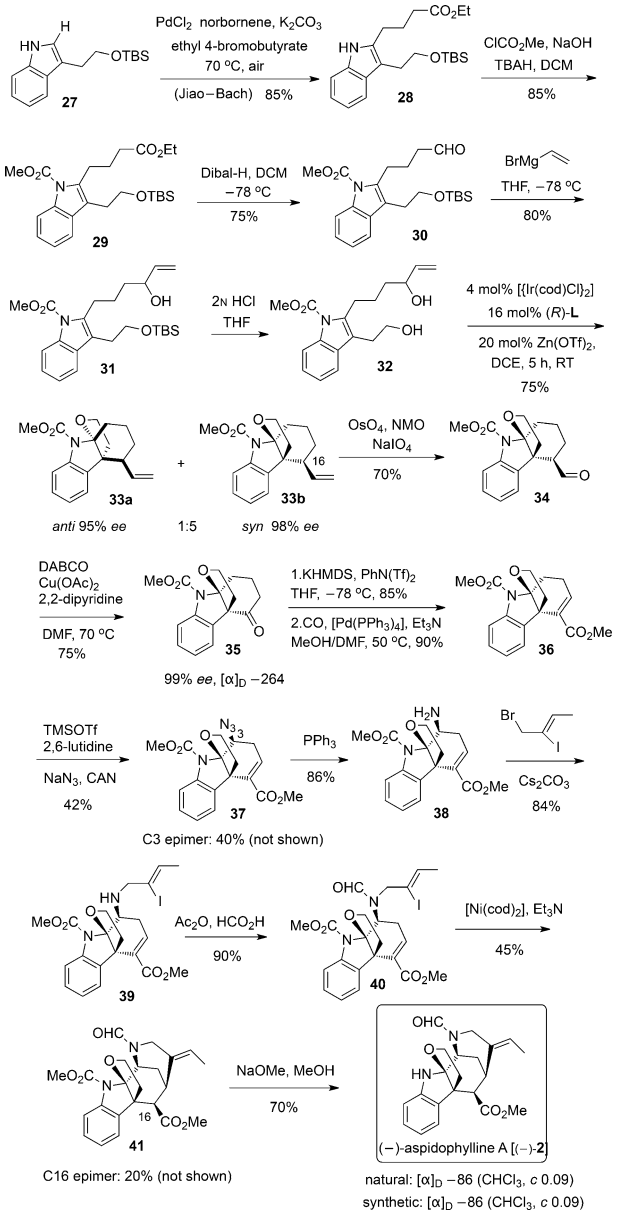
Table 2: Scope of the iridium-catalyzed indole cyclization reaction.[a,b,c,d]



[a] Reaction conditions: **14a–i** (0.1 mmol, 1.0 equiv), [{Ir(cod)Cl}$_2$] (4 mol%), (*S*)-**L** (16 mol%), promoter, solvent (3.0 mL), RT, 2–24 h monitored by TLC. [b] Yields of **16a–i** plus **16'a–i** after purification by chromatography. [c] Ratio measured by ^{1}H NMR analysis. [d] Enantiomeric excess determined by chiral-phase HPLC analysis.

reaction proceeded well with a wide range of 2,3-disubstituted indole substrates,[27] including substrates bearing the common protecting groups such as Boc, -CO_2Me, and Ts on N1 and those having a pendant heteroatom nucleophile at C3 (X = NHTs, NHBoc, OH), thus delivering a series of pyrroloindoline and furoindoline tetracyclic akuammiline frameworks (**16a–i** and **16'a–i**) in good yields with excellent enantiocontrol. 5-Substituted (OMe or Br) indoles can also undergo cyclization in good yields with excellent enantioselectivities. Interestingly, when the protecting-group free N1 substrate **14** (R, R' = H; X = -NHBoc) was used, the above cyclization gave a single diastereoisomer, **22**, together with the N1 alkylated tricycle **23**.[28] From all the cyclization products, the pyrroloindoline tetracycle **24**, obtained by removal of the Boc group of **16'a**, and furoindoline **16'h** are crystalline compounds, whose relative and absolute stereochemical configurations were verified by the X-ray crystallographic analysis.[29] In addition, the above cyclization was used in the formation of the tetracycles **25** and **25'**, which feature a seven-membered ring, however, it was unsuccessful for the formation of the five-membered ring analogues **26** and **26'**.[30]

To demonstrate the synthetic utility of this new cyclization, we turned our attention to the total synthesis of the akuammiline alkaloid (−)-**2**, and it began with production of the requisite 2,3-disubstituted indole derivative **32** for the key iridium-catalyzed cyclization. As shown in Scheme 4, we were delighted to find that the desired substrate **32** could be prepared in five steps from the known 3-(2-(tert-butyldimethylsilyloxy)ethyl)-1*H*-indole (**27**). Direct C2 alkylation of **27**, by using the protocol of Jiao and Bach,[26] proceeded uneventfully and the product **28** was advanced to the substrate **32** by using a standard four-step protocol. Given the absolute stereochemistry of the major tetracyclic furoindoline **16'h**, which had been established through X-ray crystallographic analysis (Table 2), we decided to use (*R*)-**L** as



Scheme 4. Enantioselective catalytic total synthesis of (−)-aspidophylline A [(−)-**2**] and assignment of its absolute stereochemistry. CAN = ceric ammonium nitrate, DABCO = 1,4-diazabicyclo[2.2.2]octane, DCE = 1,2-dichloroethane, HMDS = hexamethyldisilazide, NMO = *N*-methylmorpholine-*N*-oxide, TBAH = tetra-*n*-butylammonium hydroxide, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

the ligand in the iridium-catalyzed cyclization to obtain the same stereochemistry as that found in (−)-**2** (as drawn in Figure 1 and the literature).[2,3,5,6] After subjecting **32** to the standard reaction conditions of the iridium-catalyzed cyclization, an inseparable diastereomeric mixture of **33a** and **33b** in a 1:5 ratio was obtained with excellent *ee* values for both isomers.

Having assembled the desired tetracycle, we turned our attention to replacing the terminal vinyl group at C16 with a carbonyl group en route to the desired akuammiline ketone **35**. Upon oxidative cleavage of the terminal vinyl group of diastereomeric mixture, a diastereomerically pure aldehyde **34** was isolated in 70% yield with flash column chromatography. Thus the obtained aldehyde was smoothly converted into **35** in 75% yield with 99% *ee* under the copper-catalysis conditions developed by Rheenen.[31] Upon vinyl triflation of **35** and palladium-catalyzed methoxycarbonylation, the tetracyclic α,β-unsaturated ester **36** was obtained in high yield. Installation of the nitrogen atom at C3, according to Zhu's protocol, afforded the desired β-configured azide **37** in an acceptable 42% yield upon isolation, along with 40% of its α-configured epimer. Reduction of **37** under Staudinger conditions[32] provided the primary amine **38**, which was subsequently alkylated with (*Z*)-1-bromo-2-iodobut-2-ene,[33] thus yielding the vinyl iodide **39**. N-formylation of **39** under standard reaction conditions gave the N-formamide **40**. To close the final ring, a nickel-catalyzed cyclization[34] was utilized according to procedure of Ma and co-workers,[5] and then the expected pentacyclic product **41** was obtained in 45% yield. Finally, cleavage of the carbamate[6] at N1 delivered (−)-**2**. Our NMR data of the synthetic sample are in agreement with those in the literature. The synthetic (−)-**2** exhibits a rotation of −86 (*c* 0.09, $CHCl_3$), exactly identical to that of the natural substance.[2] Therefore, the absolute stereochemistry of (−)-**2** has been established as shown in Scheme 4.

In summary, we have developed a new enantioselective indole cyclization strategy for the asymmetric synthesis of akuammiline alkaloids. The cyclization reaction employs a combination of Lewis acid activation with an iridium catalyst and the ligand (*S*)-**L**, and the readily accessible 2,3-disubstituted indoles (**14**) as starting materials. Based on this reaction, the first asymmetric total synthesis, including the assignment of the absolute configuration of (−)-**2**, has been achieved.[13] Further application of the iridium-catalyzed asymmetric cascade cyclization to the total synthesis of other monoterpene indoles are under investigation and will be reported in due course.

Acknowledgments

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Keywords: cyclizations · enantioselectivity · indoles · iridium · total synthesis

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