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Rhodium(III)−N-Heterocyclic Carbene-Driven Cascade C−H Activation Catalysis

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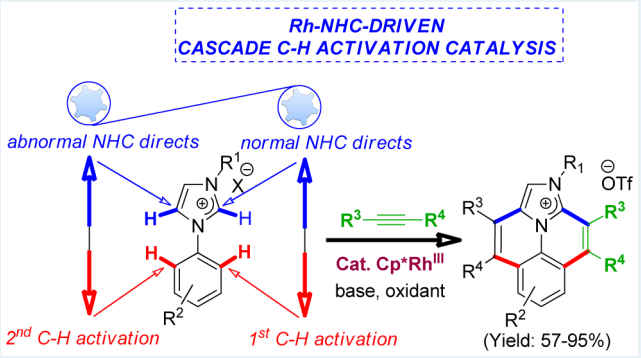
Supporting Information

ABSTRACT: Catalytic aromatic C−H bond activation and functionalization to useful molecules is highly important in chemical synthesis. This study introduces a novel use of the highly popular N-heterocyclic carbenes (NHC), for the first-time, in rhodium(III)-catalyzed cascade double aromatic C−H activation−annulation, within the backbone of readily available imidazolium substrates to synthesize a variety of nicely decorated polycyclic heteroaromatic molecules containing benzo[*ij*]imidazo[2,1,5-*de*]quinolizinium architectures which might be useful for developing new luminescent materials.



KEYWORDS: *C−H activation, rhodium(III), N-heterocyclic carbene, alkyne, annulation*

The transition-metal-catalyzed aromatic C−H bond activation/functionalization protocol represents an important template in the chemistry of synthesizing various conjugated polyheteroaromatic molecules, useful as organic semiconductors and luminescent materials.[1] Direct, step-economic functionalization with readily available starting materials, avoiding complicated multistep traditional procedures, with a great degree of efficiency and selectivity are the main advantages that led to such a huge success of the C−H activation strategy. To add more novelty and practicality, very recently, there has been special attention toward double/multiple C−H activation approach, which enables construction of highly conjugated beautiful architectures in one-pot via sequential reactions.[2] However, the discovery of such methodologies has always been challenging, and therefore, there are only a few reports of double/multiple C−H activation followed by annulative functionalization with alkynes described by the groups of Cheng and Chuang,[2a] Miura and Satoh,[2b−e] Huang,[2f] Wang,[2g] Chen,[2h] Li,[2i,j] and Shi[2k] during 2008−2014 (Scheme 1a). Strategically, a Lewis base N- or O-donor functional group, in-built within the substrate, is used as a directing group (DG) to facilitate such multiple C−H functionalization reactions. In contrast, the popular N-heterocyclic carbene (NHC) ligands have never been used as directing groups in multiple C−H functionalization chemistry mainly due to the robust, stable, and poorly reactive nature of the M−C_{NHC} bonds.[3] Herein, we demonstrate a novel strategy which not only uses the versatile M−C_{NHC} bond formation but also overcomes the challenges of the so-formed robust M−C_{NHC} bond functionalization, concomitant with a consecutive, double aromatic C−H activation−annulation, within the backbone of readily available imidazolium substrates to synthesize a variety of nicely decorated polycyclic heteroaromatic molecules containing benzo[*ij*]imidazo[2,1,5-*de*]quinolizinium scaffolds (Scheme 1b). The chemistry of the above cascade annulation relies on the unprecedented utilization of normal as well as abnormal NHC motifs as both directing and functionalizable groups in a sequential manner on a single molecular platform under rhodium(III) oxidative catalysis.[4]

Under standardized catalytic conditions, the reaction of 1-methyl-3-phenylimidazolium iodide (**1a**) (0.1 mmol) with diphenylacetylene (**2a**) (0.25 mmol) in the presence of $[Cp^*Rh^{III}Cl_2]_2$ (0.005 mmol) as catalyst precursor, anhydrous NaOAc (0.8 mmol) as base, and AgOTf (0.6 mmol) as oxidant in dichloroethane at 100 °C for 48 h afforded the bis-annulated product, 1-methyl-3,4,8,9-tetraphenylbenzo[*ij*]imidazo[2,1,5-*de*]quinolizinium triflate, **4a**, in excellent yield (91%) (Table 1), along with a trace amount of the monoannulated product, 3-methyl-4,5-diphenylimidazo[1,2-*a*]quinolinium triflate, **3a** (5%) (for detailed optimization studies, see Supporting Information, Table S1). The molecular structure of **4a** was unambiguously confirmed by single-crystal X-ray diffraction analysis, which was well supported by ^1H and $^{13}C\{^1H\}$ NMR spectra and mass spectrometry data (Table 1 and Supporting Information). It is noteworthy to mention that dioxane was also an alternative solvent for the above reaction to provide 90% yield of **4a**. Other solvents (MeCN, MeOH) were less effective in the bis-annulation reaction. Also, other oxidants $(Cu(OAc)_2$,

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Scheme 1. (a) Directing-Group-Assisted Multiple C−H Functionalization, (b) Normal and Abnormal NHC as Tandem Directing as well as Functionalizable Groups

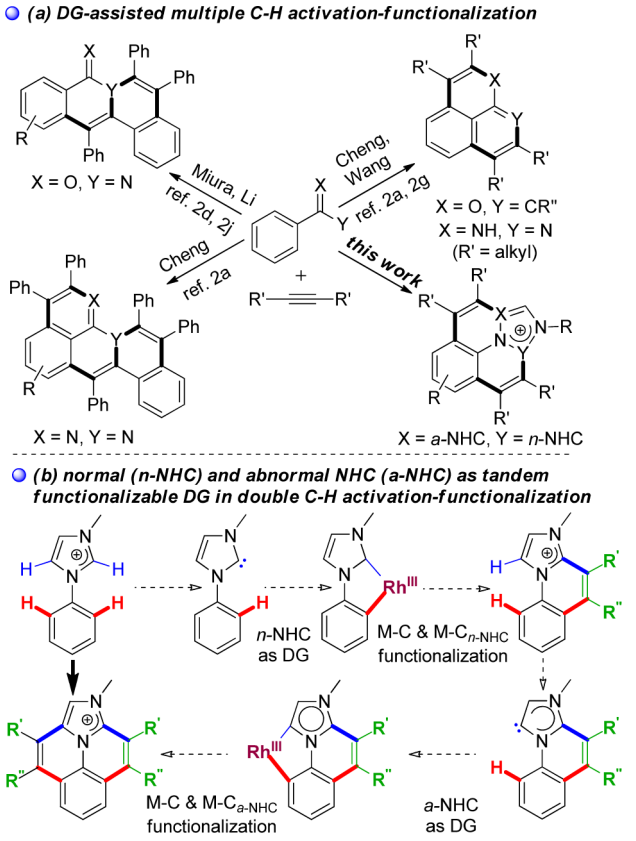
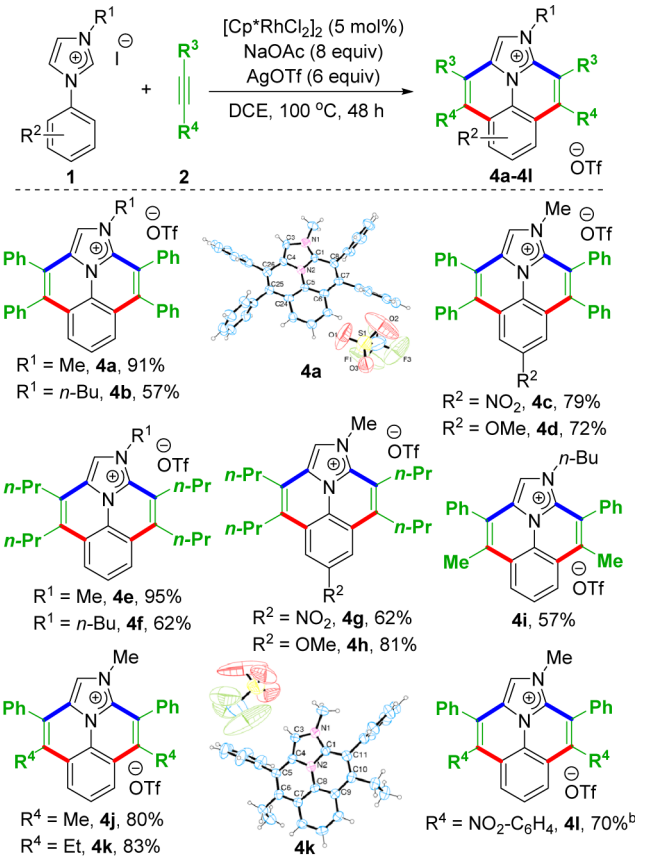


Table 1. Substrate Scope[a]



[a]Reaction conditions: **1** (0.1 mmol), **2** (0.25 mmol), catalyst (0.005 mmol), additives (as mentioned), $ClCH_2CH_2Cl$ (3.0 mL), dinitrogen atmosphere, 100 °C, 48 h. The yields indicate isolated yields after purification of the products by column chromatography. [b]A mixture of four regioisomers of **4l** was obtained in 70% combined yields.

O_2) or other catalyst precursor ($[Cp^*Ir^{III}Cl_2]_2$) were found ineffective. Similarly, shorter reaction time or lower catalyst/oxidant loading resulted in lower yield of **4a**.

With the optimized reaction conditions, this unique double C−H activation/annulative functionalization of NHC backbones was further explored by reacting various substituted imidazolium salts with several internal alkynes to provide double annulated products in moderate to good yields (Table 1). All the products were isolated and purified by column chromatography (silica gel, $CHCl_3$/acetone solvent mixture as eluent; see Supporting Information). Replacement of the methyl by an *n*-butyl group as one of the N-substituent in the NHC moiety reduced the yield of the corresponding product (**4b**, 57%). Interestingly, electronic modification of the *N*-phenyl wingtip on the *para* position did not affect the reaction, as both NO_2 and OMe substituents afforded good yields of **4c** (79%) and **4d** (72%), respectively. A similar trend was observed with dialkyl acetylene where the reaction was found to be high-yielding providing 95% of **4e** and 62% **4f**. Here also the electron-withdrawing and -donating groups on an *N*-phenyl wingtip resulted in similar good yields of the corresponding products **4g** and **4h**. Interestingly, phenyl−alkyl unsymmetrical alkynes provided single regioisomers of **4i**, **4j**, and **4k** in high yields. The structure of **4k** was unambiguously confirmed by single crystal X-ray diffraction study (Table 1 and Supporting Information). On the other hand, alkynes bearing two different aromatic rings, produced four regioisomeric products of **4l** in 70% combined yields.

To shed light on the mechanistic aspects of this novel Rh^{III}-catalyzed normal- and abnormal-NHC-directed double C−H activation/annulation reaction, a series of control studies have been performed. At first, an H/D exchange study was conducted to examine the nature of the C−H bond activation in the reaction. The results shown in Scheme 2a suggested that the $C(4)_{im}$−H and C_{phenyl}−H activations are reversible in nature. While the activation of these $C(4)_{im}$−H and C_{phenyl}−H bonds are obvious for an anticipated cyclometalation as required for the corresponding annulation reaction with the alkyne, the breaking of the $C(5)_{im}$−H bond was interesting, indicating the possibility of the substrate **3e** to act as a monodentate $C(5)_{carbene}$ ligand as well, in addition to the bidentate $C(4)_{carbene}\hat{}C_{phenyl}$ cyclometalating ligand.[5] To probe the above argument and to detect any plausible intermediate, a stoichiometric reaction of **2b**, **3e** and $[RhCp^*Cl_2]_2$ was subjected to ESI-MS analysis (Scheme 2b). The spectrum displayed the product (**4e**) peak at m/z = 375.2833 as expected; however, interestingly, the peak at m/z = 503.1966 indicates the cation $[RhCp^*(C(4)_{carbene}\hat{}C_{phenyl})]^+$ and a trace peak at m/z = 769.3744 suggested the generation of a species, $[RhCp^*(C(4)_{carbene}\hat{}C_{phenyl})(L)]^+$ (L = **3e**) in the reaction mixture in which the compound **3e** was bound to Rh^{III} in expected $C(4)_{carbene}\hat{}C_{phenyl}$ cyclometalating fashion with an additional monodentate $C(5)_{carbene}$-bound ligand.

The above encouraging results prompted us to attempt to isolate such a rhodium intermediate complex to confirm its existence in the catalysis. After several trials, a reaction between

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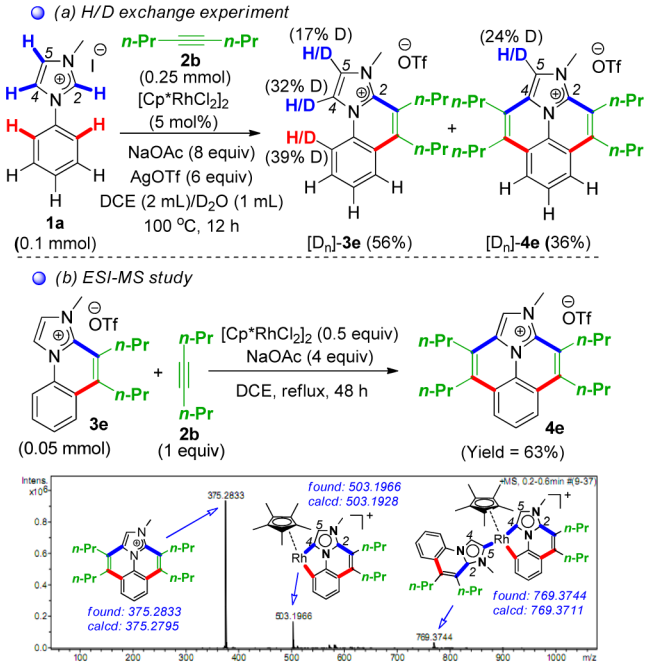
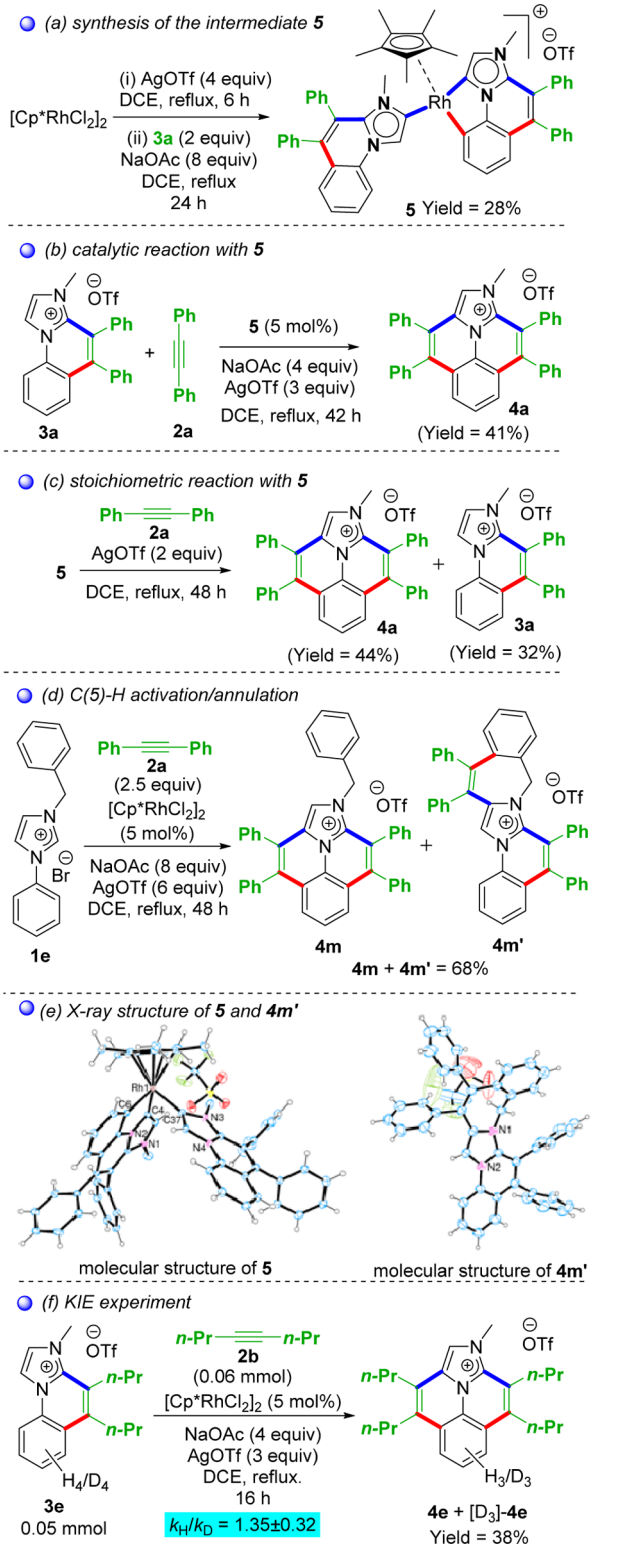
Scheme 2. Mechanistic Studies: (a) H/D Exchange, (b) ESI-MS Study



Scheme 3. Mechanistic Studies: (a) Synthesis and (b) Catalytic/(c) Stoichiometric Reaction of Intermediate 5, (d) C(5)−H Activation/Annulation, (e) X-ray Structures, (f) KIE Experiment



3a and $[RhCp^*Cl_2]_2$ in the presence of NaOAc in dichloroethane provided the complex **5** (Scheme 3a; see Supporting Information for detailed experimental procedure). The ^1H and $^{13}C\{^1H\}$ NMR and ESI-MS data of **5** suggested its structure as the one shown in Scheme 3a. Gratifyingly, the confirmation of such a structure came from the single crystal X-ray diffraction studies (Scheme 3e). As argued earlier, the molecular structure of **5** consisted of a $C(4)_{carbene}\hat{C}_{phenyl}$ cyclometalating **3a** chelated to Rh^{III} with an additional $C(5)_{carbene}$ bound **3a** at the metal center. It seems that under the basic condition applied in the reaction, the $C(5)_{im}$−H bond activated and acted as an abnormal carbene ligand to replace any anionic ligand (Cl or OAc) or solvent molecule bound to the rhodium center.

The plausible involvement of the complex **5** during the catalytic annulation reaction was examined by performing a catalytic as well as stoichiometric reaction, as shown in Scheme 3b and 3c, respectively. Thus, the stoichiometric reaction furnished the desired product **4a** in 44% yield, while the reaction with a 5 mol % loading of **5** as catalyst provided **4a** in 41% yield. These observations clearly suggested that **5** is a tenable intermediate in the present annulation reaction.

The significance of the $C(5)_{im}$−H activation (as indicated earlier by H/D exchange, ESI-MS, and crystallographic studies) during the catalysis was realized by conducting an annulation reaction with the substrate 1-benzyl-3-phenyl imidazolium bromide, **1e**, with alkyne **2a** (Scheme 3d). This reaction provided the expected bis-annulated product **4m** with an additional minor product **4m′** (in 68% overall yield). Interestingly, **4m′** consisted of a seven-membered cyclic ring system where the $C(5)_{im}$−H bond of **1e** was found to be activated and annulated with the pendant benzyl group via an aromatic C−H activation of the benzyl moiety. The molecular structure of such an interesting annulated product was confirmed by single crystal X-ray diffraction analysis (Scheme 3e). Finally, a kinetic deuterium isotope effect experiment was conducted as shown in Scheme 3f. A small k_H/k_D value of 1.35 ± 0.32 suggested that the C_{phenyl}−H activation step might not be involved in the rate-limiting step.

On the basis of the above mechanistic investigation, a plausible catalytic cycle is shown in Scheme 4.[2,4,6] The initial

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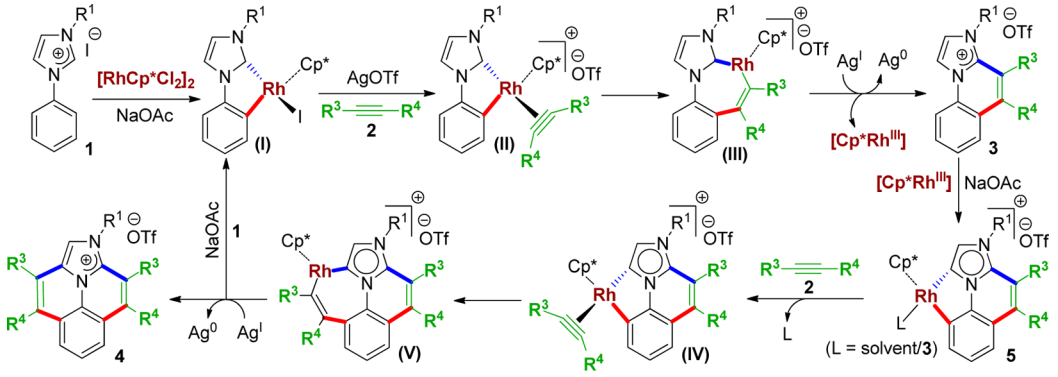
Scheme 4. Plausible Catalytic Cycle



step involves the formation of a five-membered rhodacycle **I** from the imidazolium substrate **1**, via *ortho* C−H activation directed by the coordinated NHC ligand, in the presence of NaOAc.[3d] Halide abstraction from **I** by AgOTf triggers coordination of alkyne **2** to generate intermediate **II**. Insertion of the coordinated alkyne into the Rh−C_{aryl} bond of **II** provides the seven-membered rhodacycle intermediate **III**. Subsequent reductive elimination from **III** in the presence of Ag^{I} affords the monoannulated product **3** and a Cp*Rh^{III} species. In the presence of NaOAc, **3** is activated to coordinate with the rhodium center again as an abnormal NHC which directs the *ortho* C−H activation of **3** to form the intermediate **5**. A second round of coordinative insertion of alkyne **2** (**IV** to **V**) followed by reductive elimination in the presence of Ag^{I} results in the product **4** and regenerates the Cp*Rh^{III} species to continue the catalytic cycle via reaction with **1** and NaOAc. Isolation and characterization of the other intermediates and DFT studies are underway to fully validate the proposed pathway, including the NHC/alkyne insertion possibility (in **II** to **III** and **IV** to **V**) as suggested by Bergman and Ellman, and Cavell.[7]

Some of these benzo[*ij*]imidazo[2,1,5-*de*]quinolizinium motif-containing bis-annulated products exhibited strong fluorescence emission at 455−465 nm range, which suggests the potential of this class of ionic compounds to be useful, solution-processable, new emitting materials (Figure S18). Detailed photophysical studies toward this direction are ongoing.

In conclusion, we have successfully demonstrated, for the first time, that a normal NHC and an abnormal NHC ligand not only directed two consecutive C−H activation reactions but also guided the sequential annulations via Rh−C_{NHC}/Rh−C_{aryl} bond functionalization with internal alkynes to construct a variety of nicely decorated benzo[*ij*]imidazo[2,1,5-*de*]-quinolizinium scaffold-containing polycyclic heteroaromatic molecules. A series of control studies suggested the proposed mechanistic sequence involving NHC-directed C−H activation/insertion/annulative reductive elimination/oxidative catalyst regeneration in the catalytic cycle. This new and simple method appears to have the potential for the synthesis of new class of organic functional materials. Full mechanistic investigation and diverse application of this newly developed protocol is the subject of current research in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The following files are available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b00243.

Experimental details; spectra (PDF)
CIF file of **4a** (CIF)
CIF file of **4k** (CIF)
CIF file of **4m** (CIF)
CIF file of **5** (CIF)

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Notes

The authors declare no competing financial interest.

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(5) Under identical reaction conditions but in the absence of Rh-catalyst, the D-incorporation into the imidazolium backbone protons of **1a**, $C(2)_{im}$−H, $C(4)_{im}$−H, and $C(5)_{im}$−H was observed to be 16%, 31%, and 8% respectively. However, as expected, there was no H/D exchange into the phenyl *ortho*-protons. Similarly, in case of **3e**, the $C(4)_{im}$−H and $C(5)_{im}$−H protons were exchanged with D in 31% and 12% respectively, without any H/D exchange into the phenyl *ortho*-proton. See Supporting Information for details.

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