Organic LETTERS

Letter

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Rhodium(III)-Catalyzed Vinylic C−H Activation: A Direct Route toward Pyridinium Salts

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Supporting Information

ABSTRACT: A synthetic method for highly substituted pyridinium salts from the multicomponent reaction of vinyl ketones/aldehydes, amines, and alkynes using a rhodium catalyst is demonstrated. The catalytic reaction proceeds via an in situ generated imine-assisted Rh^{III}-catalyzed vinylic C−H activation.

Pyridinium cation is an important structural motif found in many natural and bioactive compounds.[1] They were employed as intermediates in natural and heterocyclic compounds synthesis.[2,3] In addition, pyridinium salts have been used as dyes,[4a] ionic liquids,[4b,c] nonlinear optical (NLO) materials,[4d] phase transfer catalysts,[4e] acylating agents,[4f] and surfactants.[4g] S_N2 type reaction of pyridines with alkyl halides is most commonly used to synthesize quaternary pyridinium salts.[5] However, this known method cannot be applied to the synthesis of *N*-arylpyridinium salts. It is worth to mention that, there is no direct route for the synthesis of highly substituted pyridinium salts.

In recent years, transition metal catalyzed C−H activation and annulation reactions were emerged as an important strategy in the synthesis of heterocyclic and carbocyclic compounds.[6] In this context, our group[7] and others have developed the vinylic C−H activation of *α,β*-unsaturated oxime/imine with alkyne to form pyridines.[8] Recently, rhodium and ruthenium catalyzed C−H activation reactions were successfully applied to the synthesis of isoquinolinium,[9] pyridoisoquinolinium,[10] quinolizinium,[11] and cinnolinium[12] salts. We have been fascinated by organic salt compounds[9−12] and wish to establish a straightforward synthetic route to quaternary pyridinium salts. Herein, we report a convenient synthesis of pyridinium salts from vinyl ketones/aldehydes, amines, and alkynes by rhodium(III)-catalyzed vinylic C−H activation and annulation.

Treatment of benzylideneacetone (**1a**), methylamine (**2a**), and diphenylacetylene (**3a**) in the presence of 1.0 mol % of $[RhCl_2Cp^*]_2$, 2.0 equiv of $Cu(OAc)_2{\cdot}H_2O$, and 1.10 equiv of $NaBF_4$ in MeOH at 80 °C for 24 h gave *N*-methylpyridinium salt **4a** in 96% isolated yield. The present C−H activation reaction strongly relies on the choice of solvent, oxidant, and additives. Among the various solvents tested, most alcohol solvents afford product **4a** in good yield, while other solvents are less effective (Figure 1).

We have examined the effect of diverse oxidants for this reaction and none of them were suitable other than $Cu(OAc)_2$. The choice of the anion source also affects the product yield of this reaction (Scheme 1). BF_4^- and SbF_6^- anions gave product **4a** in 98 and 95% yields, respectively, higher than the other

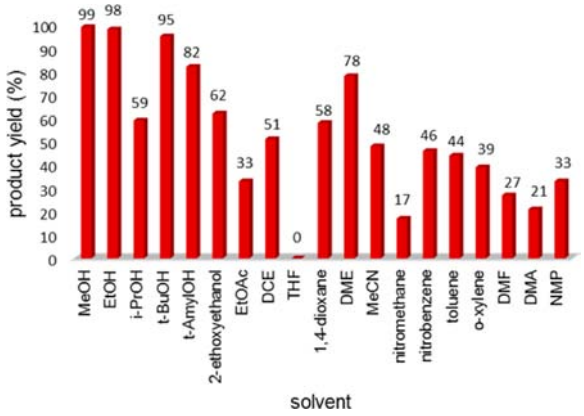
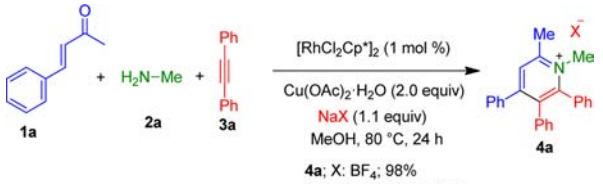


Figure 1. Effect of solvent on the pyridinium salt formation.

Scheme 1. Effect of Anion Source[a,b]



4a; X: BF_4; 98%
4a-SbF$_6$; X: SbF_6; 95%
4a-OTf; X: OTf; 87%
4a-PF$_6$; X: PF_6; 74%

[a]All reactions were carried out using vinyl ketone **1a** (0.34 mmol), methylamine **2a** (0.28 mmol), diphenylacetylene **3a** (0.34 mmol), $[Cp^*RhCl_2]_2$ (1.0 mol %), $Cu(OAc)_2{\cdot}H_2O$ (0.56 mmol), anion source (0.31 mmol), and MeOH (2.0 mL) at 80 °C for 24 h. [b]Yields were determined by the ^1H NMR integration method using mesitylene as the internal standard; amine was used as a limiting reagent.

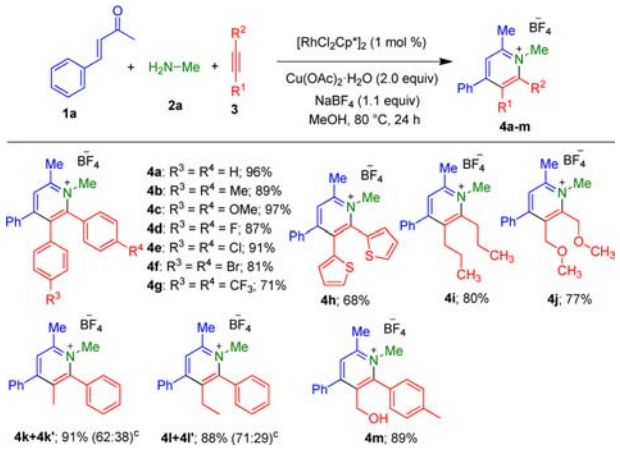
Received: January 5, 2015
Published: February 2, 2015

DOI: 10.1021/acs.orglett.5b00028
Org. Lett. 2015, 17, 924−927

anions. Because of the higher solubility of the product containing BF_4^- anion, we choose this anion for all other investigations. Other inorganic halide salts, such as NaI, NaBr, NaCl, and NaF, as an anion source are less effective to afford pyridinium salts.

Having the optimized reaction conditions in hand, we next investigated the scope of alkynes in the reaction with **1a** and **2a** (Scheme 2). Various symmetrical diaryl- and dialkyl alkynes

Scheme 2. Scope of Alkynes in the Pyridinium Salts Synthesis[a,b]



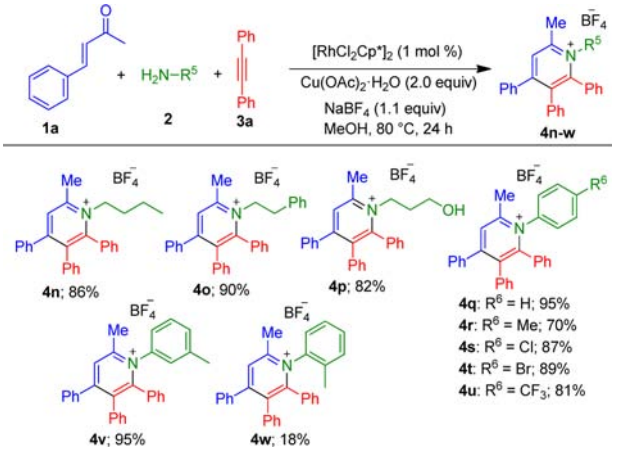
[a]All reactions were carried out using vinyl ketone **1a** (0.34 mmol), methylamine **2a** (0.28 mmol), alkyne **3** (0.34 mmol), $[Cp^*RhCl_2]_2$ (1.0 mol %), $Cu(OAc)_2{\cdot}H_2O$ (0.56 mmol), $NaBF_4$ (0.31 mmol), and MeOH (2.0 mL) at 80 °C for 24 h. [b]Isolated yields. [c]Ratios of regioisomers are given in parentheses and were determined by ^1H NMR analysis; the major isomers were shown.

reacted smoothly under the standard reaction conditions to give corresponding pyridinium salts in good to excellent yields (Scheme 2, **4a**–**j**). Unsymmetrical alkynes are also compatible but give two regioisomeric products with moderate regioselectivity. Thus, 1-phenyl-1-propyne and 1-phenyl-1-butyne gave regioisomeric pyridinium salts **4k** + **4k**′ (62:38) and **4l** + **4l**′ (71:29) in 91% and 88% yields, respectively. Interestingly, under similar reaction conditions, 3-(*p*-tolyl)prop-2-yn-1-ol afforded single regioisomeric product **4m** in 89% yield. While the exact reason for the unique regioselectivity is not known, the directing effect of the hydroxymethyl group attached to the alkyne is likely involved in this alkyne insertion process.

We then examined the scope of amines in this catalytic reaction, and the results are presented in Scheme 3. A variety of alkyl amines including butylamine, 2-phenylethanamine, and 3-aminopropan-1-ol underwent reaction with **1a** and **3a** to furnish the desired pyridinium salts in excellent yields (Scheme 3). Further, substituted aryl amines were also studied under the standard reaction conditions and most of them gave smoothly the desired pyridinium salts in excellent yields (products **4q**–**4w**) except *o*-toluidine. The large steric effect of *o*-toluidine appears to inhibit substantially the formation of product **4w**.

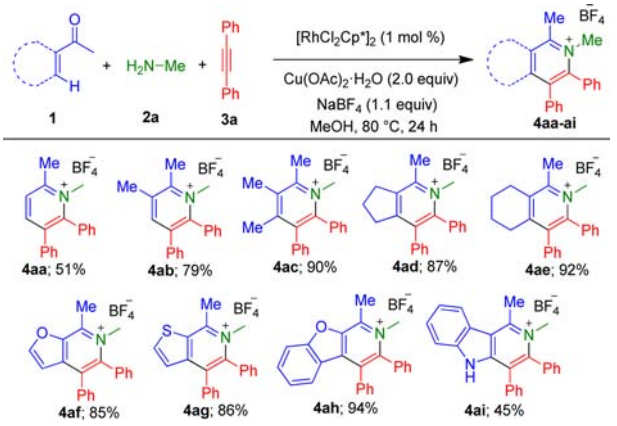
To understand the scope of vinyl ketones in the present catalytic reaction, various substituted methyl vinyl ketones were treated with **2a** and **3a** under the standard reaction conditions to give the corresponding pyridinium salts **4aa**–**4ae** in moderate to excellent yields as shown in Scheme 4. It is noteworthy that lower product yields were observed, if the substituted methyl vinyl ketone does not have a substituent at

Scheme 3. Scope of Amines in the Pyridinium Salts Formation[a,b]



[a]All reactions were carried out using vinyl ketone **1a** (0.34 mmol), amine **2** (0.28 mmol), diphenylacetylene **3a** (0.34 mmol), $[Cp^*RhCl_2]_2$ (1.0 mol %), $Cu(OAc)_2{\cdot}H_2O$ (0.56 mmol), $NaBF_4$ (0.31 mmol), and MeOH (2.0 mL) at 80 °C for 24 h. [b]Isolated yields calculated based on amines.

Scheme 4. Scope of Vinyl Ketones in the Pyridinium Salts Synthesis[a,b]



[a]All reactions were carried out using vinyl ketone **1** (0.34 mmol), methylamine **2a** (0.28 mmol), diphenylacetylene **3a** (0.34 mmol), $[Cp^*RhCl_2]_2$ (1.0 mol %), $Cu(OAc)_2{\cdot}H_2O$ (0.56 mmol), $NaBF_4$ (0.31 mmol), and MeOH (2.0 mL) at 80 °C for 24 h. [b]Isolated yields calculated based on amines.

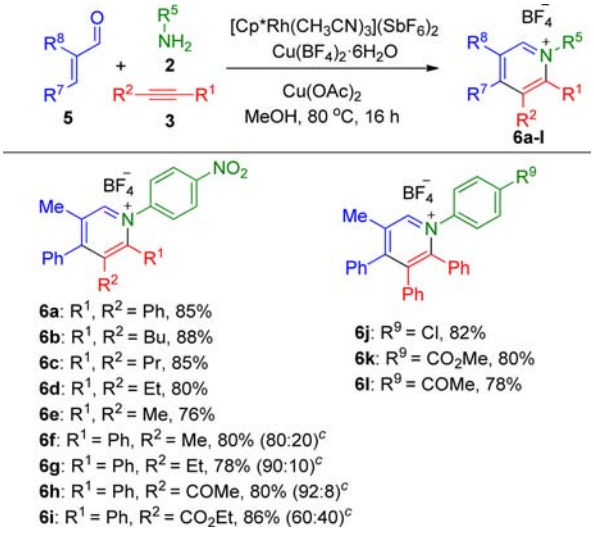
the *β*-carbon of the vinyl group. In addition to the substituted vinyl ketones, several heterocyclic methyl ketones were also examined. Thus, 2-acetylfuran and 2-acetylthiophene reacted with **2a** and **3a** to afford the expected pyridinium salts **4af** and **4ag** in good yields. Similarly, 2-acetylbenzofuran and 3-acetylindole reacted smoothly to give the desired products **4ah** and **4ai** in 94% and 45% yields, respectively.

The present pyridinium salt synthesis can be further applied to *α*,*β*-unsaturated aldehydes, but the reaction conditions are modified. After detailed optimization studies, we found the optimized reaction conditions consisting of amines **2** (0.30 mmol), alkynes **3** (0.30 mmol), unsaturated aldehydes **5** (0.360 mmol), $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (2%, 0.0060 mmol), $Cu(OAc)_2$ (0.30 mmol), and $Cu(BF_4)_2{\cdot}6H_2O$ (0.30 mmol) in MeOH (3 mL) at 80 °C with a reaction time of 16 h. The catalytic reactions gave the desired pyridinium salts in 76–88%

DOI: 10.1021/acs.orglett.5b00028
Org. Lett. 2015, 17, 924–927

isolated yields. By using these conditions, we examined α,β-unsaturated aldehyde **5** with different amines and alkynes, and their results are shown in Scheme 5. Both diaryl and dialkyl

Scheme 5. Synthesis of Pyridinium Salts from Unsaturated Aldehydes, Amines, and Alkynes[a,b]



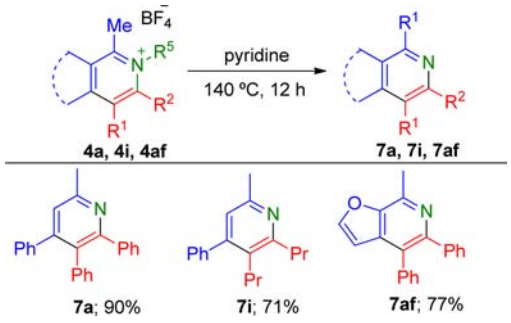
[a]Reaction conditions: amines **2** (0.30 mmol), alkynes **3** (0.30 mmol), unsaturated aldehydes **5** (0.360 mmol), $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (0.0060 mmol), $Cu(OAc)_2$ (0.30 mmol), and $Cu(BF_4)_2{\cdot}6H_2O$ (0.30 mmol) in MeOH (3 mL) at 80 °C for 16 h. [b]Isolated yields based on amines. [c]Ratios of regioisomers are given in parentheses and were determined by ^1H NMR analysis; the major isomers are shown.

symmetrical alkynes react efficiently to afford the corresponding pyridinium salts **6a**–**6e** in good yields. Unsymmetrical alkynes also underwent the [4 +2] cyclization to form pyridinium salts in high yield with good regioselectivity (Scheme 5, products **6f**–**6i**).

The *N*-methylpyridinium salts synthesized using the present method can be easily transformed into highly substituted neutral pyridines by the treatment of the salts with pyridine at 140 °C (Scheme 6).[12] Similarly, condensation of α-methylpyridinium salt (**4a**) with benzaldehyde in the presence of a base afforded 2-styrylpyridinium salt **8a** in 72% isolated yield (eq 1).[13]

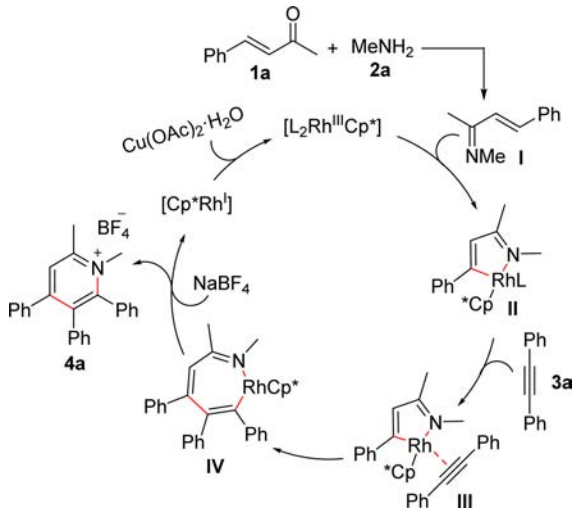
On the basis of the above results and the known literatures, a plausible catalytic cycle for the rhodium(III) catalyzed pyridinium salt synthesis is outlined in Scheme 7. The catalytic

Scheme 6. Synthesis of Pyridines from Pyridinium Salts[a,b]



[a]Reaction conditions: pyridinium salt **4** (0.240 mmol) and pyridine (2.4 mL). [b]Isolated yields.

Scheme 7. Proposed Reaction Mechanism



reaction is initiated by the coordination of α,β-unsaturated imine **I** in situ formed from **1a** and **2a** to Rh^{III}-complex followed by vinylic C–H cleavage to give a five-membered rhodacycle **II**. Coordination of alkyne **3a** to intermediate **II** and consecutive regioselective insertion into carbon–rhodium bond afford a seven-membered rhodacycle **IV**. Facile C–N bond forming reductive elimination of intermediate **IV** affords pyridinium salt **4a** and Rh^{I}. The latter is oxidized by $Cu(OAc)_2{\cdot}H_2O$ salt to generate the active Rh^{III}-catalyst for the next catalytic cycle.

In conclusion, we have developed an efficient method for the synthesis of highly substituted pyridinium salts from vinyl ketones/aldehydes, amines, and alkynes. The catalytic reaction is proceeding through a Rh(III)-catalyzed alkenyl C–H bond activation and annulations. Synthesis of highly substituted pyridines from pyridinium salts also was demonstrated.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures, characterization details, and ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Ministry of Science and Technology of the Republic of China (MOST-103-2633-M-007-001) for support of this research.

DOI: 10.1021/acs.orglett.5b00028
Org. Lett. 2015, 17, 924–927

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DOI: 10.1021/acs.orglett.5b00028
Org. Lett. 2015, 17, 924–927