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Ruthenium-Catalyzed C6-Propenylation Reactions of Substituted Pyridine Derivatives: Directed and Direct C–H Activation

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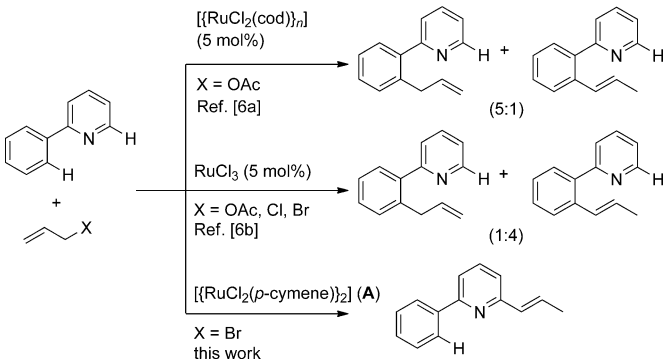
Dedicated to Professor Gautam R. Desiraju on the occasion of his 60th birthday

C–C Bond formation through transition-metal catalyzed functionalization of aryl/heteroaryl C–H bonds has recently attracted attention because these reactions provide more desirable step- and atom economy than those reactions where prefunctionalization of aryl/heteroaryl rings is required.[1,2] Pyridine derivatives are interesting in this regard. On one hand, the pyridine moiety is one of the conventional functional groups employed as a ligand for directed catalytic functionalizations of aryl C–H bonds.[2] On the other hand, catalytic C–H activation reactions that lead to functionalization of the pyridine moiety are important because the pyridine moiety is a privileged substructure of biologically active small molecules, functional organic materials, and ligands.[3] Generally, the direct C alkylation of pyridine moieties require the nitrogen atom to be electron deficient to increase the acidity of C–H bond at the C2 position; this requirement can be achieved by using *N*-oxides, *N*-iminopyridinium ylides, and pyridine compounds in the presence of Lewis acids.[4,5] Conversely, in the case of directed alkylations, the pyridine moiety needs to be electron rich because the catalytic cycle involves the coordination of the nitrogen atom with a metal complex.[2] Therefore, the direct functionalization of pyridine moieties and pyridine-directed C–H activation reactions have, in general, been approached separately by using various transition-metal complexes, which are usually complexes of palladium, rhodium, ruthenium, and nickel.[1] Herein, we describe an unexpected direct propenylation of pyridine rings using ruthenium catalysts that are generally employed for directed C–H activation reactions. Building on this unexpected reaction, the feasibility of a one-pot one-catalyst directed *ortho*-arylation reaction, as well as a direct C6-propenylation reaction of 2-phenylpyridine was also investigated.

We have been interested in developing a one-pot sequential Ru-catalyzed directed propenylation[6] and arylation of 2-aryl pyridine derivatives. The possibility of a directed propenylation reaction under the arylation conditions reported by the research group of Ackermann was explored in this regard (Scheme 1).[7] The propenylation reaction was carried



Scheme 1. Previous work on the propenylation/allylation of pyridine derivatives.

out using allyl bromide, K_2CO_3 (2.0 equiv), adamantane-1-carboxylic acid ($AdCO_2H$, 0.3 equiv), and [{Ru(*p*-cymene)Cl_2}$_2$] (**A**; 2.5 mol%) in either toluene or NMP (*N*-methyl-2-pyrrolidone) at 120°C in a screw-capped sealed tube and gave product **2a**, which was isolated in 67% and 63% yield, respectively (Scheme 2). The spectral data of **2a** suggested the presence of an *E*-configured 2-propenyl group next to the nitrogen atom of the pyridine moiety. This result was in contrast to earlier reports on the Ru-catalyzed propenylation of **1a**, reactions that involved C–H activation at the *ortho* position of the phenyl ring.[6]

The use of other allyl halides in the C6-propenylation reaction of **1a** was examined. The reaction was sluggish with allyl chloride and there was no reaction with crotyl bromide. When allyl iodide was employed, although complete consumption of **1a** was observed, the product **2a** was isolated in poor yield (Scheme 2). Interestingly, the reaction with allyl acetate led to the isolation of a mixture of products resulting from mono- and diallylation of the phenyl ring, together with propenylation products derived from migration of the double bond of the allyl group in these initial products. The identity and distribution of the mono- and diallylation products was established by subjecting the crude mixture to

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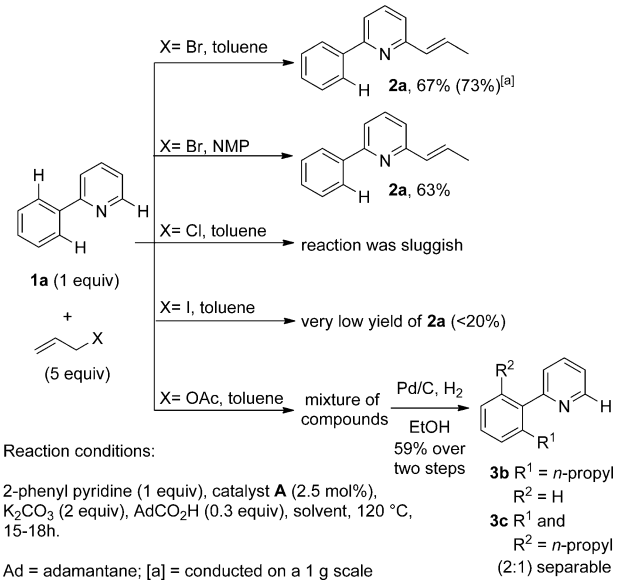
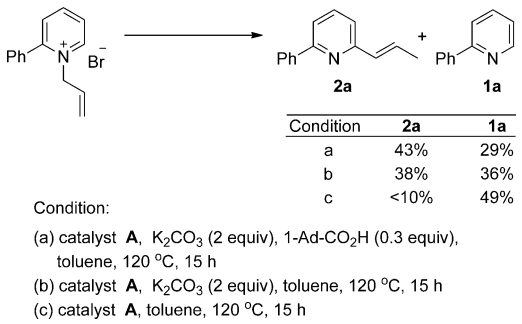


Scheme 2. Reactivity of various allyl halides and allyl acetate.

olefin hydrogenation and subsequently characterizing the separable mono- and dialkylation products, **3b** and **3c**, respectively.

The use of other ruthenium complexes in this reaction was examined under similar reactions conditions but the results were not encouraging (for details, see the Supporting Information and Table S1). Control experiments revealed that the presence of the base leads to better yields. When the reaction was carried out in the absence of ruthenium complex **A** under otherwise similar reaction conditions, the formation of **2a** was negligible (see the Supporting Information and Table S1). This result indicated that ruthenium complex **A** is essential for the reaction. The proposal of a comprehensive mechanism is, at this stage, difficult. However, the different reactivity of allyl bromide and allyl acetate suggests that the reaction might be proceeding through the N allylation of pyridine in the case of allyl bromide, a transformation that would increase the acidity of the C–H bond at the C2 position. The results obtained from a control experiment using the allyl bromide salt of **1a** (Scheme 3) as a substrate supports this argument. Further investigations are



Condition	2a	1a
a	43%	29%
b	38%	36%
c	<10%	49%

Condition:
(a) catalyst **A**, K_2CO_3 (2 equiv), 1-Ad-CO_2H (0.3 equiv), toluene, 120 °C, 15 h
(b) catalyst **A**, K_2CO_3 (2 equiv), toluene, 120 °C, 15 h
(c) catalyst **A**, toluene, 120 °C, 15 h

Scheme 3. Control experiments using *N*-allylpyridinium salt.

currently underway to understand the detailed mechanism (see the Supporting Information, Scheme SI.1 for a tentative proposal).

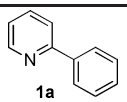
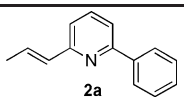
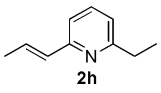
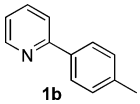
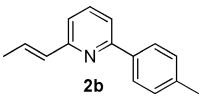
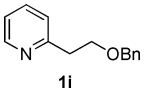
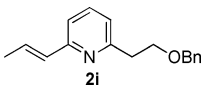
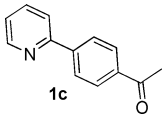
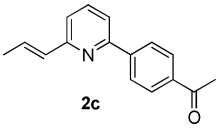
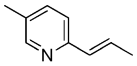
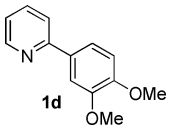
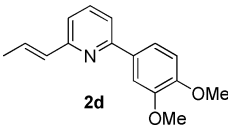
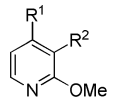
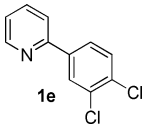
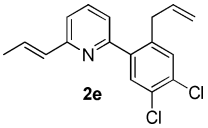
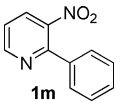
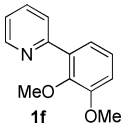
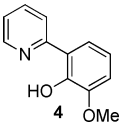
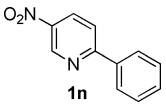
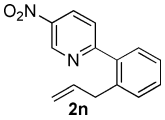
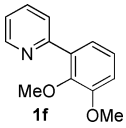
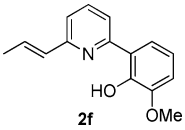
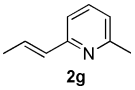
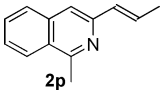
The scope of the present reaction was investigated (Table 1). Diverse 2-aryl pyridine derivatives, as well as 2- and 3-alkyl pyridine derivatives gave the corresponding 2-substituted-6-(1*E*-prop-1-enyl)-pyridine derivatives in good to excellent yields. The propenylation of 2-aryl pyridine derivatives (aryl = 4-MeC_6H_4 **1b**, 4-AcC_6H_4 **1c**, and 3,4-$(MeO)_2C_6H_3$ **1d**) proceeded smoothly and afforded the products (**2b**–**2d**) in 60–70% yields. The reaction of 2-(3,4-dichlorophenyl)pyridine (**1e**) needs special mention. For this case, the double C_{sp^2}–H activation product (**2e**) was obtained exclusively in 61% yield (Table 1, entry 5). Surprisingly, the reaction of 2-(2,3-dimethoxyphenyl)pyridine under the above reaction conditions gave the *ortho*-*O*-desmethyl compound **4** as the major product (isolated in 63% yield) and **2f** was obtained in less than 5% yield.[8] However, the same reaction in the absence of Ad-CO_2H gave the product **2f** in 62% yield (Table 1, entry 7).

Simple alkyl pyridine derivatives such as 2-picoline (**1g**), 2-ethyl pyridine (**1h**), and 3-picoline (**1j**) are also good substrates for the reaction, thus giving exclusively the C_{sp^2}–H propenylation products **2g**, **2h**, and **2j**, respectively, with complete regio- and stereoselectivity (Table 1, entries 8, 9, and 11).[9] However, pyridine **1i**, which has a 2-benzyloxyethyl group gave the required corresponding product **2i** in poor yield (Table 1, entry 10). The reactions of disubstituted pyridine derivatives having either nitro or methoxy groups gave poor results (Table 1, entries 12 and 14). For example, when subjected to the standard reaction conditions, 3-nitro-2-methoxypyridine (**1k**) and 2-methoxy-4-methylpyridine (**1l**) only the starting compounds were isolated. Whereas 3-nitro-2-phenypyridine (**1m**) did not react under these reaction conditions, the formation of small amounts of directed-propenylation product **2n** was observed when using 5-nitro-2-phenylpyridine (**1n**; see the Supporting Information for a ^1H NMR spectrum). Next, we examined the possibility of direct propenylation of quinoline and 1-methyl-isoquinoline. Surprisingly, quinoline (**1o**) decomposed under the standard reaction conditions and 1-methyl-isoquinoline (**1p**) gave the required product in low yields (Table 1, entry 16).

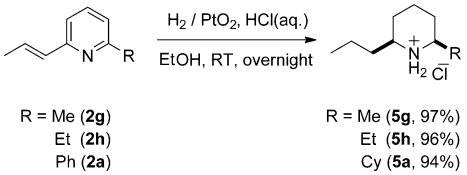
Next, considering that compound **2g** has the complete carbon framework of dihydropinidine,[10] exhaustive hydrogenolysis of compound **2g** was carried out using a catalytic amount of PtO_2 in HCl_{aq}/EtOH at 50 bar H_2 pressure and (±)-dihydropinidine (**5g**) was obtained in quantitative yield (Scheme 4) with complete selectivity for the 1,6-*cis*-disubstituted product.[11] Similarly, the hydrogenation of compounds **2h** and **2a** afforded fully reduced products **5h** and **5a**, respectively (Scheme 4).

We next investigated whether we could effect sequential direct C–H propenylation and directed C–H arylation reactions of 2-aryl pyridine derivatives in one pot.[12] Our initial experiments using **1a** as a substrate revealed that the success of the reactions depends upon the order of addition of reactants, that is, whether arylation or propenylation comes

Table 1. The scope of the Ru-catalyzed propenylation reaction of substituted pyridine derivatives.

Entry	Substrate	Product	Yield [%][a]	Entry	Substrate	Product	Yield [%][a]
1	 **1a**	 **2a**	67	9	 **1h**	 **2h**	65
2	 **1b**	 **2b**	63	10	 **1i**	 **2i**	22
3	 **1c**	 **2c**	66	11	 **1j**	 **2j**	54
4	 **1d**	 **2d**	62	12	 **1k** R^1 = H, R^2 = NO_2 **1l** R^1 = Me, R^2 = H	no reaction	–
5	 **1e**	 **2e**	61	13	 **1m**	no reaction	–
6	 **1f**	 **4**	63	14	 **1n**	 **2n**	<20
7	 **1f**	 **2f**	62[b]	15	 **1o**	starting material decomposed	–
8	 **1g**	 **2g**	67	16	 **1p**	 **2p**	42

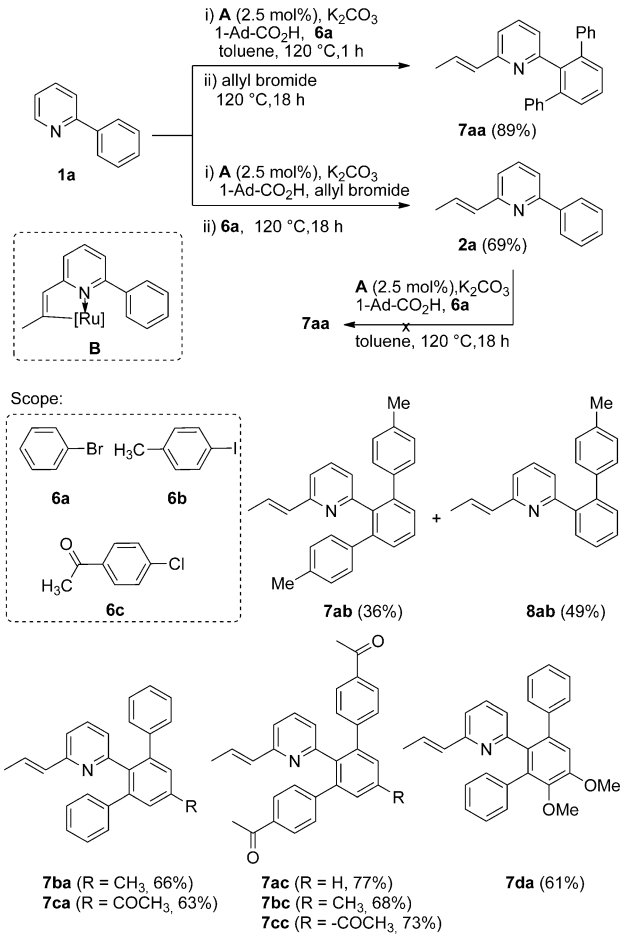
[a] Yield of isolated product. [b] Reactions without Ad-CO_2H.



Scheme 4. The synthesis of (±)-dihydropinidine and related compounds.

first. Carrying out the arylation of the phenyl ring first under the established reactions conditions (120 °C) followed by addition of allyl bromide and heating the reaction mixture at 120 °C for an additional 16 hours gave compound **7aa** in 89 % yield (Scheme 5). Surprisingly, when the reaction sequence was changed, that is, when propenylation is followed by arylation, the propenylation product **2a** was obtained exclusively in 69 % yield. Even the direct arylation of **2a** under these reaction conditions was found to be unsuccessful. This result might be due to the formation of either a stable *N*-coordinated ruthenacycle[13] or a related π complex, which can undergo neither C–H bond ruthenation nor oxidative addition across the Ar–X bond. Another possibility might be the steric hindrance around the pyridine nitrogen atom (in **2a**, the pyridine moiety is 2,6-disubstituted), a characteristic that may prevent the pyridine nitrogen atom from acting as a directing group. The scope of the one-pot protocol involving two sequential C–H bond activation reactions was explored by employing various 2-aryl pyridine derivatives and aryl halides (Scheme 5). The reaction of substrates **1b**, **1c**, and **1d** gave the diarylation and propenylation products **7ba**–**7da** in 60–70 % yields. When 4-methyl-iodobenzene (**6b**) was employed, the reaction was slow and, even after 40 hours, was incomplete; the reaction gave mono- and diarylation products **8ab** (49 %) and **7ab** (36 %), respectively. The reactions with 4-acetylchlorobenzene (**6c**) with the substrates **1a**, **1b**, and **1c** proceeded smoothly and gave products **7ac**–**7cc** in 70–80 % yields.

To conclude, we have shown that the complex, [{Ru(*p*-cymene)Cl_2}$_2$], which is known to effect the directed C–H activation of 2-aryl pyridine derivatives, can also be used to effect direct C6 propenylation of pyridine derivatives. Among the different allyl reagents screened, allyl bromide



Scheme 5. A one-pot sequential arylation and propenylation reaction of arylpyridine derivatives.

was found to be optimum for the direct propenylation. The expected directed allylation/propenylation of the phenyl ring was found to be the predominant pathway with allyl acetate. The complementary directed and direct C–H activation reactions, which are both catalyzed by [{Ru(*p*-cymene)Cl_2}$_2$], have been exploited to develop a novel one-pot protocol wherein multiple Ru-mediated C–C bond formations occur through sequential C–H activation reactions. This protocol, which we believe to be the first of its kind, will pave the way for the development of similar reactions by appropriate substrate and catalyst selection. Further investigations to understand the mechanism of this reaction and to extend the scope of this reaction to include other heterocyclic substrates are in progress.

Experimental Section

A) Representative procedure for direct propenylation: [{Ru(*p*-cymene)Cl_2}$_2$] (94 mg, 0.154 mmol) was added to a suspension of 2-phenylpyridine (1 g, 6.44 mmol), K_2CO_3 (1.79 g, 12.89 mmol), 1-AdCO_2H (348 mg, 1.93 mmol) in dry toluene (15 mL). The reaction mixture was degassed with argon for 10 min and allyl bromide (2.79 mL, 32.22 mmol) was added and the resulting solution was stirred at 120 °C for 18–20 h. The reaction mixture was poured into a mixture of diethyl ether and ice-cold water. The organic layer was separated and the aqueous layer was extracted (3×15 mL) with diethyl ether. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was purified using column chromatography through silica gel (5→7% ethyl acetate in petroleum ether) to afford compound **2a** (921 mg, 73%) as a yellow liquid.

B) Representative procedure for sequential directed and direct C–H activations: To a suspension of 2-phenylpyridine (1 g, 6.44 mmol), K_2CO_3 (1.79 g, 12.89 mmol), and 1-AdCO_2H (348 mg, 1.93 mmol) in dry toluene (15 mL), [{Ru(*p*-cymene)Cl_2}$_2$] (94 mg, 0.154 mmol) was added and the reaction mixture was flushed with argon for 10 min. To this mixture, bromobenzene (1.69 mL, 16.11 mmol) was added and the resulting mixture was heated at 120 °C for 18 h. To this mixture, allyl bromide (1.41 mL, 16.27 mmol) was added and the resulting mixture was heated at 120 °C for an additional 15–18 h. The reaction mixture was diluted with diethyl ether and water. The organic layer was separated and the aqueous layer was extracted (3 times) with diethyl ether. The combined organic layers were dried (Na_2SO_4) and solvent was removed under reduced pressure. The crude material was purified using column chromatography through silica gel (8→9% ethyl acetate in pet ether) to afford compound **7aa** (1.86 g, 83%) as a white solid.

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C–H Activation

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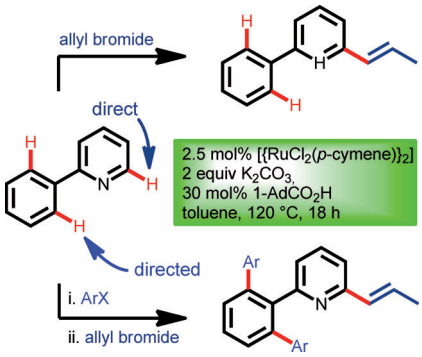
Ruthenium-Catalyzed C6-Propenylation Reactions of Substituted Pyridine Derivatives: Directed and Direct C–H Activation



One stone, two birds: Aryl pyridine derivatives in the presence of allyl bromide and a catalytic amount of [{Ru(*p*-cymene)Cl_2}$_2$] undergo an unexpected direct C6-propenylation reaction of the pyridine moiety. A one-pot one-catalyst three-component *reaction* involving sequential and selective direct and directed C–H activation reactions was also developed (see scheme).