Solvent-Controlled Rhodium-Catalyzed C6-Selective C-H Alkenylation and Alkylation of 2-Pyridones with Acrylates

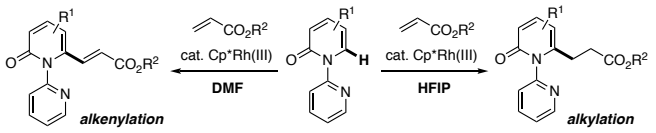
Sunit Hazra,[a] Koji Hirano,*[a] and Masahiro Miura*[a]

Dedication ((optional))

Abstract: We have developed a solvent-controlled Rh-catalyzed C6-selective alkenylation and alkylation of 2-pyridones with acrylates via a pyridine-directed C–H cleavage. Using DMF as solvent, the C–H alkenylation with acrylates selectively occurs to deliver the corresponding C6-alkenylated 2-pyridones in good yields. On the other hand, the C6-alkylated products are predominantly formed in a more polar and protic solvent, HFIP. Thus, a single set of starting substrates can be divergently transformed to the C6-functionalized 2-pyridones, which are of potent interest in medicinal and pharmaceutical chemistry.

2-Pyridones are prevalent heterocyclic motifs in natural products, bioactive molecules, and pharmaceutical agents.[1] Accordingly, chemists have developed many synthetic methods for decoration of the 2-pyridone ring. While the traditional common strategy involving catalytic cross-coupling largely relies on preactivation such as halogenation and stoichiometric metalation, recent advances in C–H activation[2] enable the more efficient and atom- and step-economical direct functionalization of 2-pyridones.[3] To date, the C3, C4, C5, and C6-selective C–H functionalizations have been reported under various transition metal catalyses. Our group has also focused on the site-selective C–H functionalization of 2-pyridones and developed the C3-selective alkylation[4] and arylation, [4b,c] and C6-selective alkylation,[5] (hetero)arylation,[6] and borylation.[7] As part of this research project, we herein wish to report a Cp*Rh(III)-catalyzed C6-selective C–H coupling of 2-pyridones with acrylates via pyridine-directed C–H cleavage (Scheme 1): the reaction in DMF efficiently occurs to deliver the corresponding C–H alkenylation products in good yields (left). On the other hand, the simple C6-alkylated products are selectively formed in the relatively acidic 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) solvent (right). The observed solvent-controlled chemodivergency can provide access to the versatile C6-functionalized 2-pyridones, which are of potent interest in the medicinal and pharmaceutical chemistry, from the single set of starting materials. Additionally, the related C–H coupling reaction with styrenes is also described.

On the basis of our recent success in the Cp*Rh(III)-catalyzed C–H activation[2d] and pyridine-directed C6-selective C–H functionalization of 2-pyridones,[5-7] we initially tested the reaction of *N*-(2-pyridyl)-2-pyridone (**1a**) with ethyl acrylate (**2a**) in the presence of $[Cp^*RhCl_2]_2$ catalyst (5 mol%), $AgSbF_6$ additive (20 mol%), and $Cu(OAc)_2•H_2O$ oxidant (1.0 equiv) under atmospheric conditions (Table 1). Whereas the reaction in 1,2-dichloroethane (DCE), toluene, 1,4-dioxane, CH_3CN, THF, and 2,2,2-trifluoroethanol (TFE) gave no coupling product (entries 1–6), the DMF solvent afforded the expected C6-alkenylated product **3aa** in 40% yield (entry 7). The structure of **3aa** was unambiguously confirmed by X-ray analysis.[8] Interestingly, additional investigation of solvent identified HFIP to uniquely promote the C6-alkylation giving **4aa** in 40% yield (entry 8). The observed unique solvent-controlled selectivity switching prompted us to perform further optimization with cyclohexyl acrylate (**2b**) as the coupling partner. Gratifyingly, even with the reduced catalyst loading (2.5 mol%), the reaction in DMF under nitrogen improved the reaction efficiency to deliver the targeted C6-alkenylated **3ab** in 80% isolated yield (entry 9). On the other hand, the C6-alkylated product **4ab** was dominantly obtained in 83% yield in HFIP under otherwise identical conditions (entry 10). The elevated temperature (80 ˚C) decreased the yield of **4ab**, but the alkylation selectivity was still retained (entry 11). We again tested TFE solvent under nitrogen conditions (entry 12). Although **4ab** was successfully isolated, the yield was much lower (30%), confirming the better performance of HFIP. Additional observations are to be noted: the alkylation in HFIP is not an oxidative coupling but a stoichiometric amount of $Cu(OAc)_2•H_2O$ is essential for acceptable conversion (entry 13), because $Cu(OAc)_2$ not only provides an acetate ligand to rhodium but also improves the lifetime of rhodium catalyst by reoxidizing an accidentally formed Rh(I) species (vide infra). The *N*-pyridyl directing group was indispensable; the corresponding *N*-methyl-2-pyridone (**1a-Me**) resulted in no reaction whereas in the case of *N*-phenyl-2-pyridone (**1a-Ph**) the C–H alkenylation occurred not on the pyridone ring but on the phenyl ring. Either $[Cp^*RhCl_2]_2$ or $AgSbF_6$ alone did not furnish any products at all (data not shown). The cationic $[Cp^*Rh(MeCN)_3][SbF_6]_2$ or $[Cp^*Rh(OAc)_2]$ instead of the combination of $[Cp^*RhCl_2]_2$ and $AgSbF_6$ showed sluggish reactivity under both the DMF and HFIP conditions (entries 14–17).



Scheme 1. Rhodium-catalyzed, solvent-controlled chemodivergent C-H couplings of 2-pyridones with acrylates: alkenylation in DMF (left) and alkylation in HFIP (right). Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl.

With two optimal conditions in hand (conditions A: entry 9 in Table 1, conditions B: entry 10 in Table 1), we examined the substrate scope and generality of the reactions (Scheme 2).

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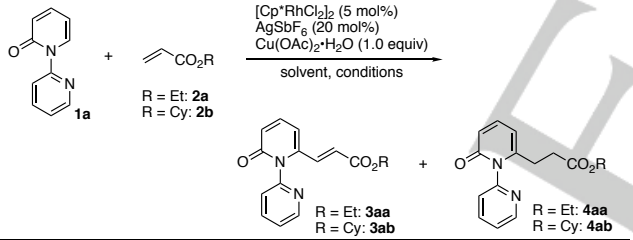
Several acrylate esters **2** were coupled with **1a** under both conditions A and B to afford the corresponding alkenylated (**3aa**–**3af**) and alkylated products (**4aa**–**4ag**) in moderate to good yields. Both the conditions were compatible with electronically diverse functional groups at the C3 position of 2-pyridone, including methyl, trifluoromethyl, ester, and halogen (**3bb**–**3fb** and **4bb**–**4fb**). In particular, the C–Br moiety left intact (**3fb** and **4fb**), which can be a good synthetic handle for further manipulations (vide infra). The electron-donating and electron-withdrawing substituents at the C4 position were also well tolerated (**3gb**–**3hb** and **4gb**–**4hb**). On the other hand, the C5-methylated pyridone showed lower reactivity probably because of steric factors (**3ib** and **4ib**). The more π-conjugated isoquinolinone substrate also afforded the target products **3jb** and **4jb** in acceptable yields. The directing effect of related pyridyl groups were also investigated: 4-methylpyridyl groups worked well under both conditions A and B (**3kb**–**3lb** and **4kb**–**4lb**) whereas the quinoline-type directing group was effective only under conditions A (**3mb** vs **4mb**). The condition-dependent different reactivity can be attributed to the difference of the product-determining step under the respective conditions (vide infra). Notably, among the substrates we tested, the solvent-dependent alkenylation/alkylation product switching was uniformly observed: under conditions A with DMF solvent, only the alkenylated products **3** were obtained. On the other hand, the corresponding alkylated compounds **4** were sole products in HFIP solvent (conditions B).

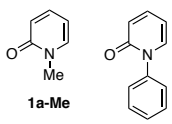
Table 1. Optimization studies for rhodium-catalyzed C–H coupling of *N*-(2-pyridyl)-2-pyridone (**1a**) with acrylate **2a** or **2b**.[a]



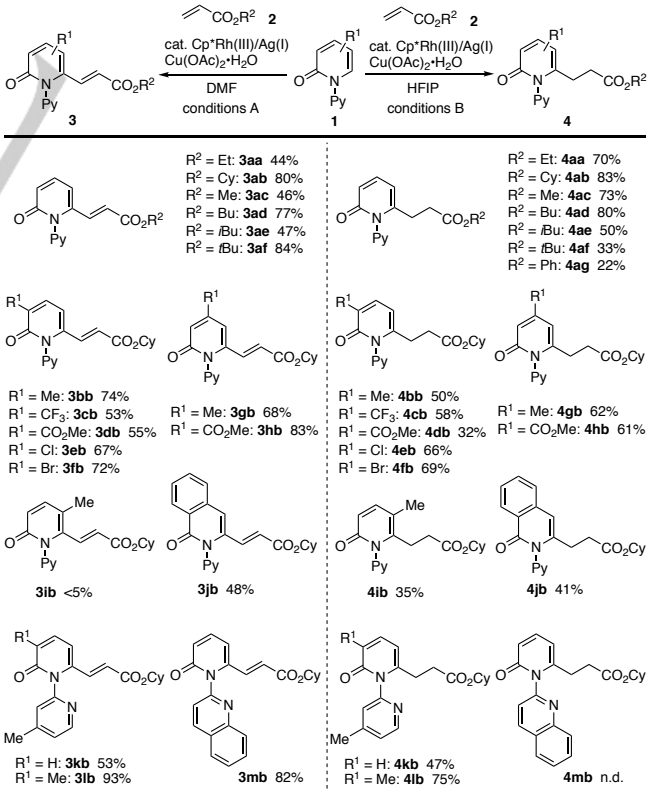
Entry	2	Solvent	Conditions	3 or 4, Yield [%][b]
1	**2a**	DCE	80 ˚C, 16 h, air	n.d.
2	**2a**	toluene	80 ˚C, 16 h, air	n.d.
3	**2a**	1,4-dioxane	80 ˚C, 16 h, air	n.d.
4	**2a**	CH_3CN	80 ˚C, 16 h, air	n.d.
5	**2a**	THF	80 ˚C, 16 h, air	**3aa**, trace
6	**2a**	TFE	80 ˚C, 16 h, air	n.d.
7	**2a**	DMF	50 ˚C, 16 h, air	**3aa**, 40%
8	**2a**	HFIP	80 ˚C, 16 h, air	**4aa**, 40%
9[c]	**2b**	DMF	50 ˚C, 6 h, N_2	**3ab**, 80%
10[c]	**2b**	HFIP	50 ˚C, 24 h, N_2	**4ab**, 83%
11[c]	**2b**	HFIP	80 ˚C, 16 h, N_2	**4ab**, 63%
12[c]	**2b**	TFE	50 ˚C, 20 h, N_2	**4ab**, 30%
13[d]	**2b**	HFIP	50 ˚C, 24 h, N_2	**4ab**, 5%[e]
14[f]	**2b**	DMF	80 ˚C, 16 h, air	n.d.
15[f]	**2b**	HFIP	80 ˚C, 16 h, air	n.d.
16[g]	**2b**	DMF	80 ˚C, 16 h, air	**4ab**, trace
17[g]	**2b**	HFIP	80 ˚C, 16 h, air	n.d.

[a] Conditions: **1a** (0.10 mmol), **2** (0.30 mmol), $[Cp^*RhCl_2]_2$ (0.0050 mmol), $AgSbF_6$ (0.020 mmol), $Cu(OAc)_2•H_2O$ (0.10 mmol), solvent (1.0 mL). [b] Isolated yields. [c] $[Cp^*RhCl_2]_2$ (0.0025 mmol) and $AgSbF_6$ (0.010 mmol). [d] $[Cp^*RhCl_2]_2$ (0.0025 mmol), $AgSbF_6$ (0.010 mmol), and $Cu(OAc)_2•H_2O$ (0.0050 mmol). [e] ^1H NMR yield. [f] With $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (0.0050 mmol) instead of $[Cp^*RhCl_2]_2$ and $AgSbF_6$. [g] With $[Cp^*Rh(OAc)_2]$ (0.0050 mmol) instead of $[Cp^*RhCl_2]_2$ and $AgSbF_6$. n.d. = not detected.

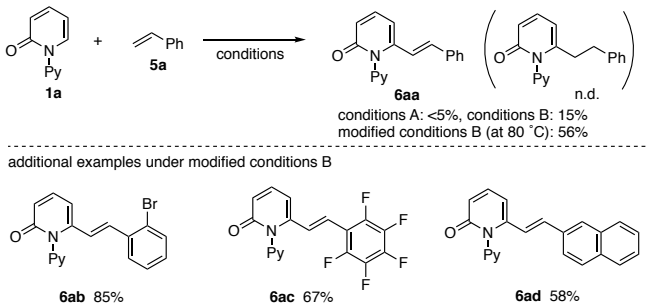
unsuccessful substrates



We next tried the reactions of **1a** with styrenes **5** instead of acrylates **2** as the coupling partners (Scheme 3). Unfortunately, treatment with styrene (**5a**) in DMF (conditions A) resulted in almost no conversion (<5%), but the HFIP solvent at the slightly higher temperature (80 ˚C, modified conditions B) promoted the reaction but led to the alkenylated product **6aa** in 56% yield exclusively. Although we could not find suitable conditions for the alkylation reaction with styrenes, the rhodium catalysis can provide a new avenue to the pyridone-containing phenylene-vinylene conjugations. The brief scope of styrenes **5** are shown also in Scheme 3.

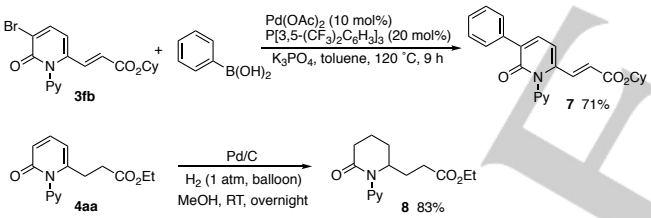


Scheme 2. Rhodium-catalyzed, solvent-controlled C–H alkenylation and alkylation of various 2-pyridones **1** with acrylates **2**. Conditions A: **1** (0.10 mmol), **2** (0.30 mmol), $[Cp^*RhCl_2]_2$ (0.0025 mmol), $AgSbF_6$ (0.010 mmol), $Cu(OAc)_2•H_2O$ (0.10 mmol), DMF (1.0 mL), 50 ˚C, 6 h, N_2. Conditions B: **1** (0.10 mmol), **2** (0.30 mmol), $[Cp^*RhCl_2]_2$ (0.0025 mmol), $AgSbF_6$ (0.010 mmol), $Cu(OAc)_2•H_2O$ (0.10 mmol), HFIP (1.0 mL), 50 ˚C, 24 h, N_2. Yields of isolated products are given. n.d. = not detected. Py = 2-pyridyl.



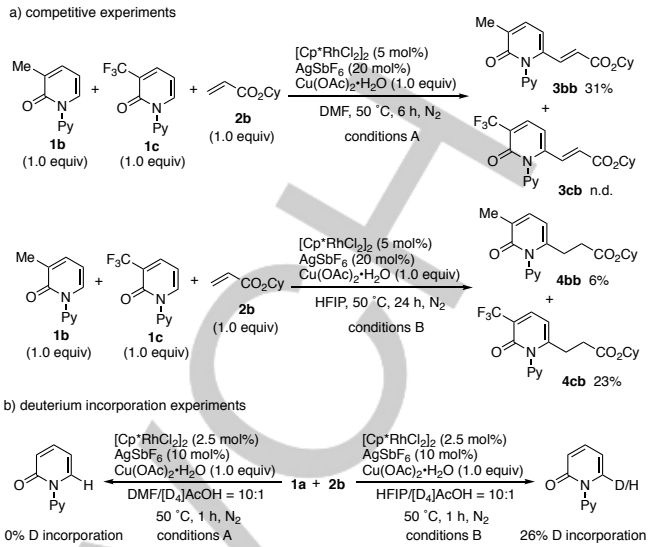
Scheme 3. Reaction of **1a** with styrenes **5** under modified conditions B. Conditions: **1** (0.10 mmol), **5** (0.30 mmol), $[Cp^*RhCl_2]_2$ (0.0025 mmol), $AgSbF_6$ (0.010 mmol), $Cu(OAc)_2•H_2O$ (0.10 mmol), HFIP (1.0 mL), 80 ˚C, 16 h, N_2. n.d. = not detected. Py = 2-pyridyl.

The obtained products could be further derivatized (Scheme 4). The Br-substituted alkenylated 2-pyridone **3fb** underwent the Suzuki-Miyaura coupling reaction under the $Pd(OAc)_2$/P[3,5-$(CF_3)_2C_6H_3]_3$ catalysis[7a] to form the corresponding C3-arylated compound **7** in a good yield. Additionally, the hydrogenation of alkylated **4aa** delivered the saturated piperidone derivative **8**.



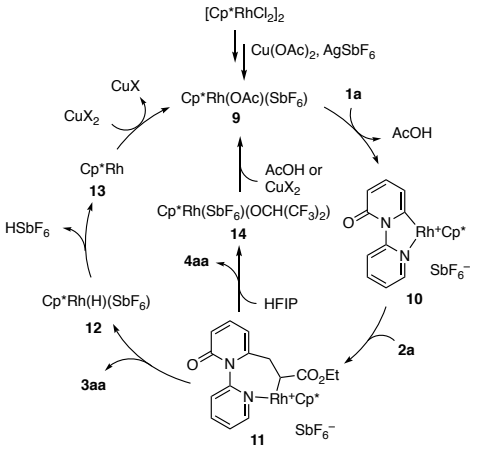
Scheme 4. Derivatization of alkenylated and alkylated 2-pyridones.

To get insight into the reaction mechanism, we performed some competitive and control experiments (Scheme 5). The competitive reaction of electron-rich methyl-substituted **1b** and electron-poor trifluoromethyl-substituted **1c** with cyclohexyl acrylate (**2b**) under conditions A afforded the methyl-substituted alkenylated product **3bb** selectively. In contrast, the more electron-poor **1c** was preferably alkylated under conditions B (Scheme 5a). The aforementioned phenomena suggest that the product-determining step is highly dependent on the solvent used. Thus, we then carried out the deuterium incorporation reactions with $[D_4]$AcOH as co-solvent. Interestingly, under conditions A almost no deuterium incorporation was observed while a significant amount of C6-deuterium-labeled pyridone [D]**1a** was recovered under conditions B (Scheme 5b).

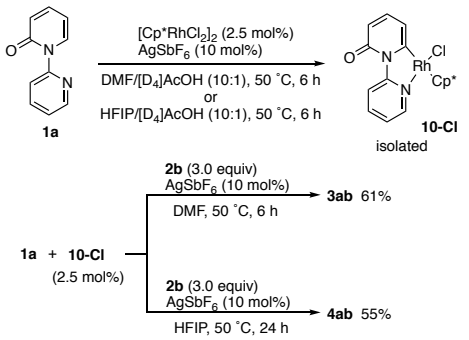


Scheme 5. Competitive and control experiments.

On the basis of the above findings and literature information, we are tempted to propose that the reaction mechanism of **1a** with **2a** is as follows (Scheme 6). First, the starting $[Cp^*RhCl_2]_2$ is converted to an active $Cp^*Rh(OAc)(SbF_6)$ **9** by the action of $AgSbF_6$ and $Cu(OAc)_2$. Subsequent pyridine-directed C6-selective C–H cleavage occurs with the liberation of AcOH to form the five-membered rhodacycle **10**. Under conditions A with the DMF solvent, the insertion of acrylate **2a** into the Rh–C bond in **10** (**10** to **11**) is followed by β-H elimination to afford the alkenylated product **3aa**. The concurrently formed $Cp^*Rh(H)(SbF_6)$ **12** finally goes back to **9** through the elimination of $HSbF_6$ (**12** to **13**) and reoxidation with CuX_2 (**13** to **9**). On the other hand, in the HFIP solvent, the rhodacycle intermediate **11** selectively undergoes protonolysis with the somewhat acidic proton of HFIP to form the corresponding alkylated product **4aa** along with $Cp^*Rh(SbF_6)(OCH(CF_3)_2)$ **14**, which is also converted to **9** via ligand exchange with AcOH or CuX_2. The key five-membered rhodacycle **10-Cl** corresponding to **10** is known[9] and was isolated also in our hands (Scheme 7). The preformed rhodacycle **10-Cl** actually catalyzed the coupling reaction of **1a** with **2b** under conditions A and B to deliver the alkenylated **3ab** and alkylated **4ab** in 55% and 61% yields, respectively. Given the results observed in Scheme 5, in the DMF solvent the C–H cleavage step (**9** to **10**) is irreversible and product-determining step: the more electron-rich 2-pyridone **1b** undergoes the C–H cleavage over the electron-deficient **1c** to be directly transformed to the product **3bb** preferably. On the other hand, the C–H cleavage process is reversible in the HFIP solvent, and thus the product selectivity is determined not in the C–H cleavage but in the insertion step of acrylate. The acrylate can be preferably inserted to the more electron-deficient Rh–pyridone bond bearing the trifluoromethyl group, thus leading to **4cb** in preference to **4bb**.

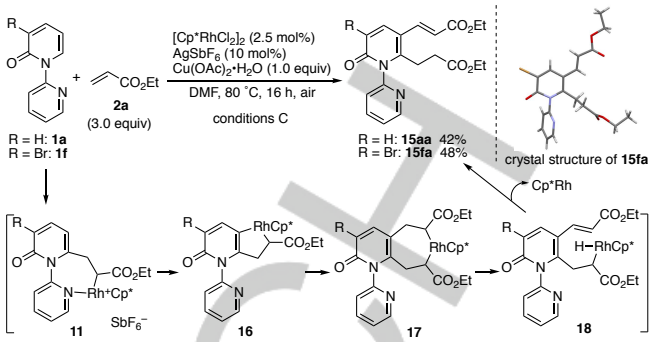


Scheme 6. Plausible mechanism X = OAc or SbF_6.



Scheme 7. Isolation and catalytic activity of rhodacycle **10-Cl**.

Our final observation is somewhat a unique double substitution at the C6 and C5 positions of 2-pyridone (Scheme 8). In the DMF solvent at the higher reaction temperature (80 °C) under air (conditions C), **1a** reacted with 2.0 equiv of **2a** to afford the C6-alkylated-C5-alkenylated product **15aa** in 42% yield. Under same conditions C, the bromo-substituted **1f** was also transformed to the double substitution product **15fa**; the structure of which was confirmed by X-ray analysis.[8] The possible reaction course can include the metallacycles **16** and **17**, which are formed from the rhodacycle **11** via second C–H cleavage at the C5 position. Formation of similar intermediates was proposed in the related rhodium-catalyzed C–H coupling of **1a** with alkynes.[10] Subsequent regioselective β-hydride elimination and reductive elimination from **18** afford the observed doubly substituted product **15**. The control experiment with the isolated **4aa** under conditions C resulted in no conversion, thus confirming that **4aa** is not the intermediate toward **15aa**.



Scheme 8. Double substitution of **1** and plausible mechanism.

In conclusion, we have developed a Cp*Rh(III)-catalyzed, pyridine-directed C6-selective C–H alkenylation and alkylation of 2-pyridones with acrylates. By the judicious choice of solvents, the alkylation/alkenylation selectivity is successfully controlled. The observed chemodivergency can provide efficient access to versatile C6-functionalized 2-pyridones from the same starting substrates, and thus the present study will find applications in the design of new drug candidates based on the pyridone heterocyclic core. Further improvement of catalyst turnover, expansion of substrate scope, and development of related C–H coupling with 2-pyridones are under investigation in our laboratory.

Acknowledgements ((optional))

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Conflict of Interest

The authors declare no conflict of interest.

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[8] CCDC 1896074 (**3aa**) and 1896073 (**15fa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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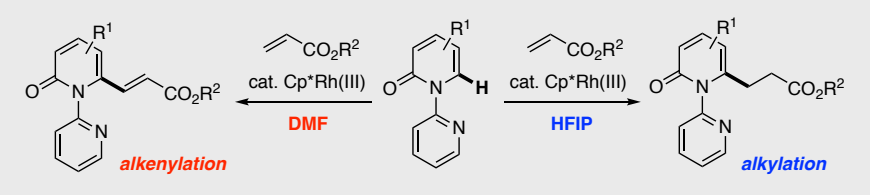

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Solvent-Controlled Rhodium-Catalyzed C6-Selective C-H Alkenylation and Alkylation of 2-Pyridones with Acrylates

At a fork: A Cp*Rh(III)-catalyzed, pyridine-directed C6-selective C–H alkenylation and alkylation of 2-pyridones has been developed. Using DMF as solvent, the C–H alkenylation with acrylates selectively occurs to deliver the corresponding C6-alkenylated 2-pyridones in good yields. On the other hand, the C6-alkylated products are predominantly formed in a more polar and protic solvent: HFIP. The observed solvent-dependent product switching can provide divergent access to the C6-functionalized 2-pyridones.