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Directing-Group-Controlled Ring-Opening Addition and Hydroarylation of Oxa/azabenzonorbornadienes with Arenes via C−H Activation

Keyang Zhang,[▽] Ruhima Khan,[▽] Jingchao Chen, Xuexin Zhang, Yang Gao, Yongyun Zhou,* Kangkui Li, Youxian Tian, and Baomin Fan*

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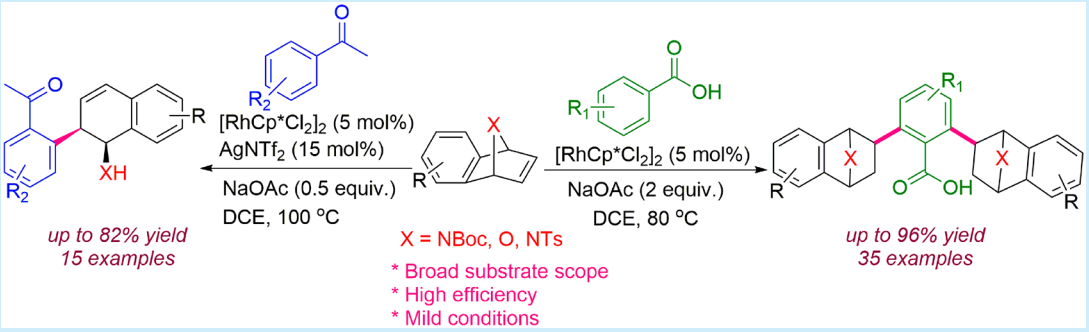

ABSTRACT: An efficient method for the directing group controlled rhodium-catalyzed addition reaction of oxa/azabicylic alkenes with aromatic ketones and benzoic acids has been developed. The ketones and benzoic acids afforded different addition products when reacted with oxa/azabicyclic alkenes. The reaction between ketones and azabenzonorbornadienes furnished the ring-opening addition products. The reaction between benzoic acids and aza/oxabicyclic alkenes proceeded in the absence of silver salt, giving the 1:2 hydroarylation products in yields up to 96%.

The direct functionalization of C−H bonds has become a prominent method for the construction of new C−C bonds in organic synthesis.[1] The regioselectivity in C−H bond functionalization controlled by various directing groups (DG) is now regarded as an atom- and step-economical synthetic tool, since such transformations do not require prefunctionalization.[2] Since the pioneering work by Murai and co-workers on Ru-catalyzed addition of C−H bonds to olefins,[3] the transition-metal-catalyzed C−H bond functionalization with various directing groups has provided a straightforward method for the regioselective construction of C−C and C-heteroatom bonds.[4] Among the various directing groups, the weakly coordinating ketone-directed *ortho*-C−H bond functionalization reactions offer an efficient and straightforward method for the synthesis of highly functionalized ketones. These reactions are catalyzed by transition metals such as Ru, Rh, Pd, Ir, Mn, Co, etc.[5] Recently, low coordinating carboxylates have also been successfully used as directing groups for *ortho*-C−H bond functionalization for the construction of C−C, C−O, C−N, C−S, C−P, C−halogen bonds in synthetic chemistry. The growing interest in the application of carboxylate as DG is because they are broadly abundant and they can be removed tracelessly or used for further functionalization/derivatization.[6] After the pioneering work by Miura et al.,[7] there have been various reports on the carboxylate-directed *ortho*-C−H bond functionalization of arenes.[8]

The transition-metal-catalyzed addition and ring-opening reaction of strained 7-oxa/azabenzonorbornadienes provide significant pathways for the introduction of new functionalities into the framework of organic compounds. Hence, it has emerged as an important transformation and has been employed in the preparation of a variety of organic products of biological interest featuring diverse functional groups.[9] Since the first work reported by the Li group,[10] the transition-metal-catalyzed addition of C−H bond to strained oxa/azanorbornadienes has become an interesting approach for the synthesis of polyaromatic compounds. In this context, Miura et al. demonstrated the rhodium-catalyzed direct coupling of arenes with heterobicyclic alkenes to form *ortho*-naphthylated products.[11a] There have been reports on the coupling reactions

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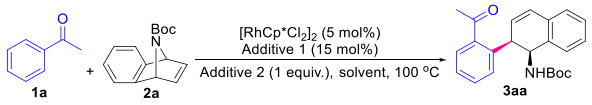
of oxa/azanorbornadienes with arenes via C−H bond activation under the catalysis of Ru,[12] Rh,[11,13] Co,[14] etc. Despite these achievements, it is still interesting to explore new C−H functionalization reactions with oxa/azanorbornadienes. Very recently, Li and co-workers demonstrated the first application of 7-azabenzonorbornadienes in Rh-catalyzed enantioselective desymmetrizative coupling reaction with *N*-pyrimidylindoles via C−H activation.[15a] The same group reported the Rh-catalyzed chemo-divergent coupling reaction of oxa/azabicyclic olefins with sulfoxonium ylides.[15b] We have been paying interest in the asymmetric ring-opening reactions (ARO) of oxa/azanorbornadienes.[16] As a part of our study, we have demonstrated the Rh(III)-catalyzed ring-opening addition of azabenzonorbornadienes with cyclic *N*-sulfonyl ketimines through C−H bond functionalization.[17] In continuation of our interest in the C−H bond functionalization reaction of oxa/azabenzonorbornadienes, we herein report the Rh-catalyzed ring-opening addition and hydroarylation of bicyclic alkenes through *ortho* C−H activation controlled by weakly coordinating directing groups ketone and carboxylate groups. The methodology provides a mild pathway for the synthesis of highly substituted aromatic compounds.

Considering the efficiency of $[RhCp^*Cl_2]_2$ in the ketone directed C−H bond functionalization of arenes, at the onset of our investigation, the reaction between acetophenone **1a** and azabenzonorbornadiene **2a** was performed using $[RhCp^*Cl_2]_2$ (5 mol %) as the metal catalyst in the presence of additives $AgSbF_6$ (15 mol %) and NaOAc (1 equiv) in 1,4-dioxane at 100 °C for 48 h. The regioselective ring-opening addition of **2a** occurred at the *ortho*-position of ketone and the desired product **3aa** was observed only in trace amounts (see Table 1, entry 1). The reaction was stereoselective as the *cis*-isomer was obtained as the only product. Screening of various solvents indicated that DCE was the most appropriate solvent (Table 1, entry 3). No reaction occurred in the absence of silver salt, showing that the additive is important for the present reaction (Table 1, entry 4). Next, a series of additives were screened.

Table 1. Optimization Table for Ring-Opening Addition Reaction[a]



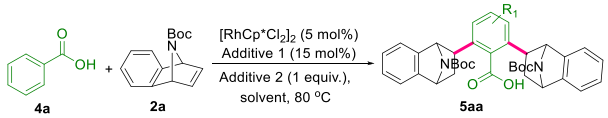
entry	additive 1	additive 2	solvent	time (h)	yield[b] (%)
1	$AgSbF_6$	NaOAc	1,4-dioxane	48	trace
2	$AgSbF_6$	NaOAc	CH_3CN	48	NR[c]
3	$AgSbF_6$	NaOAc	DCE	48	25
4	–	NaOAc	DCE	48	NR[c]
5	$AgNTf_2$	NaOAc	DCE	24	61
6	$ScOTf_3$	NaOAc	DCE	56	trace
7	$AgNTf_2$	–	DCE	24	NR[c]
8	$AgNTf_2$	LiOAc	DCE	36	55
9[d]	**$AgNTf_2$**	**NaOAc**	**DCE**	**12**	**66**
10[e]	$AgNTf_2$	NaOAc	DCE	17	51
11[f]	$AgNTf_2$	NaOAc	DCE	76	61
12[g]	$AgNTf_2$	NaOAc	DCE	24	53

[a]Reaction conditions: **1a** (0.6 mmol), **2a** (0.2 mmol), $[RhCp^*Cl_2]_2$ (5 mol %), additive 1 (15 mol %), additive 2 (1 equiv), solvent (2 mL). [b]Isolated yield. [c]NR = No reaction. [d]NaOAc (0.5 equiv) was used. [e]NaOAc (0.25 equiv) was used. [f]Reaction temperature was 80 °C. [g]$[RhCp^*Cl_2]_2$ (2.5 mol %) was used.

Gratifyingly, the yield was enhanced to 61% in 24 h when $AgNTf_2$ was used (Table 1, entry 5). The reaction did not occur when $AgNTf_2$ was used as the sole additive, demonstrating the indispensable role of NaOAc in the present reaction (Table 1, entry 7). To our delight, the desired product **3aa** was obtained in increased yield of 66% in just 12 h when 0.5 equiv of NaOAc was used (Table 1, entry 9). So, the following investigation was continued using 0.5 equiv of NaOAc (Table 1, entry 12) (see the Supporting Information for details).

The efficiency of $[RhCp^*Cl_2]_2$ in the carboxylate-group-directed C−H activation reaction has been reported by many groups.[18] We extended our study by using carboxylates as directing groups instead of ketones (see Table 2). Initially,

Table 2. Optimization of Reaction Conditions for Carboxylate Directed C−H Functionalization Reaction[a]



entry	additive 1	additive 2	solvent	time (h)	yield[b] (%)
1	$AgSbF_6$	NaOAc	DCE	3	95
2	$AgSbF_6$	NaOAc	THF	24	29
3	–	NaOAc	DCE	8	93
4	–	–	DCE	36	NR[c]
5	–	KOAc	DCE	15	85
6	–	K_2CO_3	DCE	13	trace
7	–	PivOH	DCE	11	NR[c]
8[d]	–	**NaOAc**	**DCE**	**8**	**96**
9[e]	–	NaOAc	DCE	4	92
10[f]	–	NaOAc	DCE	18	93

[a]Reaction conditions: **4a** (0.2 mmol), **2a** (0.2 mmol), $[RhCp^*Cl_2]_2$ (5 mol %), additive 1 (15 mol %), additive 2 (1 equiv), solvent (2 mL). [b]Isolated yield. [c]NR = No reaction. [d]NaOAc (2 equiv) was used. [e]Reaction temperature was 100 °C. [f]$[RhCp^*Cl_2]_2$ (2.5 mmol %) was used.

commercially available benzoic acid **4a** was treated with azabenzonorbornadiene **2a** in the presence of $[RhCp^*Cl_2]_2$ (5 mol %), $AgSbF_6$ (15 mol %), and NaOAc (1 equiv) in DCE at 80 °C. The reaction proceeded smoothly in 3 h, giving the 1:2 addition product **5aa** at both *ortho*-positions in excellent yield of 95% (Table 2, entry 1). Screening of other solvents gave inferior results. Surprisingly, the addition product **5aa** was obtained in 93% in 8 h when the reaction was performed without any silver salt, indicating that the addition reaction could be performed without using the expensive silver salts (Table 2, entry 3). Hence, the following studies were performed without using silver salts. No reaction occurred in the absence of the additional additive (Table 2, entry 4). Upon using a strong base (K_2CO_3), the addition product **5aa** was obtained in 82% after 6 h. However, upon extending the reaction time to 13 h, **5aa** reacted with the solvent DCE, giving the corresponding ester in 69% (Table 2, entry 6)[8s] (see the Supporting Information for details).

Having obtained the optimized reaction conditions, the scope of this interesting transformation was investigated. The reaction was compatible for a wide range of aromatic ketones (Scheme 1). Acetophenones bearing electron-withdrawing as well as electron-donating substituents at *para*-position (**1a**−**1f**) reacted smoothly with azabenzonorbornadiene **2a** to furnish

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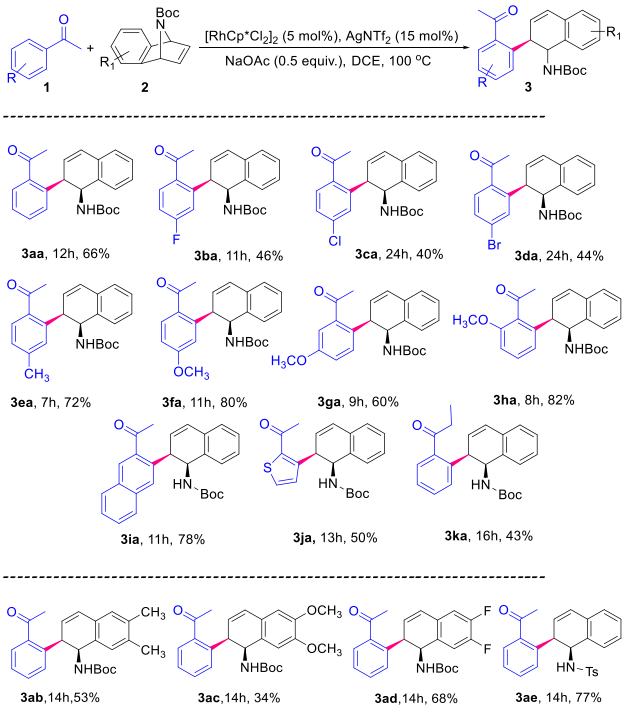
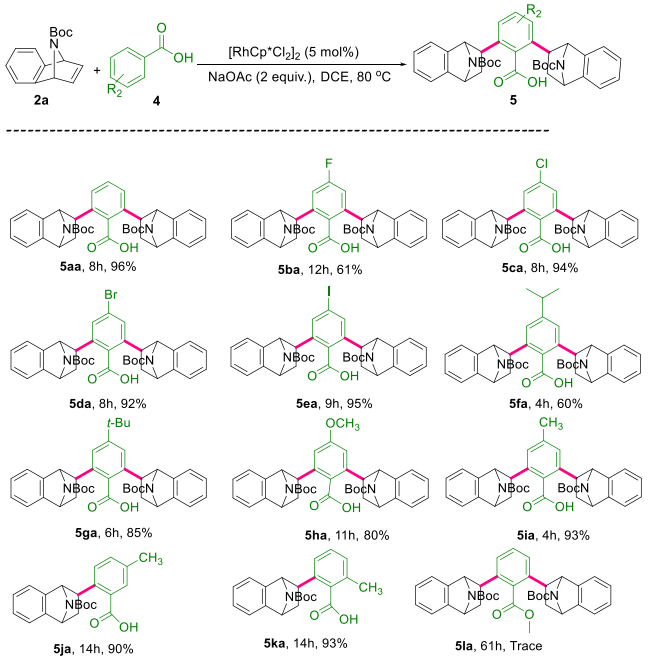
Scheme 1. Substrate Scope of Ring-Opening Addition Reaction[a,b]



[a]Reaction conditions: **1** (0.6 mmol), **2** (0.2 mmol), $[RhCp^*Cl_2]_2$ (5 mol %), $AgNTf_2$ (15 mol %), NaOAc (0.5 equiv), DCE (2 mL) at 100 °C. [b]Isolated yield.

Scheme 2. Substrate Scope with Respect to Benzoic Acids[a,b]



[a]Reaction conditions: **2** (0.2 mmol), **4** (0.2 mmol), $[RhCp^*Cl_2]_2$ (5 mol %), NaOAc (2 equiv), DCE (2 mL) at 80 °C. [b]Isolated yield.

the corresponding ring-opening addition products (**3ba**−**3fa**) in moderate to good yields. The electron-donating $-OCH_3$ group at both *meta*- and *ortho*-positions participated in the reaction and afforded the addition products **3ga** and **3ha** in 60% and 82% yields, respectively.

The methodology was also suitable for naphthylene derivative (**1i**) and heterocyclic compound 1-(thiophen-2-yl)ethan-1-one (**1j**). The methodology worked for the ketone with a longer aliphatic chain and gave the product **3ka** in 43% yield. The applicability of the catalytic system was evaluated with respect to bicyclic alkenes. *N*-Boc protected azabicylic alkenes with both electron-donating and electron-withdrawing substituents participated under the optimized reaction conditions to give the addition products (**3ab**, **3ac**, **3ad**) in low to good yields. *N*-tosyl-protected azabenzonorbornadiene also reacted smoothly.

Next, the substrate scope of the hydroarylation reaction via carboxylate-group-directed C−H activation reaction between different substituted benzoic acids and bicyclic alkenes was examined (see Scheme 2). The electronic nature of substituents at *para*-position of benzoic acid did not have a remarkable effect on the efficiency of the reaction. Benzoic acids with electron-withdrawing and electron-donating groups at the *para*-position participated in the addition reaction and the corresponding 1:2 addition products (**5ba**−**5ia**) were obtained in moderate to excellent yields. In the case of methyl group at *meta*- and *ortho*-positions, the 1:1 addition products (**5ja**, **5ka**) were obtained as the only products in 90% and 93% yields. This selectivity could be attributed to the steric interaction between the substituent and the incoming bicyclic alkene.[19a] Unfortunately, methyl benzoate was sluggish and the reaction was incomplete, even after extending the reaction time to 61 h, and gave the 1:2 addition product **5la** only in trace amounts.

The applicability of the present methodology was further illustrated with respect to different substituted bicyclic alkenes **2** in reaction with benzoic acid **4a** (Scheme 3). Azabenzonorbornadienes with both electron-donating and electron-withdrawing groups on the benzene ring were found to be suitable reaction partners under the optimized reaction conditions and furnished the corresponding 1:2 addition products **5ab**−**5af** in 82%−94% yields. *N*-tosyl-protected azabenzonorbornadiene **2g** also reacted smoothly with benzoic acid to give the corresponding product **5ag** in 93% yield. Next, the substrate scope was extended to oxabenzonorbornadienes. In the case of oxabicyclic alkenes, the reaction between oxabenzonorbornadiene **2h** and **4a** was incomplete under the optimized reaction condition used for azabenzonorbornadienes. Gratifyingly, upon using 2 equiv of KOAc instead of NaOAc, the reactants were consumed in 5 h and the desired 1:2 addition product **5ah** was obtained in 92% yield. 7-Oxabenzonorbornadienes with different substituents on the benzene ring reacted smoothly to give the desired products **5ai**−**5al** in good to excellent yields. The present methodology was found to be unsuitable for oxabenzonorbornadienes with electron-withdrawing substituents as a complex mixture was formed and the desired addition products could not be isolated.

The synthetic application of the present methodology was further demonstrated by reacting the addition product **5ah** with *p*-TSA in DCE at 80 °C for 36 h (see Scheme 4).[15b] The hindered 2,6-diaryl benzoic acid **6ah** was obtained in 74% yield.

To obtain a mechanistic insight of the present transformation, control experiments were performed (Scheme 5). Significant incorporation of deuterium (45%) at both the

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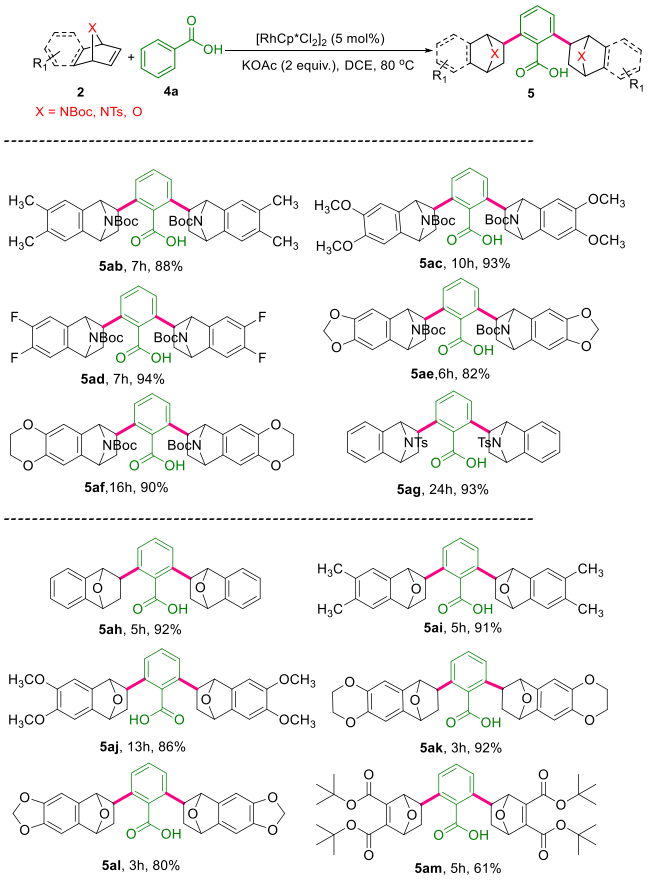
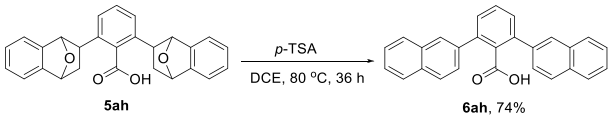
Scheme 3. Substrate Scope of Oxa/Azabicyclic Alkenes[a,b]



[a]Reaction conditions: **2** (0.2 mmol), **4** (0.2 mmol), $[RhCp^*Cl_2]_2$ (5 mol %), NaOAc (2 equiv), DCE (2 mL) at 80 °C. [b]Isolated yield.

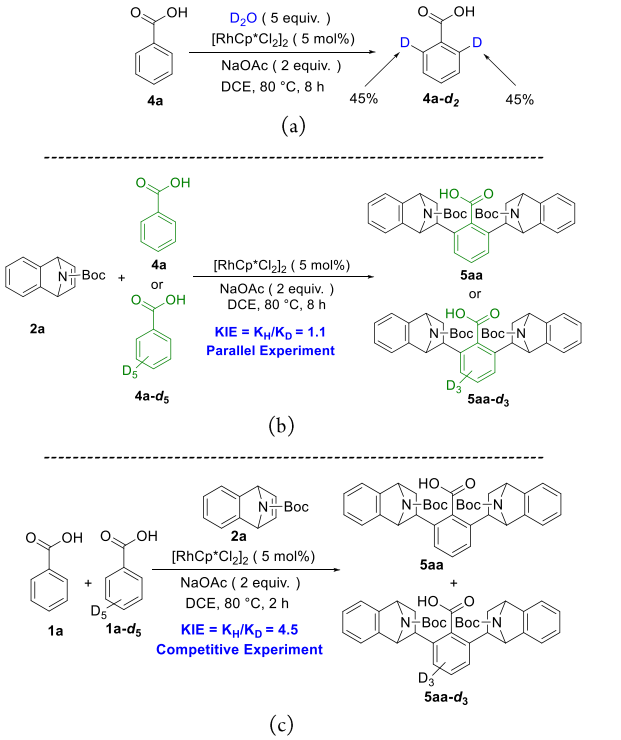
Scheme 4. Derivatization of 5ah



ortho-positions was observed when benzoic acid **4a** was subjected to the standard reaction conditions with 5 equiv of D_2O (see Scheme 5a). This indicates the reversibility of the C−H bond cleavage step.[19a] Next, parallel experiments using benzoic acid **4a** or **4a**-d_5 with azabenzonorbornadiene resulted into a kinetic isotope effect (KIE) value of 1.1 (see Scheme 5b). Finally, when a competitive reaction was performed between **4a** and **4a**-d_5 with **2a** under the standard reaction conditions, a KIE value of 4.5 was observed (see Scheme 5c). These results indicate that the rate-determining step involves cleavage of the C−H bond.[12b,17,19b] Based on the control experiments and the literature reports,[5c,d,11,13,17,18a,19] we have speculated possible reaction pathways for the present addition reactions in the Supporting Information.

In summary, we have successfully developed an efficient regioselective Rh-catalyzed addition reaction between arenes and oxa/azabicyclic alkenes. The reaction was controlled by weakly coordinating directing groups ketone and carboxylate groups. The reaction proceeded via C−H bond functionalization at the *ortho*-position of the arenes. In the case of ketone-directed addition reaction, the stereoselective ring-opening C−H addition products were obtained in 34%−82% yields. Interestingly, for the carboxylate-directed C−H bond functionalization reaction, the expensive silver salt was not required. Both oxa- and aza-bicyclic alkenes with different substituents participated under the developed reaction conditions and the 1:2 addition products were obtained in good to excellent yields. The present protocol showed a wide range of functional group tolerance and offered a synthetic method for the construction of highly substituted polycyclic organic compounds.

Scheme 5. Control Experiments



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00765.

Experimental procedures and compounds characterization data, including the NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Baomin Fan − *Key Laboratory of Chemistry in Ethnic Medicinal Resources, Yunnan Minzu University, Kunming 650500, China; School of Chemistry and Environment, Institution Yunnan Minzu University, Kunming 650500, China;* orcid.org/0000-0003-1789-3741; Email: FanBM@ynni.edu.cn

Yongyun Zhou − *Key Laboratory of Chemistry in Ethnic Medicinal Resources, Yunnan Minzu University, Kunming 650500, China; School of Chemistry and Environment, Institution Yunnan Minzu University, Kunming 650500, China*; Email: zhouyy@ynni.edu.cn

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Authors

Keyang Zhang − *Key Laboratory of Chemistry in Ethnic Medicinal Resources, Yunnan Minzu University, Kunming 650500, China*

Ruhima Khan − *Key Laboratory of Chemistry in Ethnic Medicinal Resources, Yunnan Minzu University, Kunming 650500, China*

Jingchao Chen − *Key Laboratory of Chemistry in Ethnic Medicinal Resources, Yunnan Minzu University, Kunming 650500, China*

Xuexin Zhang − *Key Laboratory of Chemistry in Ethnic Medicinal Resources, Yunnan Minzu University, Kunming 650500, China*

Yang Gao − *Key Laboratory of Chemistry in Ethnic Medicinal Resources, Yunnan Minzu University, Kunming 650500, China*

Kangkui Li − *Key Laboratory of Chemistry in Ethnic Medicinal Resources, Yunnan Minzu University, Kunming 650500, China*

Youxian Tian − *Key Laboratory of Chemistry in Ethnic Medicinal Resources, Yunnan Minzu University, Kunming 650500, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00765

Author Contributions

[▽]These authors contributed equally.

Notes

The authors declare no competing financial interest.

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