

Rhodium-Catalyzed *Ortho*-Vinylolation of 2-Arylpyridines and Its Application in the Total Synthesis of Palmatine

Shan Lv¹ Ruifang Nie¹ Lingmei Guo¹ Yang Zheng¹ Yanzhao Liu¹ Li Guo¹ Yong Wu¹

¹Sichuan Engineering Laboratory for Plant-Sourced Drug and Research Center for Drug Industrial Technology, Key Laboratory of Drug-Targeting and Drug Delivery System of the Education Ministry, West China School of Pharmacy, Sichuan University, Chengdu, China

Address for correspondence Li Guo, PhD, West China School of Pharmacy, Sichuan University, Chengdu 610041, China (e-mail: guoli@scu.edu.cn).

Yong Wu, PhD, West China School of Pharmacy, Sichuan University, Chengdu 610041, China (e-mail: wyong@scu.edu.cn).

Pharmaceut Fronts 2020;2:e94–e99.

Abstract

Keywords

- ▶ rhodium-catalyzed
- ▶ C–H activation
- ▶ *ortho*-vinylolation
- ▶ potassium vinyltrifluoroborate
- ▶ palmatine

An efficient protocol by Rh-catalyzed direct C–H vinylolation of 2-arylpyridines with a commercially available and air-stable potassium vinyl donor has been developed. This method affords the corresponding pyridinyl styrene derivative with moderate to excellent yields under mild conditions, which is extremely beneficial to the total synthesis of the natural product palmatine.

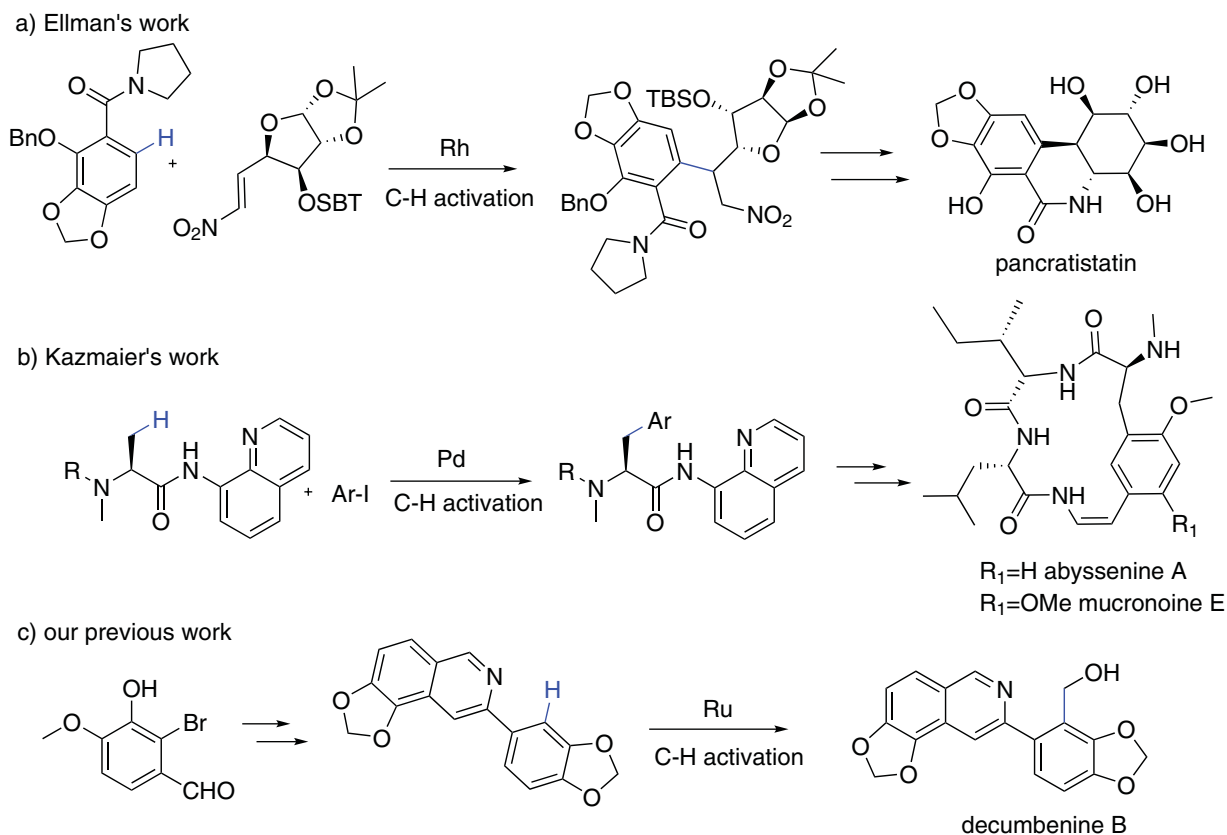
Introduction

In the past few decades, transition metal catalyzed C–H bond functionalization has witnessed significant progress as it avoids tedious and costly preactivation of starting materials and minimizes the formation of byproducts.^{1–3} After decades of development, it has become a useful tool in the total synthesis of natural products.^{4–6} A lot of research studies have proved that transition metal catalyzed C–H activation is a simpler and more time-saving methodology for the synthesis of natural products compared with traditional transformations. Here are just a few examples. Ellman's group⁷ synthesized the natural product pancratistatin through an amide-directed C–H activation in 2017 (**Scheme 1a**), and Kazmaier's group⁸ completed the synthesis of cyclopeptide alkaloids abyssenine A and mucronine E by C–H functionalization of *N*-methylated amino acids and peptides in 2018 (**Scheme 1b**). Meanwhile, our previous work⁹ successfully synthesized the natural compound decumbenine B via Ru(III)-catalyzed *ortho*-hydroxymethylation (**Scheme 1c**).

Palmatine, an isoquinoline alkaloid isolated from *Fibraurea recisa Pierre* (Chinese name: Huangteng), has a wide range of pharmacological and biological activities, such as antibacterial, antifungal, and antiviral effects.^{10,11} Clinically, palmatine has been used for the treatment of surgical infections, respira-

tory and urinary tract infections, conjunctivitis, and gynecological inflammation.¹² Due to the wide range of applications and exact efficacy in clinic, the demand for palmatine in the pharmaceutical market is growing. However, palmatine is in short supply because of the long growth cycle of the medicinal plant, or long synthetic route with low yield, environmentally unfriendliness, and high cost, etc.^{13,14} Therefore, developing a new and effective method to synthesize palmatine still has great practical significance. Based on structural analysis and our interest in C–H functionalization,^{15–18} a retrosynthetic analysis route was proposed, as shown in **Scheme 2**. Through this route, palmatine could be synthesized in only four steps, and among this, the two-step C–H activation reactions are crucial. Fortunately, our group has completed the synthesis of intermediate B by a water-mediated C–H activation using primary amines and sulfoxonium ylides.¹⁹ Therefore, the *ortho*-vinylolation of isoquinoline B is our main research object.

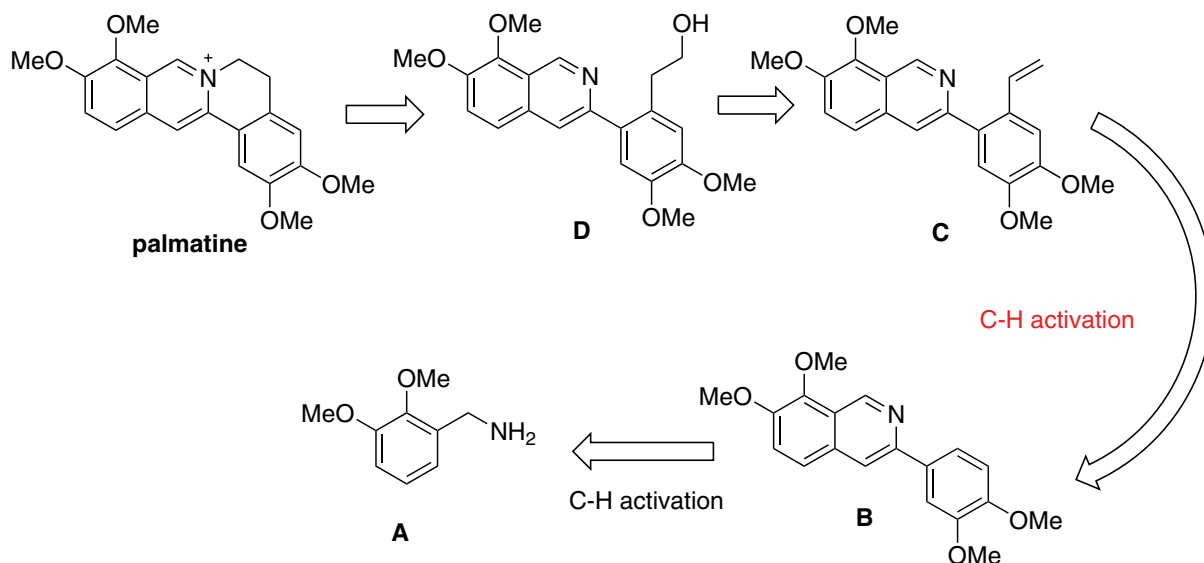
As far as we know, there are no literatures on the direct C–H vinylolation of 3-arylisoquinolines. Based on the similarity of physical and chemical properties between 2-arylpyridines and 3-arylisoquinolines, we decided to study the *ortho*-vinylolation of 2-arylpyridines. Independent studies by the groups of Kakiuchi,²⁰ Ellman,²¹ Mei,²² and Xu²³ reported that the direct C–H vinylolation of 2-arylpyridines could be accomplished with different vinyl sources catalyzed by ruthenium, or rhodium



Scheme 1 Some examples of total synthesis of natural products by C–H functionalization.

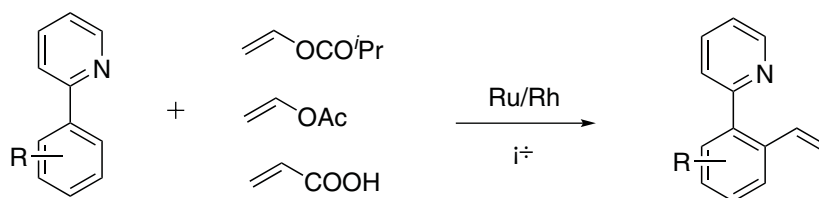
(Scheme 3a), but there remains some limitations, particularly with regard to high reaction temperature, toxic reactant, low yield, and using ligand additive. So it is of great value to explore a mild and efficient method to complete direct *ortho*-vinylation of 2-arylpyridines. Very recently, Zhou and coworkers reported an efficient Rh-catalyzed direct C2-alkenylation of indoles,²⁴ which is the first example for building a C2 block utilizing commercially available and air-stable potassium

vinyltrifluoroborate as the vinyl source. We are interested in the practicability of this vinyl source in the C–H bond functionalization and wonder if it can be used in 2-arylpyridines. Considering all the above facts, herein, we developed Rh-catalyzed direct C–H vinylation of 2-arylpyridines with potassium vinyltrifluoroborate as the vinyl source under mild conditions (Scheme 3b), and further completed the total synthesis of palmatine.

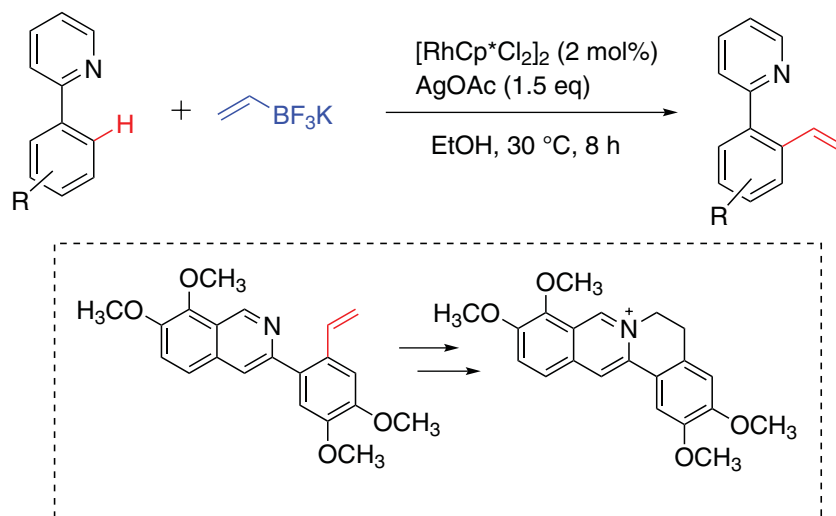


Scheme 2 Retrosynthetic analysis of palmatine.

a) C-H vinylation of 2-arylpyridine



b) this work



Scheme 3 Direct C–H vinylation.

Results and Discussion

We started the vinylation reaction using 2-phenylpyridine (**1a**) and potassium vinyltrifluoroborate (**2a**) as the model substrates. The reaction using $[\text{RhCp}^*\text{Cl}_2]_2$ (2 mol%) as a catalyst and AgOAc (1.5 equiv.) as an additive in MeOH/TFE (1:1) at 40 °C for 8 hours under air furnished the corresponding products **3a** and **3a'** in 78% (entry 1, ►Table 1), while the use of other cationic Rh sources resulted in a large decrease in yield (entries 2–3, ►Table 1). Almost no reaction occurred when switching to other catalysts, including Ru, Ir, and Co (entries 4–8, ►Table 1), proving that catalyst Rh is curial for this transformation. Then a variety of solvents including DCE (1,2-dichloroethane), HFIP (hexafluoroisopropanol)/EtOH, DCM, HFIP, EtOH, and PEG-400 were tested, and we were surprised to find that EtOH gave the best result and afforded **3a** and **3a'** in 83% yield in the presence of $[\text{RhCp}^*\text{Cl}_2]_2$ (2 mol%) and AgOAc (1.5 equiv.) (entries 9–14, ►Table 1). Further screening of oxidants revealed that Cu(OAc)₂, AgF, and CuF₂ were inferior to AgOAc (entries 13, 15–17, ►Table 1). Gratifyingly, decreasing reaction temperature to 30 °C also afforded the desired product in high yield (82%, entry 18, ►Table 1). To our satisfaction, switching the amount of **2a** to 1.1 equivalents did not lower the yields of **3a** and **3a'**. And more importantly, the ratio of the corresponding mono- and divinylated products **3a** and **3a'** was significantly

improved (entry 19, ►Table 1). Thus, the optimal reaction conditions were finally determined as follows: **1a** (0.2 mmol), **2a** (0.22 mmol), $[\text{RhCp}^*\text{Cl}_2]_2$ (2 mol%), AgOAc (1.5 equiv.), in EtOH at 30 °C for 8 hours under air.

Having the optimized conditions in hand, we then explored the practicality of this novel method by applying the procedure to the vinylation of a wide range of arenes (►Fig. 1).

Generally, 2-phenylpyridines with substituents at different positions of the aromatic ring all reacted smoothly with **2a**, giving the corresponding products in moderate to good yields. For example, 2-phenylpyridines containing methyl substituents at the *ortho*-, *meta*- and *para*-positions of the benzene ring afforded the desired products **3b**, **3d**, and **3h** and **3h'** in 75, 90, and 55% yields, respectively. Both electron-donating and withdrawing groups were tolerated, as demonstrated by the isolation of 66% of **3e** and 81% of **3g**. Similarly, the reaction of chloro-substituted 2-phenylpyridine provided the corresponding product **3f** in a lower yield. To our satisfaction, this method is compatible well with 3-phenylisoquinoline and gave the corresponding products **3i** and **3i'** in moderate yield. When the aromatic ring without substitution at the *ortho*- or *meta*-positions was used, divinylated products are obtained, such as **3h'** and **3i'**. On the basis of these results, we decided to verify the synthetic applicability of the developed protocol for the synthesis of the natural isoquinoline alkaloid palmatine.

Table 1 Optimization of the reaction conditions^a

Entry	Catalyst	Oxidant	Solvents	Yield (%) ^b	
				3a + 3a'	3a:3a' ^c
1	[RhCp*Cl ₂] ₂	AgOAc	MeOH/TFE	78	1:0.45
2	[Rh(OAc) ₂] ₂	AgOAc	MeOH/TFE	N.R. ^d	–
3	[Cp*Rh(MeCN) ₃](SbF ₆) ₂	AgOAc	MeOH/TFE	45	1:0.43
4	[RuCl ₂ (<i>p</i> -cymene)] ₂	AgOAc	MeOH/TFE	13	1: 0.45
5	[IrCp*Cl ₂] ₂	AgOAc	MeOH/TFE	N.R.	–
6	Co(acac) ₃	AgOAc	MeOH/TFE	N.R.	–
7	Co(acac) ₂	AgOAc	MeOH/TFE	N.R.	–
8	[Cp*Co(CO)I ₂]	AgOAc	MeOH/TFE	N.R.	–
9	[RhCp*Cl ₂] ₂	AgOAc	DCE	50	1:0.5
10	[RhCp*Cl ₂] ₂	AgOAc	HFIP/EtOH	73	1:0.45
11	[RhCp*Cl ₂] ₂	AgOAc	DCM	47	1:0.45
12	[RhCp*Cl ₂] ₂	AgOAc	HFIP	10	1:0.47
13	[RhCp*Cl ₂] ₂	AgOAc	EtOH	83	1:0.45
14	[RhCp*Cl ₂] ₂	AgOAc	PEG-400	43	1:0.5
15	[RhCp*Cl ₂] ₂	Cu(OAc) ₂	EtOH	79	1:0.45
16	[RhCp*Cl ₂] ₂	AgF	EtOH	70	1:0.45
17	[RhCp*Cl ₂] ₂	CuF ₂	EtOH	64	1:0.47
18 ^e	[RhCp*Cl ₂] ₂	AgOAc	EtOH	82	1:0.45
19 ^{e,f}	[RhCp*Cl ₂] ₂	AgOAc	EtOH	82	1:0.08

^aReaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (2 mol%), oxidant (1.5 eq.), solvents (1 mL), 40°C for 8 hours under air.

^bIsolated yields by chromatography on silica gel.

^cThe ratio of **3a** and **3a'** was determined by ¹H NMR spectroscopy.

^dNo reaction.

^e30°C.

^f**2a** (0.22 mmol).

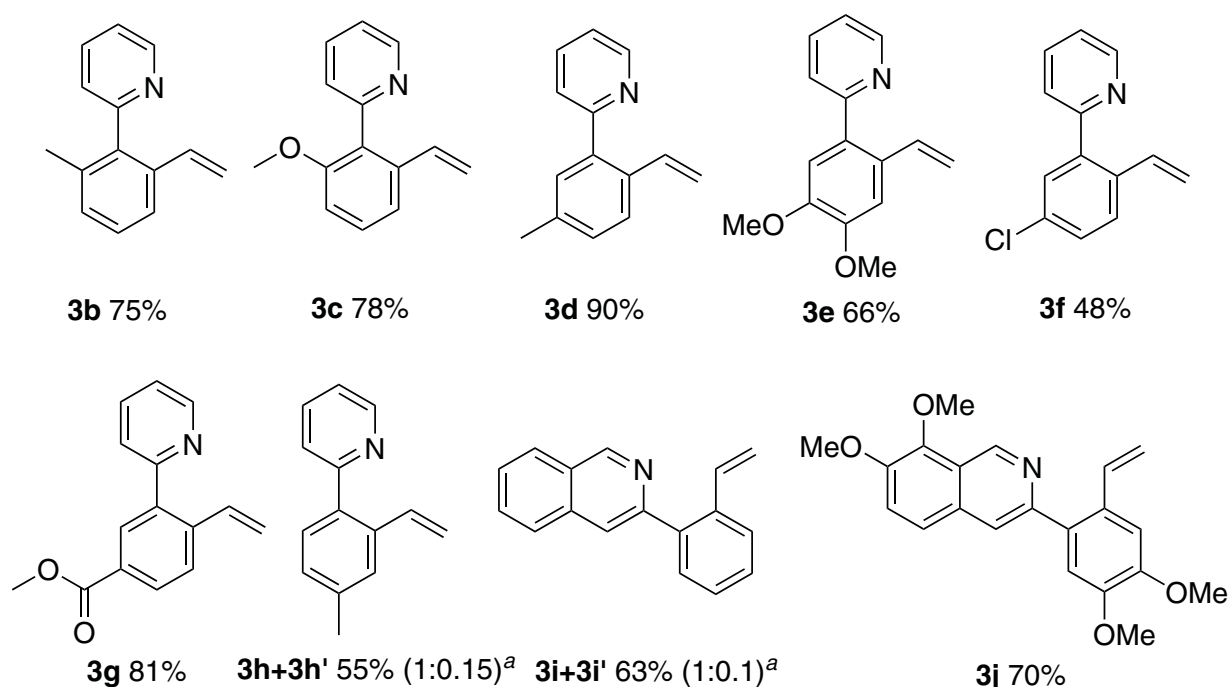
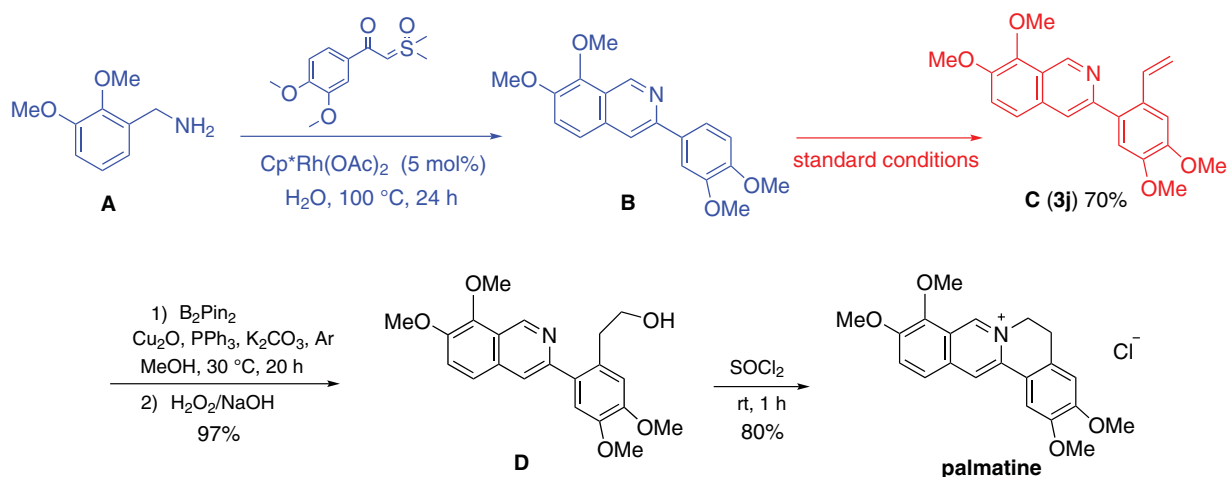


Fig. 1 Substrate scope. Reaction conditions: **1** (0.2 mmol), **2a** (0.22 mmol), [RhCp*Cl₂]₂ (2 mol%), AgOAc (1.5 equiv.), EtOH (1 mL), under air, 30°C, 8 hours, Isolated yields. ^aRatio of single to double C–H activation products by ¹H NMR.



Scheme 4 Total synthesis of palmatine by C–H activation.

As shown in **Scheme 4**, palmatine was successfully synthesized from commercially available materials in only four steps, and the crucial two-step C–H activation reactions both were first reported by our group. First, intermediate **B** was obtained by Rh-catalyzed C–H activation/cyclization of primary amine **A** with sulfoxonium ylide according to our recent work.¹⁵ Second, compound **B** reacted with potassium vinyltrifluoroborate under standard conditions, giving the key intermediate **C (3j)** in 70% yield. Finally, compound **C** was easily converted into palmatine through hydroboration oxidation and cyclization reactions.^{25,26}

Conclusions

In summary, we have developed a mild and efficient protocol by Rh-catalyzed direct C–H *ortho*-vinylolation of 2-arylpyridines using commercially available and air-stable potassium vinyltrifluoroborate as a vinyl source. The salient features of this protocol include using a low-toxicity solvent (EtOH) as reaction solution, mild reaction conditions, and moderate to excellent yields. More importantly, 3-arylisquinolines, the skeleton of palmatine, were well tolerated in this process. Thus a short and efficient synthesis route of palmatine over four steps was developed with this methodology.

Conflict of Interest

The authors declare no conflicts of interest.

Acknowledgments

We are grateful for support from the National Natural Science Foundation of China (NSFC; grants 81373259 and 81573286).

References

- Saha D, Mukhopadhyay C. Metal nanoparticles: an efficient tool for heterocycles synthesis and their functionalization via CH activation. *Curr Organocatal* 2019;6(02):79–91
- Romero AH. Fused heteroaromatic rings via metal-mediated/catalyzed intramolecular C–H activation: a comprehensive review. *Top Curr Chem (Cham)* 2019;377(04):21
- Maraswami M, Loh TP. Transition-metal-catalyzed alkenyl sp^2 C–H activation: a short account. *Synthesis* 2019;51(05):1049–1062
- Abrams DJ, Provencher PA, Sorensen EJ. Recent applications of C–H functionalization in complex natural product synthesis. *Chem Soc Rev* 2018;47(23):8925–8967
- Karimov RR, Hartwig JF. Transition-metal-catalyzed selective functionalization of C (sp^3)-H bonds in natural products. *Angew Chem Int Ed Engl* 2018;57(16):4234–4241
- Yakura T, Nambu H. Recent topics in application of selective Rh (II)-catalyzed CH functionalization toward natural product synthesis. *Tetrahedron Lett* 2018;59(03):188–202
- Potter TJ, Ellman JA. Total synthesis of (+)-pancratistatin by the Rh(III)-catalyzed addition of a densely functionalized benzamide to a sugar-derived nitroalkene. *Org Lett* 2017;19(11):2985–2988
- Kinsinger T, Kazmaier U. C–H functionalization of *N*-methylated amino acids and peptides as tool in natural product synthesis: synthesis of abyssenine A and mucronine E. *Org Lett* 2018;20(23):7726–7730
- Zhang Y, Yang Z, Guo L, et al. Total synthesis of the isoquinoline alkaloid decumbenine B via Ru(III)-catalyzed C–H activation. *Org Chem Front* 2018;5(10):1604–1607
- Yuan Y, Peng W, Liu Y, Xu Z. Palmatine attenuates isoproterenol-induced pathological hypertrophy via selectively inhibiting HDAC2 in rats. *Int J Immunopathol Pharmacol* 2017;30(04):406–412
- Tarabasz D, Kukula-Koch W. Palmatine: a review of pharmacological properties and pharmacokinetics. *Phytother Res* 2020;34(01):33–50
- Dhingra D, Kumar V. Memory-enhancing activity of palmatine in mice using elevated plus maze and morris water maze. *Adv Pharmacol Sci* 2012;2012:357368
- Li Z, Zhao S, Kong X. Research progress of palmatine and its analogues. *Guangdong Huagong* 2015;42(08):7–9
- Bian X, He L, Yang G. Synthesis and antihyperglycemic evaluation of various protoberberine derivatives. *Bioorg Med Chem Lett* 2006;16(05):1380–1383
- Guo L, Tang B, Nie R, et al. C–H alkenylation/cyclization and sulfamidation of 2-phenylisatogens using *N*-oxide as a directing group. *Chem Commun (Camb)* 2019;55(71):10623–10626
- Liu YZ, Hu Y, Lv GH, et al. Synthesis of 1,2-benzothiazines via C–H activation/cyclization in a recyclable, mild system. *ACS Sustain Chem& Eng* 2019;7(15):13425–13429
- Lai R, Wu X, Lv S, et al. Synthesis of indoles and quinazolines via additive-controlled selective C–H activation/annulation of *N*-arylamidines and sulfoxonium ylides. *Chem Commun (Camb)* 2019;55(28):4039–4042
- Zhang HL, Jing L, Zheng Y, et al. Rhodium-catalyzed *ortho*-cyanation of 2-aryl-1,2,3-triazole: an alternative approach to suvoronant. *Eur J Inorg Chem* 2018;2018(06):723–729

- 19 Nie R, Lai R, Lv S, et al. Water-mediated C-H activation of arenes with secure carbene precursors: the reaction and its application. *Chem Commun (Camb)* 2019;55(76):11418–11421
- 20 Matsuura Y, Tamura M, Kochi T, Sato M, Chatani N, Kakiuchi F. The Ru(cod)(cot)-catalyzed alkenylation of aromatic C-H bonds with alkenyl acetates. *J Am Chem Soc* 2007;129(32):9858–9859
- 21 Otley KD, Ellman JA. An efficient method for the preparation of styrene derivatives via Rh(III)-catalyzed direct C-H vinylolation. *Org Lett* 2015;17(05):1332–1335
- 22 Mei ST, Jiang K, Wang NJ, et al. Rhodium-catalyzed direct C-H vinylolation of arenes to access styrenes with vinyl acetate as a vinyl source. *Eur J Inorg Chem* 2015;2015(28):6135–6140
- 23 Xu J, Chen C, Zhao H, et al. Rhodium(I)-catalysed decarbonylative direct C-H vinylolation and dienylation of arenes. *Org Chem Front* 2018;5(05):734–740
- 24 Zhou CN, Xie HH, Zheng ZA, et al. Synthesis of terminal vinylindoles via Rh^{III}-catalyzed direct C-H alkenylation with potassium vinyltrifluoroborate. *Chemistry* 2018;24(21):5469–5473
- 25 Hong SB, Liu MY, Zhang W, et al. Copper-catalyzed hydroboration of arylalkenes at room temperature. *Tetrahedron Lett* 2015;56(18):2297–2302
- 26 Zhang L, Zuo Z, Wan X, Huang Z. Cobalt-catalyzed enantioselective hydroboration of 1,1-disubstituted aryl alkenes. *J Am Chem Soc* 2014;136(44):15501–15504