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Kinetic Resolution and Dynamic Kinetic Resolution of Chromene by Rh-Catalyzed Asymmetric Hydroarylation **

Qingjing Yang, Yanbo Wang, Shihui Luo and Jun (Joelle) Wang*

Abstract: A highly efficient kinetic resolution and dynamic kinetic resolution of chromene is reported for the first time *via* a Rh-catalyzed asymmetric hydroarylation pathway. This newly developed approach offers a versatile access of various chiral 2,3-diaryl-chromenes containing two vicinal stereogenic centers as well as the recovered chiral flavenes in high yields with excellent *ee* (*s* factor is up to 532). Particularly noteworthy is that this strategy can be further extended to the establishment of a dynamic version of kinetic resolution of chromene acetals, in which it allows complete access of chiral isoflavanes and α-aryl hydrocoumarin successfully.

Flavonoids are privileged structural motifs in numerous natural products and pharmaceutical molecules, which show many biological activities such as antitumor, antioxidant, antibacterial and anti-inflammatory properties.[1] Flavene, flavane and isoflavane which feature a chiral center are subgroups of flavonoid. Given the prevalence of this structural unit, there has been considerable interest in developing methods for the generation of flavene skeletons. Nevertheless, facile access of their corresponding optically active variants *via* asymmetric catalysis remains limited. [2]

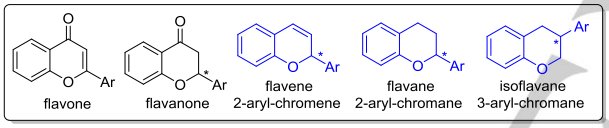
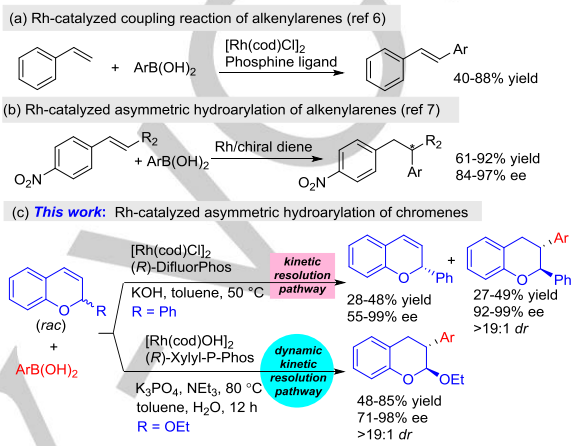


Figure 1. Structures of chiral flavonoids.

Rh-catalyzed asymmetric arylation have been intensively investigated in recent years, however, the alkenes were limited mainly to those activated by proximal electron-withdrawing substituents (represented by carbonyl groups).[3] In fact, examples concerning the Rh-catalyzed asymmetric arylation of alkene are rare. In 2008, Lautens reported an asymmetric hydroarylation process in the reaction of bicyclo[2.2.1]heptane system.[4] Recently, Hayashi also reported several successful examples of aymmetric hydroarylation of cycloalkene.[5] To the alkenylarene substrates, Lautens reported the Rh-catalyzed asymmetric addition of arylboronic acid compounds to simple styrenes that resulted in Heck-type products, owing to the alkylrhodium intermediate often prefers β-H elimination rather than protonation (Scheme 1a).[6] The asymmetric hydroarylation of styrene was realized by Lam where the strongly electron-withdrawing group (-nitro) at the *para*-position of arene was prerequisite to afford the desired hydroarylation product (Scheme 1b).[7] Thus, we select *2H*-chromene skeleton as substrates, in which the arylrhodium intermediates do not have *syn* β-hydrogens for β-hydrogen elimination, and they will undergo protonation to give hydroarylation products.



Scheme 1. Rh-catalyzed addition of arylboronic acids to alkenylarene

We embarked on this investigation using *rac*-flavene **1a** as the benchmark substrate and phenylboronic acid **2a** as the arylating agent (Table 1). To our delight, the arylation product **3aa** with vicinal chiral center was obtained as single diastereomer in 48% isolated yield with 94% *ee*, and the recovered **1a** was also obtained in 31% yield with 95% *ee*, catalyzed by the chiral Rh complex *in-situ* generated from 2.5 mol % $[Rh(cod)Cl]_2$ and 6 mol % (*R*)-Binap (Table 1, entry 1). With the hopeful initial results, other chiral bisphosphine ligands with different backbones were then evaluated. Generally, all these ligands provided hydroarylation product **3aa** with *trans*-stereoselectivity exclusively in 32-55% yields and 77-97% *ee* accompanied with 25-44% yields of enantio-enriched starting materials in 67-99% *ee* (*s*-factor is 39-183). Among ligands being surveyed, (*R*)-Difluorphos gave the best yield and enantioselectivity with excellent selectivity factor (183) (Table 1, entry 4). Further optimization of the solvents and reaction temperature revealed that the optimal reaction condition was 2.5 mol % $[Rh(cod)Cl]_2$ combination with 6 mol % (*R*)-Difluorphos in toluene at 50 °C, using 2.5 equivalent KOH as base (*see* supporting information).

With the optimized reaction conditions, we next examined the scope of flavenes with various substituents on benzopyran or C2-phenyl ring (Table 2). The substituents on both the benzopyran core and C2-aryl group had limited effect on the enantioselectivity. Generally, the reactions provided the *trans*-arylated products **3aa-3oa** as the single diastereomer with excellent enantioselectivities (92-98% *ee*) accompanied with recovered (*R*)-flavenes in 87->99% *ee* (*s* factor is 74-244). No significant steric effects were observed as good yield and high *ee* were maintained for flavene **1h** with the *ortho* substituent on the C2-phenyl ring, as well as product **3ha**. The hydroarylation of 2-aryl chromenes with electron-donating group at the 6- or 7-

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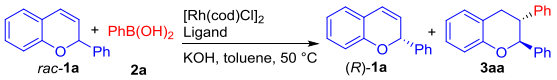
position (**1l**, **1m** and **1n**) were found sucessful, and furnished the desired products **3la**-**3na** in good yields (42-44% yield) with excellent enantioselectivities (95-97% *ee*). The *racemic* flavenes bearing -F or -Cl group (**1k** and **1o**) were also tolerated. To our delight, 2-alkyl-chromene **1p** also worked well under this reaction conditions, giving hydroarylation product **3pa** in 40% yields and 93% *ee* and recovering starting material in 30% yields with 99% *ee* (*s* factor is 155). The enantioenriched chromenes obtained by the kinetic resolution could be easily transform to the chromane scaffold by hydrogenation without notable loss of the enantiomeric purity.It should be noted that the hydrogenation product of (*R*)-**1q** is an inhibitor of rhinovirus (BW683C).[8]

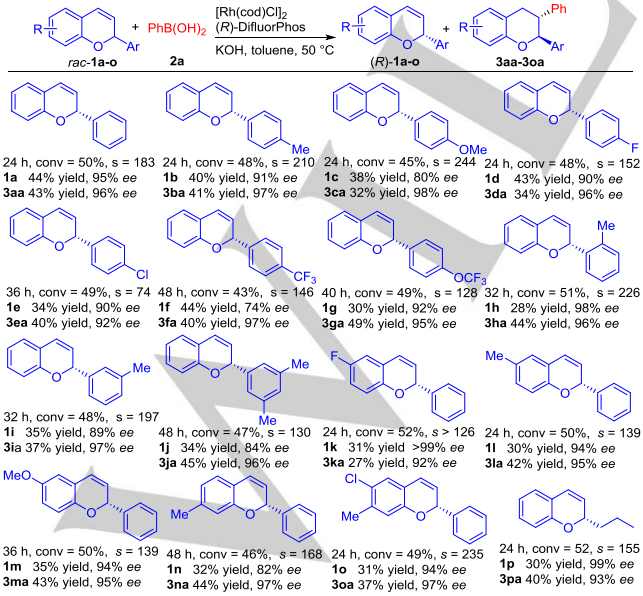
Table 1. Initial screening of ligands. [a]

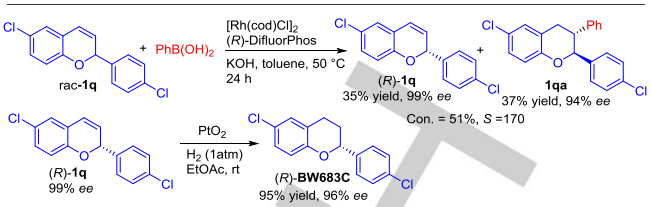


entry	ligand	**1a**[b] yield %	**1a**[d] *ee* %	**3aa**[b,c] yield %	**3aa**[d] *ee* %	conv[e] (%)	*S*[f]
1	(*R*)-Binap	31	95	48	94	50	121
2	(*R*)-Xyl-Binap	28	99	32	77	56	39
3	(*R*)-Synphos	25	99	55	85	54	64
4	(*R*)-Difluorphos	44	95	43	96	50	183
5	(*R*)-Biphep	36	67	42	97	41	132
6	(*R*)-Segphos	26	97	44	93	51	116
7	(*R*)-P-Phos	38	80	44	97	45	162
8	(*R*)-Xyl-P-Phos	40	84	33	97	48	175
9	(*R*)-Garphos	28	92	48	92	50	79

[a] Reaction conditions: $[Rh(cod)Cl]_2$ (2.5 mol %) and ligand (6 mol %) in solvent (1 mL) were stirred at rt for 30 min under argon. **1a** (0.2 mmol), **2a** (0.48 mmol), KOH (0.5mmol) were then added. The result mixtures were stirred at 50 °C for 24 h. [b] Isolated yield. [c] Diastereomeric ratio (dr) > 99:1 (determined by ^{1}H NMR). [d] Determined by chiral HPLC. [e] Calculated conversion, $C = ee_{1a}/(ee_{1a} + ee_{3a})$. [f] Selectivity factor (s) = $\ln[(1 - C)(1 - ee_{1a})]/\ln[(1 - C)(1 + ee_{1a})]$. cod = 1,5-cyclooctadiene.

Table 2. Scope of flavenes[a] and transformation of flavene (*R*)-**1q**.

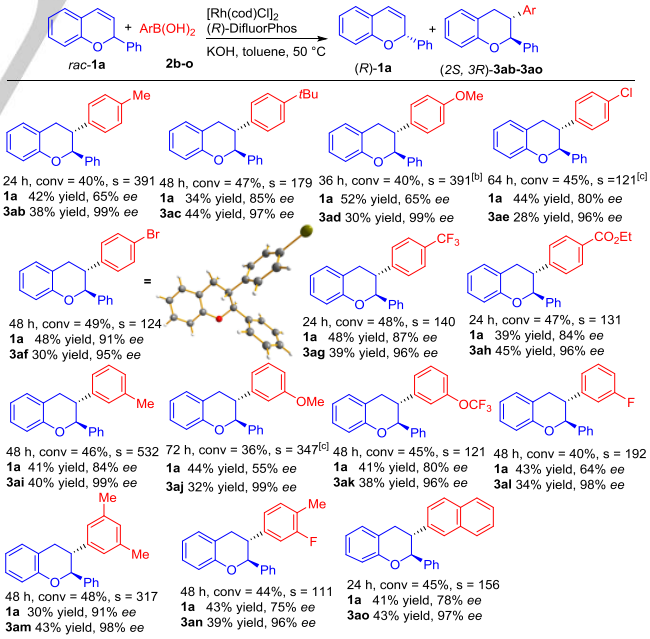




[a] Reaction conditions: $[Rh(cod)Cl]_2$ (2.5 mol %) and (*R*)–Difluorphos (6 mol %) in solvent (1 mL) were stirred at rt for 30 min under argon. **1a-o** (0.2 mmol), **2a** (0.48 mmol), KOH (0.5 mmol) were then added. The mixture was stirred at 50 °C for indicate period of time. Isolated yields were shown; *ee*s were determined by HPLC analysis.

To further test the efficacy of the catalyst system in obtaining the substituted chiral 2,3-diaryl-chromanes, a series of arylboronic acids **2b-2o** were examined (Table 3). Most of the desired 2,3-diaryl-chromanes were obtained in good yields (28-45% yields) with excellent enantioselectivities (95-99% *ee, s* factor is 111-532). Arylboronic acids having electron-withdrawing substituents (-CF_3, -CO_2Et) on the aromatic ring were accommodated with excellent product enantioselectivities (**3ag** and **3ah**). The electron-donating methoxy group was also compatible, albeit with lower conversion (**3ad**, **3aj**). The chloro and bromo groups remained intact under the present reaction conditions (**3ae** and **3af**), that allows further potential functionalization. However, the reactions of *ortho*-substituted arylboronic acids were sluggish, and only afforded trace products. Finally, the configuration of recovered **1a** was assigned as *R* configuration by comparison with literature data of the known compound,[2c] and this absolute configuration of **3af** was unambiguously confirmed as (*2S, 3R*) by X-ray crytallographic analysis.[9]

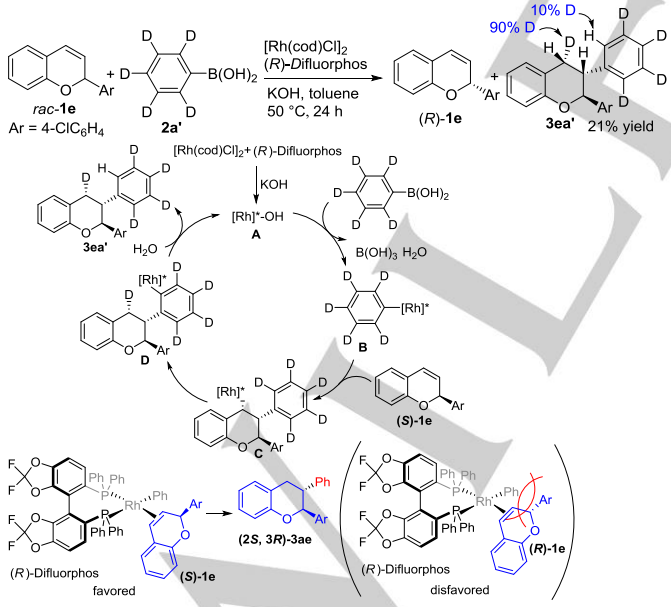
Table 3. Scope of arylboronic acids.[a]



[a] Reaction conditions: $[Rh(cod)Cl]_2$ (2.5 mol %) and (*R*)–Difluorphos (6 mol %) in solvent (1 mL) were stirred at rt for 30 min under argon. **1a** (0.2 mmol), **2b-o** (0.48 mmol), KOH (0.5 mmol) were then added. The mixture was stirred at 50 °C for indicate period of time. Isolated yields; *ee*s were determined by HPLC analysis. [b] Tris(4-carbo methoxyphenyl)boroxine was used. [c] $[Rh(cod)Cl]_2$ (5 mol %) and (*R*)-Difluorphos (12 mol %) were used.

To better understand the mechanism, a deuterium labeling experiment was performed (*see* supporting information for detail). The hydroarylation of **1e** under the optimized conditions using D_5-phenylboronic acid **2a'** gave the product **3ea'** labelled with deuterium at the C4-position (90% D) (Scheme 2). A small amount of deuterium (10% D) was reserved at the *ortho*-position of phenyl group derived from the D_5-phenylboronic acid. On the basis of the deuterium incorporation studies, the hydroarylation mechanism is proposed and is shown in Scheme 2. Phenylrhodium species **B**, generated from chiral hydroxorhodium species **A** by transmetalation, adds to flavene **1e** to generate alkylrhodium intermediate **C**. With the conformationally rigid structure of intermediate **C**, cis hydrogens for β-elimination are not available, and hence 1,4-Rh shift from alkyl carbon to *ortho* position of phenyl ring[4a, 5c] takes place to generate intermediate **D** because Rh-C_{sp2} intermediate was thermodynamically more stable than Rh-C_{sp3} intermediate. Thus, intermediate **D** leads to the main product of **3ea'** after protonolysis. The (2*S*, 3*R*) configuration of the product 2,3-diaryl chromene **3ae** which was obtained with (*R*)-Difluorphos is rationalized by the coordination of flavene (*S*)-**1e** to chiral phenylrhodium species with its α-*re* face. The coordination of chiral Rh-Ph complex with flavene (*R*)-**1e** is much less favorable due to the high steric repulsions between arene moiety of flavene and the phenyl group at the phenylrhodium species. In such a situation, (*S*)-flavene is competitively consumed allowing isolation of (2S, 3*R*) 2,3-diaryl chromene together with a remaining optically pure substrate (*R*)-flavene.

Scheme 2. Deuterium labeling experiment, proposed mechanism and stereochemical pathway for the Rh-catalyzed hydroarylation of flavene.

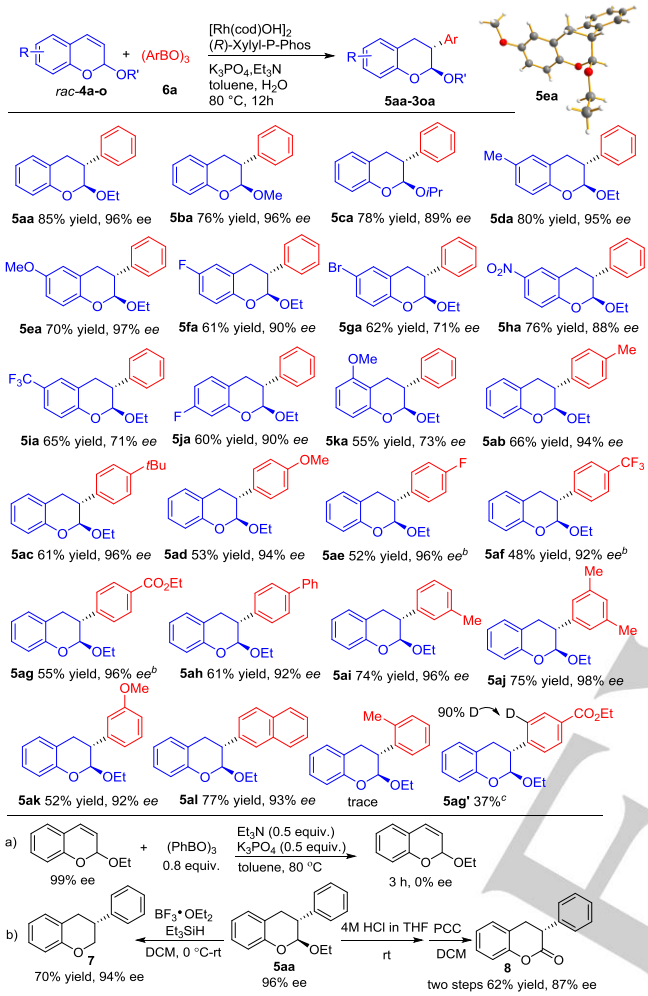


This developed kinetic resolution of flavenes *via* Rh-catalyzed asymmetric hydroarylation of 2-aryl chromene is highly efficient (*s* factor is up to 532). Additional attempt of dynamic kinetic resolution process in which the maximum theoretical yield is 100% would be highly desirable. The fundamental requirement of DKR is that the two substrate enantiomers can undergo rapid *in situ* interconversion under the same reaction conditions.[10] Based on Metz's kinetic resolution of flavanones[11], a dynamic kinetic resolution version was developed through a conjugate elimination/conjugate addition pathway in concert with asymmetric ketone transfer hydrogenation step.[12] Therefore, we surveyed the chromene acetal **4a** in our preliminary trial. In previous report, the addition of the aryl-rhodium to chromene acetals occured at the C2-position to give 2-aryl chromene under base-free conditions.[13] Herein, the hydroarylation product **5aa** was obtained in 43% yield with 90% *ee*, accompanied with several decomposition byproducts catalyzed by 2.5 mol % $[Rh(cod)Cl]_2$ combination with 6 mol % (*R*)-Difluorphos, using 2.5 equivalent KOH as base. As expected, the recovered substrate was found to be a racemate. Encouraged by these preliminary results, we further optimize the reaction parameters for the possible dynamic kinetic resolution process (*see* supporting information Table S3). The use of (*R*)-Xyl-P-Phos ligand provided relatively good product yield and enantioselectivity. Further investigation of Rh precursor disclosed that $[Rh(cod)OH]_2$ showed higher reactivity. The product yield was further improved by using phenyl boroxine instead of $PhB(OH)_2$. Both the product yields and *ee* values were sensitive to the additive base. After extensive and elaborative optimization, we identified that the addition of 0.5 equivalent K_3PO_4 and 0.5 equivalent triethylamine rendered the full consuming of substrate and less byproducts, while maintaining high enantioselectivity. Under this condition, the interconversion of enantiomers is very rapid, and full racemization of optically pure ethoxy-chromene **4a** finished in 3 h (Table 4, Eq. a).

With these modified reaction conditions, the scope of the chromene acetals and arylboroxines was then tested. Both methyl acetal **4b** and isopropyl acetal **4c** were suitable substrates. Different substituent groups (such as -Me, -MeO, -F, -Br, $-NO_2$, $-CF_3$) at the 5-, 6- or 7-position of chromene acetal all worked well, and gave the desired products in 55-80% yields and 71-97% *ee*s. The absolute configuration of the product **5ea** was determined to be (2*S*, 3*R*) by single crystal X-ray crystallographic analysis.[9] The scope of organoboron reagents appeared to be broad, and both electron-withdrawing (e.g., product **5af**, **5ag**) and electron-donating group (e.g., product **5ad**, **5ak**) were found compatible under these conditions, while arylboronic acids with electron-withdrawing groups gave better results than corresponding arylboroxines. When D_2O was used as the co-solvent, the product **5ag'** was labelled with 90% deuterium at the *ortho*-position of phenyl group derived from phenylboroxine where the 1,4-Rh shift was happened. Reductive removal of the ethoxy group from acetal **5aa** was accomplished using BF_3•OEt_2 and triethylsilane to give (*R*)-isoflavane **7** with 70% yield and 94% *ee* (Table 4, Eq. b).[14] The hydrolysis and oxidation of acetal moiety **5aa** were also presented in a single procedure to give α-aryl hydrocoumarin **8** with 62% yield in a slightly decreased *ee* (87%) (Table 4, Eq. b).[15] In fact, both isoflavane and α-aryl hydrocoumarin are biologically active compounds, and relevant catalytic approaches for accessing

enantiomerically pure form of isoflavane[16] and α-aryl hydrocoumarin[17] are very limited.

Table 4. Scope of chromene acetals and arylboroxines,[a] racemization of ethoxy-chromene **4a**, and transformation of product **5aa**.



[a] Reaction conditions: $[Rh(cod)OH]_2$ (2.5 mol %) and (*R*)-Xylyl-P-Phos (6 mol %), and H_2O (0.2mmol) in toluene (1 mL) were stirred at rt for 30 min under argon. **4a-k** (0.2 mmol), $(ArBO)_3$ (0.16 mmol), and K_3PO_4 (0.1 mmol) and Et_3N (0.1 mmol) were then added. The mixture were stirred at 80 °C for 12 h. Isolated yields were shown; *ee*s were determined by HPLC analysis. [b] $ArB(OH)_2$ (0.48 mmol) was used instead of aryl boroxine (0.16 mmol) and H_2O (0.2 mmol). [c] 25 eq of D_2O was used instead of H_2O. DCM = dichloromethane. PCC = Pyridinium chlorochromate.

In summary, a novel kinetic resolution and dynamic kinetic resolution of chromene *via* Rh-catalyzed asymmetric hydroarylation is well-developed. Under the mild conditions, a variety of chiral 2,3-diaryl-chromanes containing two vicinal stereogenic centers as well as the recovered flavenes were afforded in good yields with excellent *ee*s. The deuterium labeling experiment and proposed mechanism revealed why hydroarylation product was resulted here instead of Heck-type products (*s* factor is up to 532). In addition, the strategy was further applied to the development of dynamic kinetic resolution of chromene acetals. The products obtained could be easily converted into either chiral isoflavanes (3-aryl chromanes) or hydrocoumarin successfully. We believe the study would have versatile application in the synthesis of natural products and bioactive compounds which contain chromene core.

Keywords: Asymmetric catalysis • Kinetic Resolution • Dynamic Kinetic Resolution • Hydroarylation • Flavonoids

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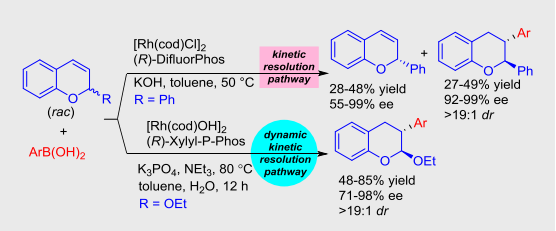

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