Organic LETTERS

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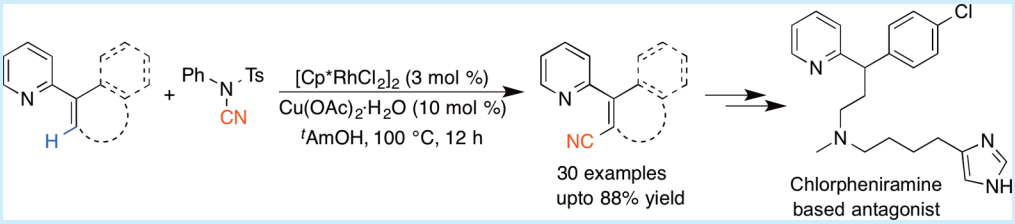
Rhodium-Catalyzed Cyanation of C(sp^2)−H Bond of Alkenes

Manthena Chaitanya and Pazhamalai Anbarasan*

Department of Chemistry, Indian Institute of Technology Madras, Chennai 600036, India

Supporting Information



ABSTRACT: Efficient and selective rhodium-catalyzed cyanation of chelation-assisted C−H bonds of alkenes has been accomplished using environmentally benign *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS) as a cyanating reagent. The developed methodology tolerates various functional groups and allows the synthesis of diverse substituted acrylonitriles in good to excellent yields. Furthermore, the potential of the methodology was demonstrated through the formal synthesis of chlorpheniramine-based antagonist.

Acrylonitriles/vinyl nitriles are the most common scaffolds embedded in various dyes, agrochemicals, herbicides, and natural products.[1] These α,β-unsaturated nitriles also form a core motif of biologically important pharmaceuticals.[2] Representative examples include entacapone[3] and rilpivirine,[4] which are used in the treatment of Parkinson's disease and HIV infections, respectively (Figure 1). Besides the potential application in

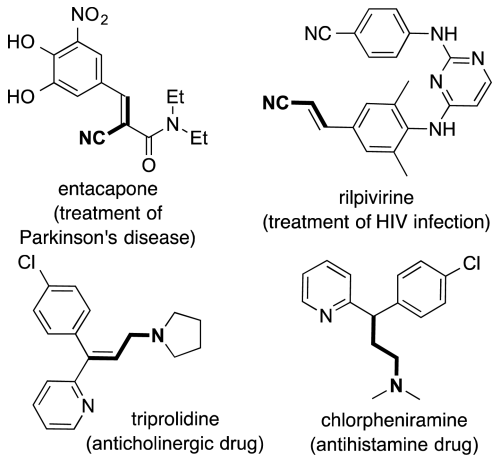


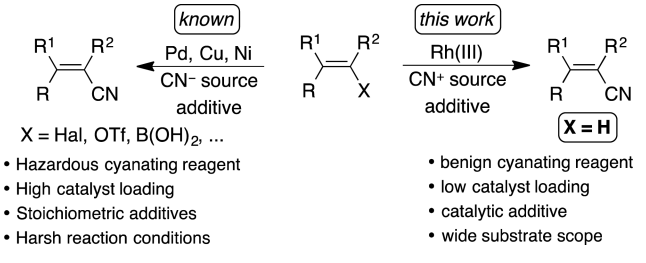
Figure 1. Representative examples of biologically important pharmaceuticals.

biological systems, they were also employed as versatile intermediates and building blocks in medicinal/organic chemistry, which can be readily converted into various important functional groups such as acrylic acid derivatives, amines, aldehydes, nitrogen-based heterocycles, etc. For instance, the synthesis of chlorpheniramine-based antagonist utilizes the acrylonitrile derivative as a key intermediate.[5]

Typical synthetic routes to acrylonitrile derivatives include the Wittig/Horner−Wadsworth−Emmons reaction,[6] Peterson olefination,[7] acrylamide/oxime dehydration,[8] carbocyanation of alkynes,[9] cross-metathesis,[10] and direct conversion of allylic carbon to nitrile.[11] However, many of them suffer from limited substrate scope and/or poor stereoselectivity. Alternative and modern methods are based on the transition-metal-catalyzed cyanation of alkenyl (pseudo)halides[12] and alkenyl metal reagents,[13] which afford acrylonitriles with complete retention of configuration. Nonetheless, use of expensive alkenyl halides, hazards related to handling of cyanating reagents, high catalyst loading due to the cyanide poisoning and/or stoichiometric amount of additives, and harsh reaction conditions are unfavorable (Scheme 1).[14]

In this context, the efficient and selective cyanation of highly abundant C−H bonds with readily accessible cyanating reagent is the most economically viable and environmentally benign strategy for the synthesis of acrylonitriles. Although various directing groups that assisted the cyanation of arene[15] C−H bonds have been extensively studied,[16] the direct cyanation of

Scheme 1. Synthesis of Acrylonitriles



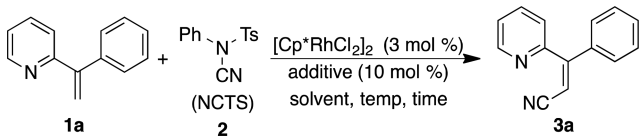
Received: June 16, 2015

DOI: 10.1021/acs.orglett.5b01746
Org. Lett. XXXX, XXX, XXX−XXX

chelation-assisted alkene C−H bonds is rather limited.[17] Due to the potential of direct cyanation of alkene C−H bonds and our interest[18] in the rhodium-catalyzed cyanation of C−H bonds,[19] we herein report the selective rhodium-catalyzed cyanation of a chelation-assisted C−H bond of alkenes.[20]

We started our investigation on the cyanation of a C−H bond employing alkene, 2-(1-phenylvinyl)pyridine (**1a**), as a model substrate. Reaction of **1a** with NCTS **2** in the presence of 1 mol % of $[Cp^*RhCl_2]_2$ and 10 mol % of $AgSbF_6$ in toluene at 120 °C provided the expected cyanated product **3a** in only a detectable amount (Table 1, entry 1). Increasing the catalyst loading to 3 mol % gave the product **3a** in 29% yield after 36 h (Table 1, entry 2). Studying the reaction at 100 and 140 °C afforded the product **3a** in 34 and 21% yield, respectively (Table 1, entries 3 and 4). Next, the effect of coadditives like NaOAc and $Cu(OAc)_2{\cdot}H_2O$ were examined at 100 °C. Although NaOAc did not improve the yield, addition of $Cu(OAc)_2{\cdot}H_2O$ furnished **3a** in comparable yield (Table 1, entries 5 and 6).

Table 1. Rhodium-Catalyzed Cyanation of 2-(1-Phenylvinyl)pyridine (1a): Optimization[a]



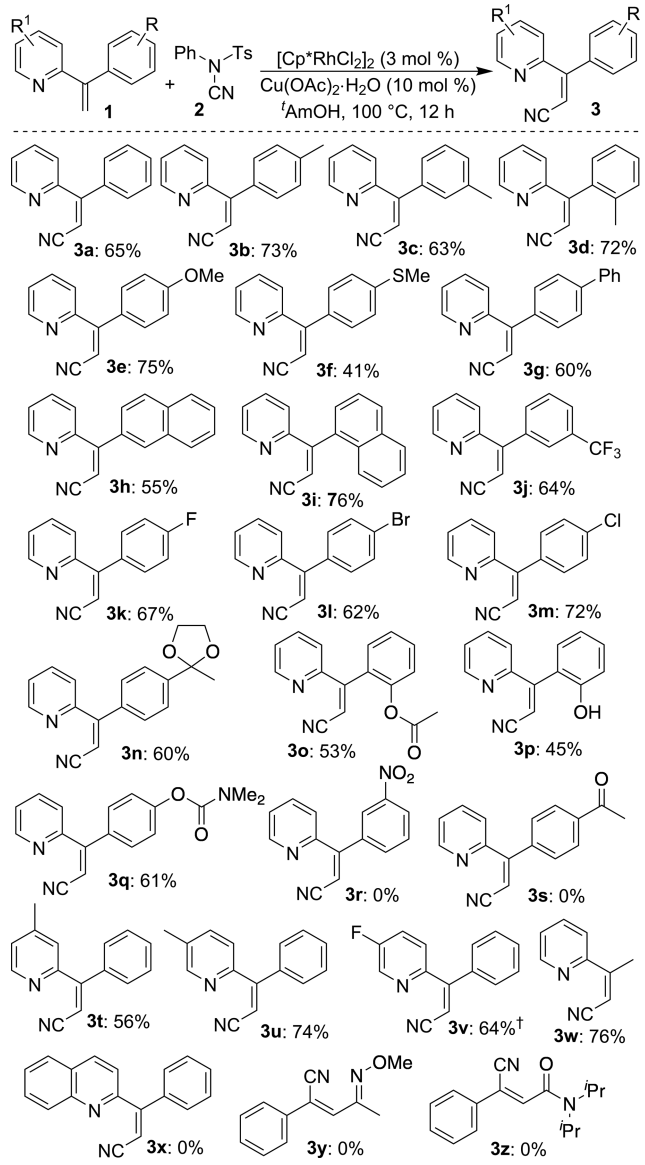
entry	additive	solvent	temp (°C)	time (h)	yield[b] (%)
1[c]	$AgSbF_6$	toluene	120	36	<5
2	$AgSbF_6$	toluene	120	36	29
3	$AgSbF_6$	toluene	100	36	34
4	$AgSbF_6$	xylene	140	36	21
5	$AgSbF_6$/NaOAc[d]	toluene	100	36	17
6	$AgSbF_6$/ $Cu(OAc)_2{\cdot}H_2O$[d]	toluene	100	36	38
7	$Cu(OAc)_2{\cdot}H_2O$	toluene	100	36	38 (11)[e]
8	$Cu(OAc)_2{\cdot}H_2O$	1,2-DCE	100	36	13
9	$Cu(OAc)_2{\cdot}H_2O$	1,4-dioxane	100	36	40
10	$Cu(OAc)_2{\cdot}H_2O$	^{t}AmOH	100	12	65
11[f]	$Cu(OAc)_2{\cdot}H_2O$	^{t}AmOH	100	12	20

[a]Reaction conditions: **1a** (1 equiv), NCTS **2** (2 equiv), $[Cp^*RhCl_2]_2$ (3 mol %), additive (10 mol %), solvent (2 mL), temp, time. [b]Isolated yield. [c]1 mol % of $[Cp^*RhCl_2]_2$. [d]20 mol % of coadditive was used. [e]$Cu(OAc)_2{\cdot}H_2O$ (30 mol %). [f]1.2 and 2.5 equiv of NCTS.

Interestingly, with $Cu(OAc)_2{\cdot}H_2O$ as the only additive, in the absence of $AgSbF_6$, formation of cyanated product **3a** was observed in 38% yield (Table 1, entry 7). Next, an increase in the mol % of copper acetate did not afford any positive influence. It is important to note that cyanation of **1a** was not observed in the absence of rhodium catalyst and even with the presence of 10 mol % of $Cu(OAc)_2{\cdot}H_2O$, which suggests the reaction was indeed catalyzed by rhodium. Consequently, various solvents were screened, keeping the reaction conditions as $[Cp^*RhCl_2]_2$ (3 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (10 mol %) at 100 °C (Table 1, entries 8−10). Among them, ^{t}AmOH was proven to be the best solvent and gave the product **3a** in improved yield of 65% after 12 h (Table 1, entry 10). Furthermore, no improvement in the formation of **3a** was observed when the number of equivalents of cyanating reagent was changed to either 1.2 or 2.5 equiv (Table 1, entry 11). Finally, the best optimized conditions for the cyanation of C−H bond of alkene are 2 equiv of **2**, $[Cp^*RhCl_2]_2$ (3 mol %), $Cu(OAc)_2{\cdot}H_2O$ (10 mol %), ^{t}AmOH, 100 °C, 12 h.

After identifying the best optimized reaction conditions, we studied the scope and limitation of the present methodology by changing the substitution on the arene and directing group. As shown in Scheme 2, simple alkyl- and aryl-substituted arenes containing alkenes gave the corresponding products **3b−d,g,h** in good yield. Electron-donating (−OMe, −SMe) aryls possessing acrylonitriles **3e** and **3f** were achieved in 75 and 41% yield, wherein the formation of **3f** was observed in lower yield possibly due to the sulfur poisoning. Sterically hindered *ortho*-substituted aryl groups were tolerated under the present conditions to afford the corresponding products **3d** and **3i** in 72 and 76% yield, respectively. Medicinally important trifluoromethyl- and fluoro-substituted arenes containing acrylonitriles **3j** and **3k** were synthesized in good yield. Readily functionalizable bromo- and chloro-substituted arenes also underwent smooth reaction to

Scheme 2. Rhodium-Catalyzed C−H Cyanation of Alkenes: Substrate Scope



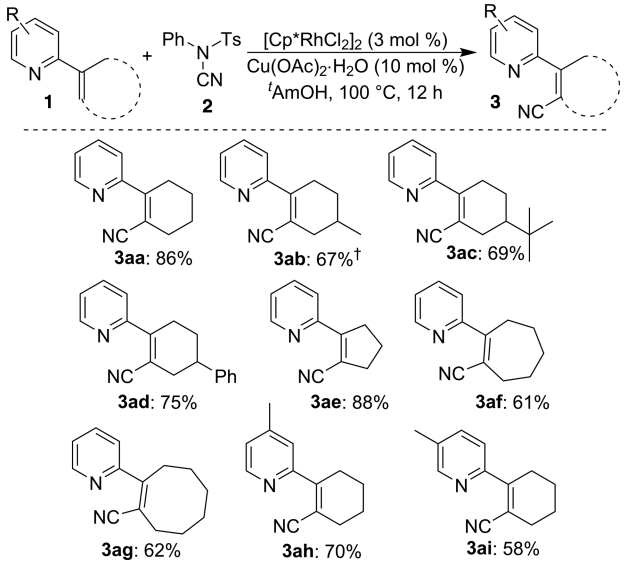
†^{1}H NMR yield.

DOI: 10.1021/acs.orglett.5b01746
Org. Lett. XXXX, XXX, XXX−XXX

furnish the corresponding products **3l** and **3m** in 62 and 72% yield, respectively. Most interestingly, reactive functional groups such as acetal, ester, free hydroxy, and carbamates were also well tolerated under the present conditions to afford the corresponding cyanated products **3n**, **3o**, **3p**, and **3q** in good yield. However, strongly electron-withdrawing and chelating nitro- and acetyl-substituted aryl-containing alkenes did not furnish the expected cyanated product (**3r** and **3s**). Next, the substitutions on the directing group and pyridine ring were also investigated. Most of the substituted pyridines underwent smooth reaction to give the cyanated products **3t**, **3u**, and **3v** in good yield. On the other hand, other directing groups such as quinoline, oxime, and amide were not successful under the present cyanation conditions. Gratifyingly, replacement of the aryl moiety in **1** with a methyl group also afforded the cyanated product **3w** in 76% yield.

Having shown the broad scope of 1,1-disubstituted alkenes, we envisioned the rhodium-catalyzed cyanation of different trisubstituted alkenes (Scheme 3). Thus, various substituted 2-

Scheme 3. Rhodium-Catalyzed C−H Cyanation of Cycloalkenes

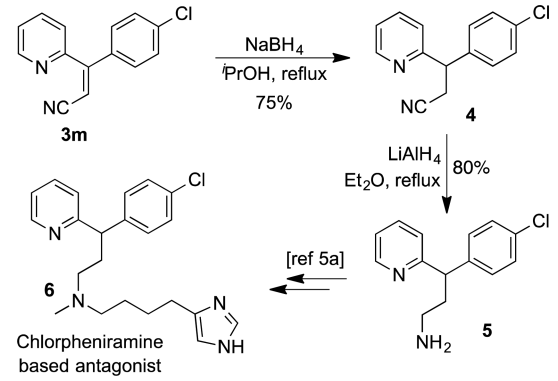


†^{1}H NMR yield.

cycloalkenylpyridines were subjected to the conditions optimized for the rhodium-catalyzed cyanation of C−H bond of alkenes. Cyanation of 2-cyclohexenylpyridine under the optimized conditions provided the cyanated product **3aa** in 86% yield. Similarly, substituted cyclohexenylpyridines also underwent smooth reaction to give cyanated products **3ab**−**ad** in good yield. Changing the ring size of cycloalkene to 5-, 7-, and 8-membered rings also furnished the corresponding products **3ae**−**ag** in 88%, 61%, and 62% yield, respectively. Furthermore, substitution on the pyridine ring was also well tolerated and afforded the products **3ah** and **3ai** in good yields.

Having established the rhodium-catalyzed cyanation of the alkene C−H bond, we were interested in the demonstration of application of the developed method through the formal synthesis of chlorpheniramine[21]-based antagonist **6**. Thus, the initial reduction of alkene in vinyl nitrile **3m** with sodium borohydride afforded the nitrile **4** in 75% yield (Scheme 4). Next, amine **5**, the potential intermediate for the synthesis of **6**,[5a] was achieved in good yield from nitrile **4** through reduction with $LiAlH_4$. This successful transformation revealed the potency of

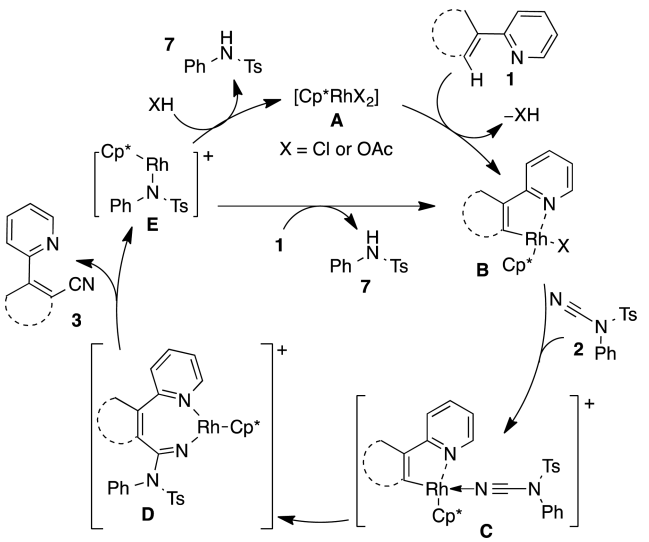
Scheme 4. Synthesis of Chlorpheniramine-Based Antagonist 6



the present method in the synthesis of biologically important intermediates/molecules.

On the basis of previous reports on the rhodium-catalyzed cyanation of arene C−H bonds,[16d,19a] we propose the following mechanism for the rhodium-catalyzed cyanation of the chelation-assisted C−H bond of alkenes (Scheme 5). Initially, reaction of **1**

Scheme 5. Plausible Mechanism



with reactive Rh(III) species **A** would afford the cyclic rhodium species **B** through C−H bond functionalization. Coordination of NCTS **2** with **B** would give the new rhodium species **C**. Next, migration of the vinyl motif to the nitrile carbon atom of the cyanating reagent would readily afford the intermediate **D**. Formation of product **3** and the reactive rhodium species **E** could be readily envisaged via the rearrangement of rhodium species **D**. Ligand exchange in **E** with XH will regenerate the active rhodium species **A** to complete the catalytic cycle. Instead, rhodium species **E** could also react directly with **1** to form the cyclic rhodium species **B** to complete/continue the catalytic cycle.

In conclusion, we have successfully demonstrated the direct rhodium-catalyzed cyanation of chelation-assisted C−H bonds of alkenes employing readily accessible NCTS as cyanating reagent. The present method tolerates various alkene substrates with different functional groups, which allows the synthesis of diverse vinyl nitrile derivatives in good to excellent yields. Furthermore, the potential of the present methodology was

DOI: 10.1021/acs.orglett.5b01746
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demonstrated through the synthesis of a key intermediate for the synthesis of a chlorpheniramine-based antagonist.

■ ASSOCIATED CONTENT

Supporting Information

Experimental methods, characterization data, and ^{1}H and ^{13}C NMR spectra of isolated compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01746.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: anbarasansp@iitm.ac.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Indian Institute of Technology Madras New Faculty Scheme and Board of Research in Nuclear Sciences (BRNS) through the DAE Young Scientist Award (Project No. 2012/20/37C/14/BRNS) for financial support. M.C. thanks the Council of Scientific & Industrial Research (CSIR) for a fellowship.

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DOI: 10.1021/acs.orglett.5b01746
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