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

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Abstract

An efficient protocol by Rh-catalyzed direct C–H vinylation 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.

Keywords

- rhodium-catalyzed
- C–H activation
- *ortho*-vinylation
- potassium vinyltrifluoroborate
- 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 group[7] synthesized the natural product pancratistatin through an amide-directed C–H activation in 2017 (**Scheme 1a**), and Kazmaier's group[8] 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 work[9] 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, respiratory 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*-vinylation of isoquinoline B is our main research object.

As far as we know, there are no literatures on the direct C–H vinylation of 3-arylisoquinolines. Based on the similarity of physical and chemical properties between 2-arylpyridines and 3-arylisoquinolines, we decided to study the *ortho*-vinylation of 2-arylpyridines. Independent studies by the groups of Kakiuchi,[20] Ellman,[21] Mei,[22] and Xu[23] reported that the direct C–H vinylation of 2-arylpyridines could be accomplished with different vinyl sources catalyzed by ruthenium, or rhodium

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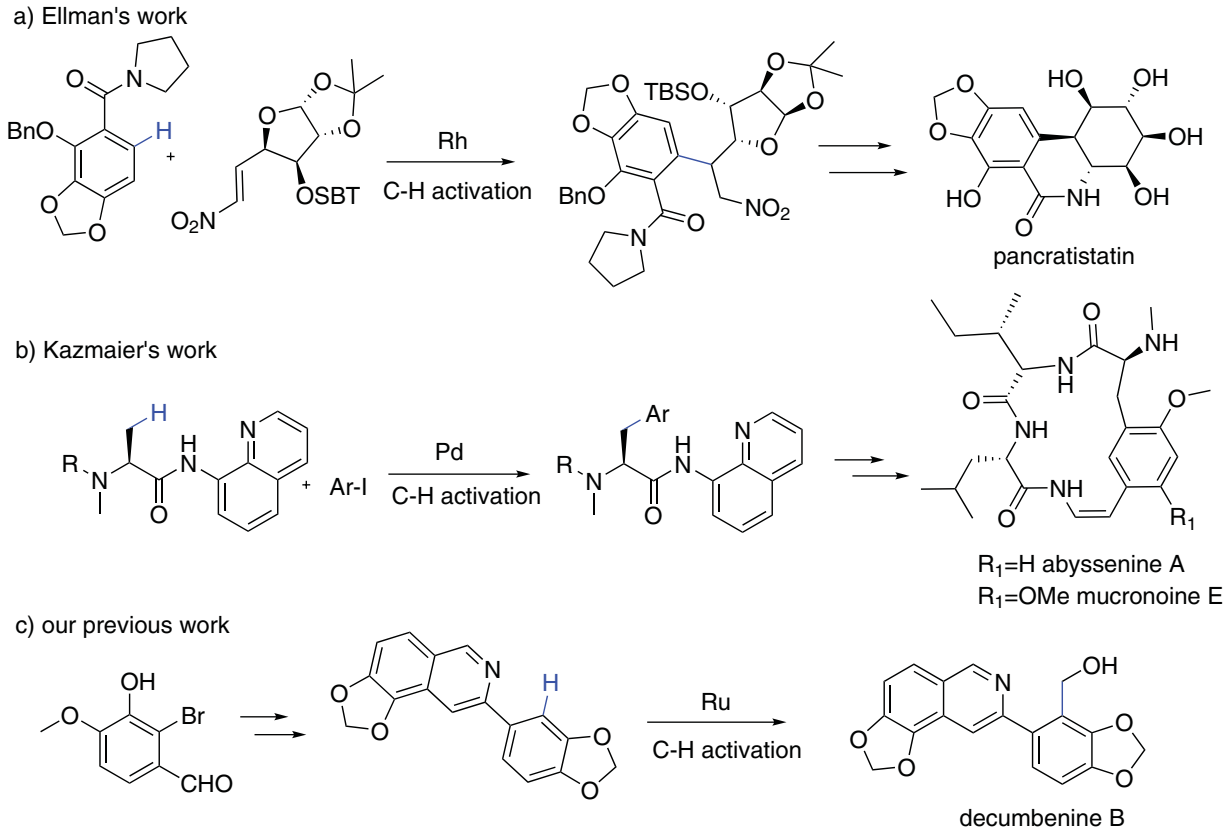
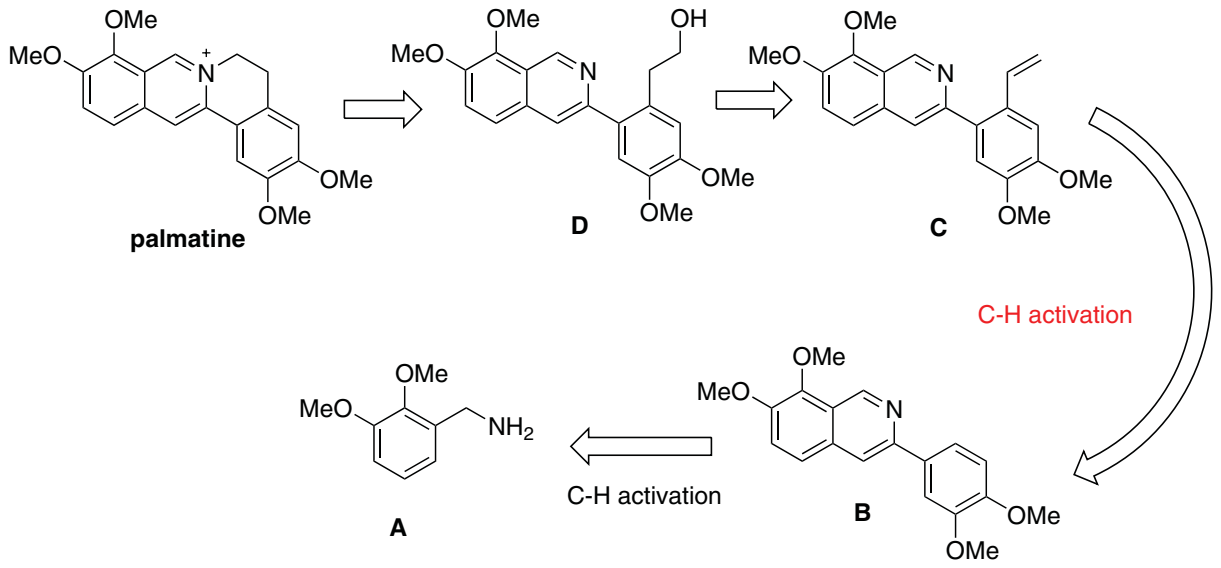
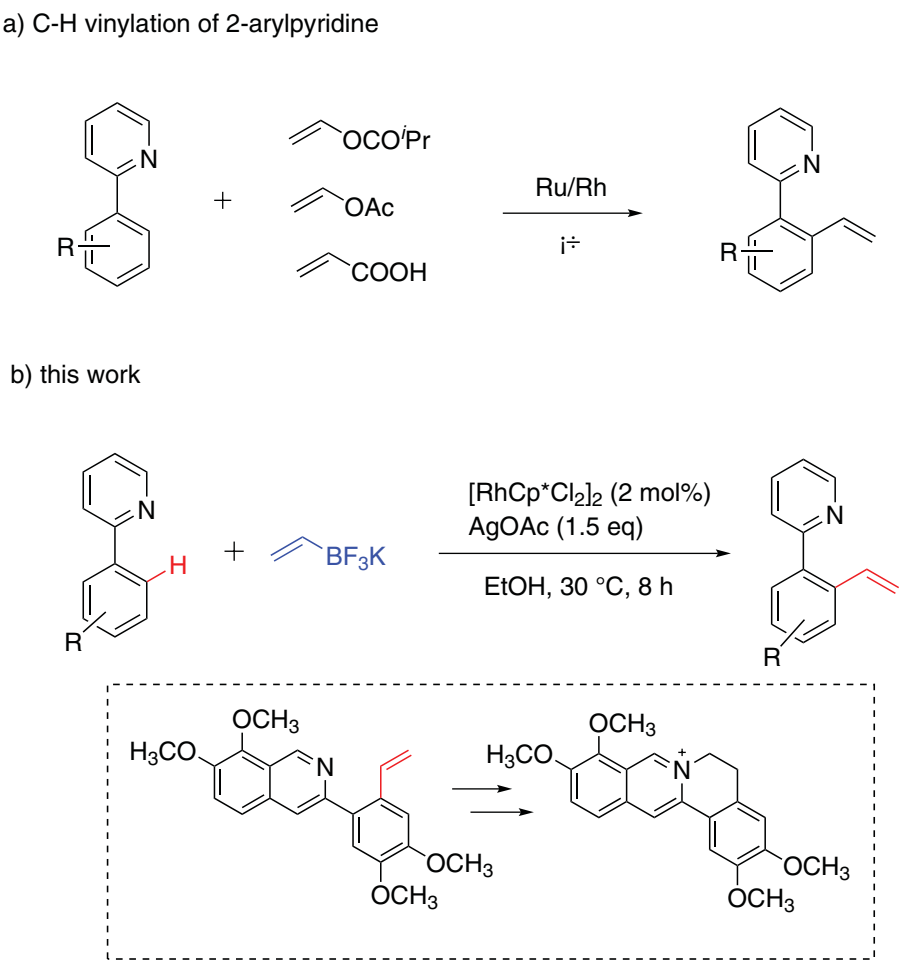


Scheme 1 Some examples of total synthesis of natural products by C–H functionalization.

(**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.



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 [RhCp*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 [RhCp*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 CuF$_2$ 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), [RhCp*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]

FO1					
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	$[RuCl_2(p\text{-cymene})]_2$	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**

[a]Reaction 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.
[b]Isolated yields by chromatography on silica gel.
[c]The ratio of **3a** and **3a′** was determined by ^{1}H NMR spectroscopy.
[d]No reaction.
[e]30°C.
[f]**2a** (0.22 mmol).

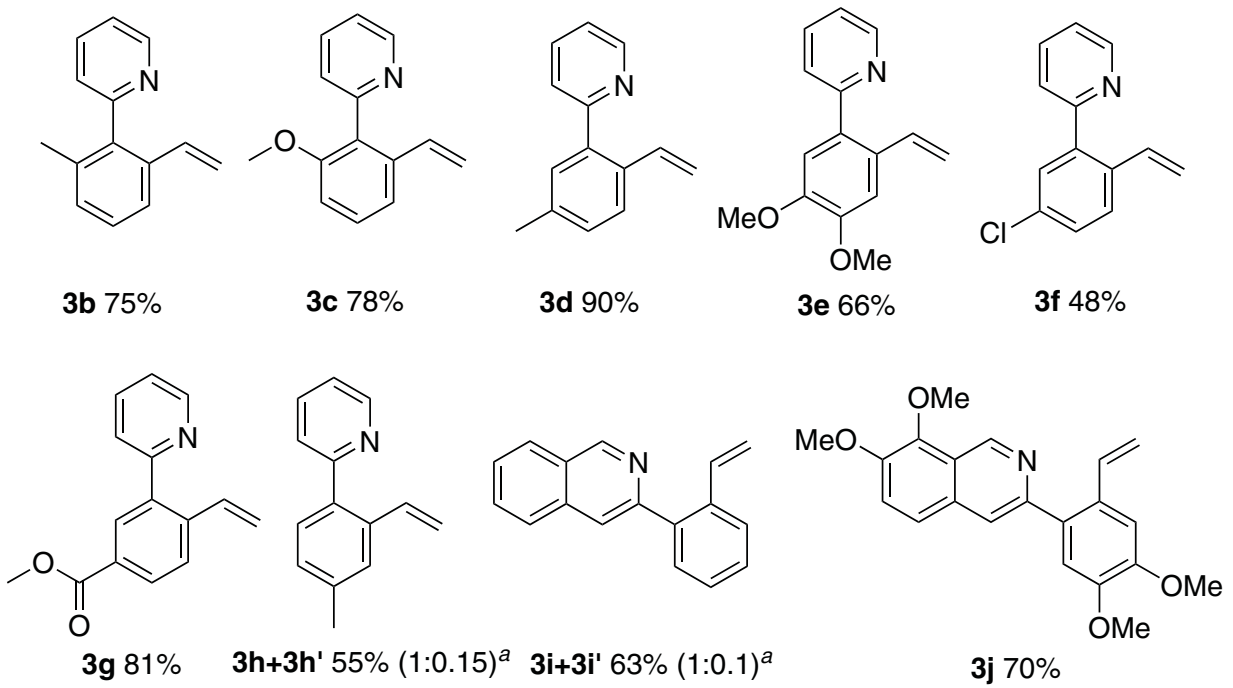
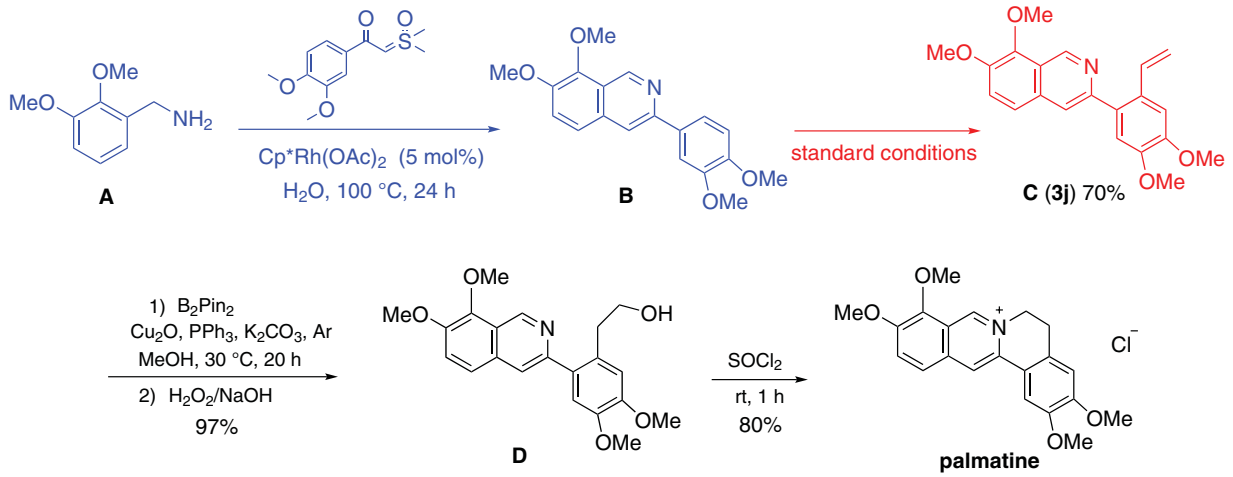


Fig. 1 Substrate scope. Reaction conditions: **1** (0.2 mmol), **2a** (0.22 mmol), $[RhCp^*Cl_2]_2$ (2 mol%), AgOAc (1.5 equiv.), EtOH (1 mL), under air, 30°C, 8 hours, Isolated yields. [a]Ratio of single to double C–H activation products by ^{1}H NMR.



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*-vinylation 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-arylisoquinolines, 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

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