ACS Catalysis

Cite This: *ACS Catal.* 2018, 8, 2473−2478

Research Article

pubs.acs.org/acscatalysis

Ruthenium-Catalyzed α-Olefination of Nitriles Using Secondary Alcohols

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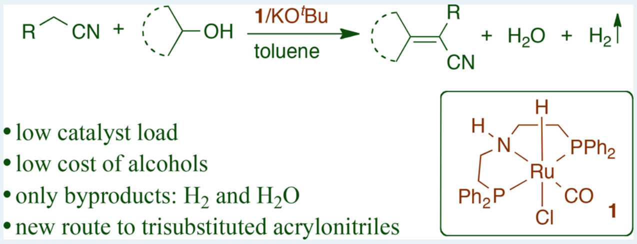
Supporting Information

ABSTRACT: Ruthenium(II) pincer-catalyzed α-olefination of nitriles is reported. This simple protocol provides a transformation for the catalytic synthesis of β-disubstituted vinyl nitriles using secondary alcohols. This catalytic method has an extensive substrate scope, as arylmethyl nitriles, heteroarylmethyl nitriles, and aliphatic nitriles as well as cyclic, acyclic, symmetrical, and unsymmetrical secondary alcohols are all employed in the reaction to provide diverse α-vinyl nitriles. C$=$C bond formation proceeds through activation of the O−H bond of secondary alcohols via an unsaturated 16-electron intermediate ruthenium pincer complex and further condensation of in situ-formed ketones with nitriles. Remarkably, H_2 and H_2O are the only byproducts of this method.



- low catalyst load
- low cost of alcohols
- only byproducts: H_2 and H_2O
- new route to trisubstituted acrylonitriles

KEYWORDS: *α-olefination, ruthenium, nitriles, alcohols, acceptorless dehydrogenation, green synthesis*

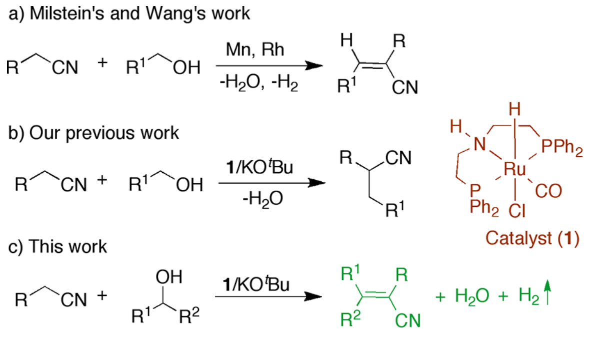
INTRODUCTION

Construction of the C$=$C bond is central to chemical synthesis. While there are several available methods for introducing an unsaturation intramolecularly into a substrate, methods for intermolecular olefin synthesis remain scarce. As researchers work strategically toward this goal, the Wittig reaction with its variants,[1] Peterson olefination,[2] and carbonyl coupling reactions[3] are employed via conventional methods. However, these transformations, in general, require extensive prefunctionalization of reactants and involve a stoichiometric amount of toxic reagents. Catalytic methods for the intermolecular olefin synthesis are limited to ruthenium-catalyzed alkene metathesis[4] and rhodium-catalyzed diazo coupling.[5]

Vinyl nitriles are important intermediates in organic synthesis and prevalent among natural products and pharmaceuticals.[6] They serve as key building blocks and intermediates in number of chemical transformations. Notably, vinyl nitriles have found applications in optoelectronic materials and in the synthesis of light-emitting diodes.[7] Conventional synthesis of vinyl nitriles requires a stoichiometric amount of base, which mediates the reaction of carbonyl compounds and nitriles (Knoevenagel condensation).[8] However, base-promoted condensation reactions involving side reactions such as the aldol reaction, the Cannizzaro reaction, and self-condensation of nitriles are limited to the substrates that are not sensitive to the basic conditions.[8b,9] Thus, attractive alternative methods have been devised for the condensation of carbonyl compounds and nitriles to provide the vinyl nitriles. However, such methods often require the use of toxic reagents and elongated synthetic processes that lead to the generation of copious amounts of waste and poor yields.[10,11]

Acceptorless dehydrogenation of alcohols[12] and concomitant condensation of the resulting carbonyl compounds with nucleophilic molecules afforded atom economical and sustainable chemical transformations.[13,14] In this direction, employing the borrowing hydrogen concept, attractive methods for the construction of C−C and C−N bonds were developed.[13−15] Recently, we have reported the ruthenium-catalyzed α-alkylation of arylmethyl nitriles using primary alcohols as alkylating reagents (Scheme 1b).[16] Water is the only byproduct in this green and efficient alkylation reaction, which was enabled by metal−ligand cooperation operative in Ru−pincer complex **1**, and the reactions proceeded via the borrowing hydrogen pathway. As a continuation of this work, we explored the coupling of secondary alcohols and nitriles, which delivered the β-disubstituted vinyl nitriles (Scheme 1c). Remarkably,

Scheme 1. Catalytic α-Olefination of Nitriles Using Alcohols



Received: November 24, 2017
Revised: February 2, 2018

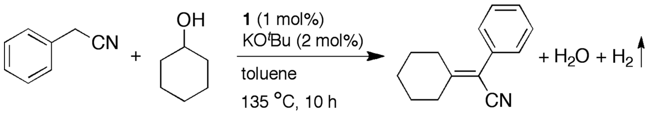
DOI: 10.1021/acscatal.7b04013

liberated H_2 and water are the only byproducts from this green catalytic method. To the best of our knowledge, secondary alcohols were never utilized in the transition metal-catalyzed acceptorless dehydrogenative coupling with nitriles to provide vinyl nitriles. However, while this work was being prepared, Milstein and Wang reported the manganese- and rhodium-catalyzed α-olefination of nitriles by employing primary alcohols (Scheme 1a).[17]

RESULTS AND DISCUSSION

At the outset, phenylacetonitrile, a slight excess of cyclohexanol and ruthenium pincer catalyst **1** (1 mol %, Ru-MACHO) were reacted in toluene. Although complete conversion of nitrile was observed in 16 h, the desired olefin product **2a** was isolated in only moderate yields (entries 1 and 2, Table 1). Analysis of the reaction mixture using ^{1}H nuclear magnetic resonance (NMR) indicated the possible formation of aldol condensation products resulting from the in situ-formed cyclohexanone intermediate. However, contrary to the primary alcohol, no alkylation product was observed.[16] Thus, the catalytic olefination was performed using 2 equiv of cyclohexanol, which resulted in quantitative conversion of nitrile in 10 h, and the olefin product was isolated in 84% yield (entry 3, Table 1). In addition, decreasing the catalyst load from 1 to 0.5 mol % and the temperature from 135 to 120 °C turned out to be detrimental to the progress of the reaction as incomplete conversions were observed even after 24 h (entries 4 and 5, respectively, Table 1). A control experiment using only a base and an experiment without catalyst and base proved that the olefination requires a catalyst (entries 6 and 7, respectively, Table 1).

Table 1. Optimization of the Reaction Conditions for the α-Olefination of Nitriles Catalyzed by 1[a]



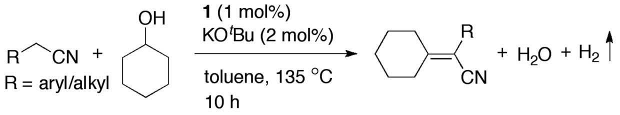
entry	alcohol (equiv)	time (h)	conv. (%)[b]	yield (%)[c]
1	1.05	16	>99	70
2	1.2	16	>99	78
3	2	10	>99	84
4[d]	2	24	57	40
5[e]	2	24	78	60
6[f]	2	24	–	–
7[g]	2	24	–	–

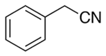
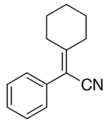
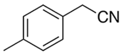
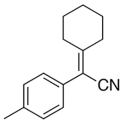
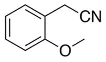
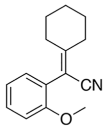
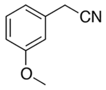
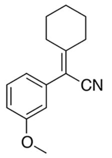
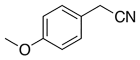
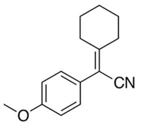
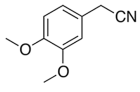
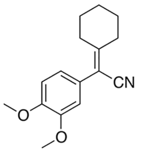
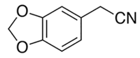
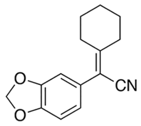
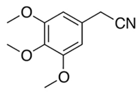
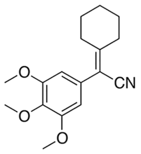
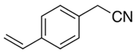
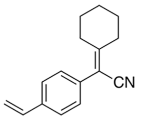
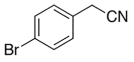
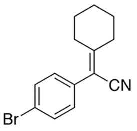
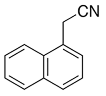
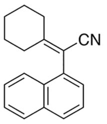
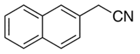
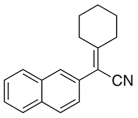
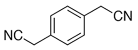
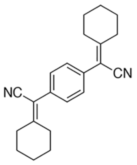
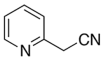
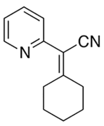
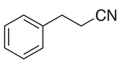
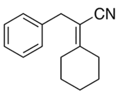
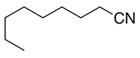
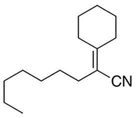
[a] Reaction conditions: phenylacetonitrile (1 mmol), cyclohexanol (2 mmol), catalyst **1**, base and toluene (1.5 mL) heated at 135 °C under open conditions with an argon flow. [b] Conversion of nitrile was determined by gas chromatography (GC) using benzene as an internal standard. [c] Isolated yields after column chromatography. [d] Using 0.5 mol % catalyst and 1 mol % base. [e] Heated at 120 °C. [f] Only 2 mol % base was used. [g] Reaction performed without catalyst and base.

Having established the optimum reaction conditions, we examined the scope of the different nitriles with respect to the catalytic olefination reaction using cyclohexanol (Table 2). Reaction of cyclohexanol with 4-methyl phenylacetonitrile afforded the corresponding olefin product **2b** in 78% yield. When 2-methoxy phenylacetonitrile was subjected to the reaction under standard condition, a diminished conversion (77%) and yield (**2c**, 72%) of the product were obtained, indicating that the catalytic olefination is sensitive to steric hindrance in the proximity. However, *m*- and *p*-methoxyphenylacetonitrile provided 94% and quantitative conversions, respectively, and the corresponding products **2d** and **2e** were isolated in very good yields. Similarly, reactions with di- and trimethoxy-substituted arylmethyl nitriles afforded the desired olefin products **2f**−**2h** in good to excellent yields. Notably, 4-vinyl-substituted arylmethyl nitriles provided complete conversion under standard experimental conditions, and the corresponding product **2i** was obtained in 72% yield. The presence of an electron-withdrawing substituent on the aryl ring was also tolerated. Reaction of 4-bromophenylacetonitrile with cyclohexanol provided the α-olefinated product **2j** in 70% yield; however, complete conversion of nitrile required 24 h. When we examined 1-naphthylacetonitrile under standard experimental conditions, only 34% olefin product was isolated. Thus, the catalyst load was increased to 2 mol %, which provided the product **2k** in 80% yield. A similar reactivity was also observed with 2-naphthylacetonitrile (entry 12, Table 2). In addition, a dinitrile such as 1,4-phenylenediacetonitrile was tested for the olefination reaction using cyclohexanol, which provided divinyl nitrile **2m** in 48% yield. Despite the 99% conversion of dinitrile, the observed low yield of the product may be due to deleterious side reactions. Notably, heteroarylmethyl nitriles are also well tolerated in the olefination reaction. When (pyridin-2-yl)acetonitrile was used, the α-olefinated product **2n** was isolated in 62% yield. Remarkably, aliphatic nitriles were amenable to catalytic synthesis of vinyl nitriles upon reaction with secondary alcohols. Reaction of 3-phenylpropionitrile and nonanenitrile was evaluated, which resulted in the corresponding vinyl nitrile products **2o** and **2p** in 62% and 48% yields, respectively.

The scope of the secondary alcohols with respect to the catalytic olefination using different nitriles was further investigated. In general, a variety of secondary alcohols can be employed under the reaction conditions to deliver α-olefinated products in good to excellent yields (Table 3). When 4-methyl cyclohexanol was reacted with phenylacetonitrile and 2-(3,4,5-trimethoxyphenyl)acetonitrile, the corresponding olefin products were obtained in 75% and 93% yields, respectively (**3a** and **3b**, respectively, Table 3). Similarly, 4-*tert*-butyl cyclohexanol also exhibited very good reactivity. Remarkably, the nitrogen-containing cyclic secondary alcohol, 1-phenethylpiperidin-4-ol, underwent olefination with 2-(3,4,5-trimethoxyphenyl)acetonitrile to provide the product in 60% isolated yield (**3d**). Cycloheptanol reacted with phenylacetonitrile and 2-(4-methoxyphenyl)acetonitrile to provide the corresponding products in 86% (**3e**) and 70% (**3f**) isolated yields, respectively. A bulky cyclic alcohol such as cyclooctanol provided the corresponding olefin product **3g** in 46% yield with a 2 mol % catalyst load; in addition, increasing the catalyst load to 5 mol % enhanced the yield of **3g** to 66%. A sterically demanding substrate, 2-adamantanol delivered the α-olefinated product **3h** in 69% yield. Ultimately, an aliphatic secondary alcohol such as 3-pentanol and 4-heptanol was subjected to catalytic olefin synthesis, which provided the corresponding vinyl nitriles **3i** and **3j** in 58% and 48% isolated yields, respectively. Finally, unactivated unsymmetrical secondary alcohols such as 2-butanol, 2-hexanol, and 2-heptanol were investigated with different arylmethyl nitriles using catalyst **1** (5 mol %, 24 h), which provided vinyl nitrile products **3k**−**m** as an *E*/*Z* mixture in moderate yields. Overall, this protocol allows rapid access to highly branched β-disubstituted vinyl nitriles

Table 2. Ruthenium-Catalyzed α-Olefination of Nitriles Using Cyclohexanol[a]



entry	nitrile	product		conv. (%)[b]	yield (%)[c]
1			**2a**	>99	84
2			**2b**	85	78
3			**2c**	77	72
4			**2d**	94	80
5			**2e**	>99	85
6			**2f**	70	65
7			**2g**	92	87
8			**2h**	92	83
9			**2i**	>99	72
10[d,e]			**2j**	>99	70
11[d]			**2k**	90	80
12[d]			**2l**	>99	81
13			**2m**	99	48
14[f]			**2n**	70	62
15[f]			**2o**	80	62
16[f]			**2p**	68	48

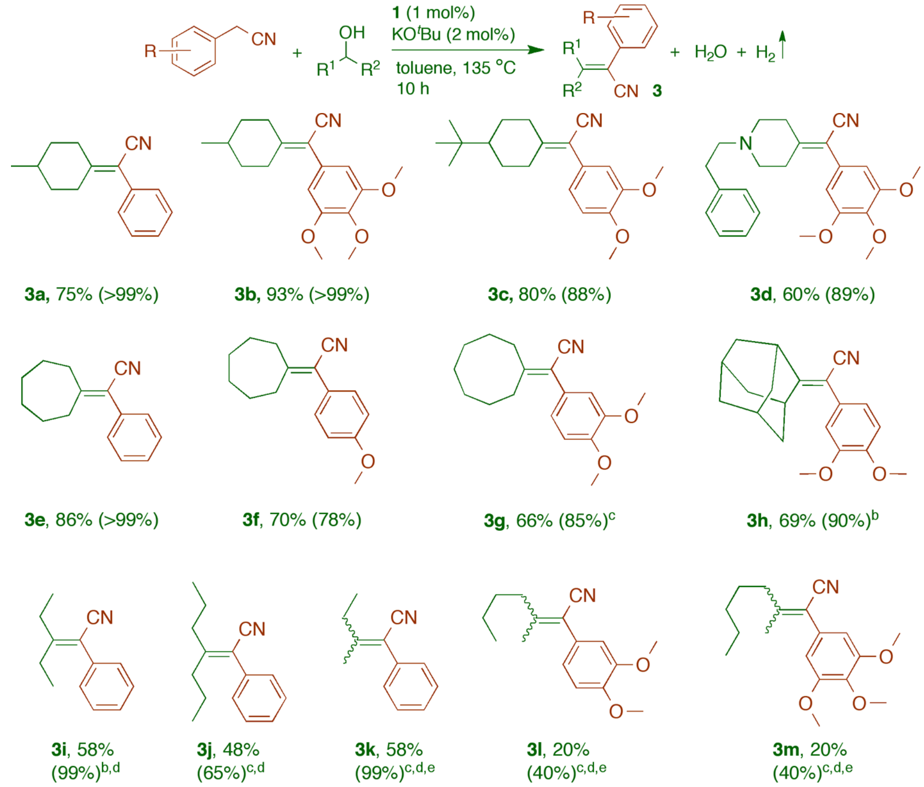
[a] Reaction conditions: nitrile (1 mmol), cyclohexanol (2 mmol), toluene (1.5 mL), catalyst **1** (1 mol %), and KO^{t}Bu (2 mol %) heated at 135 °C under open condition with an argon flow. [b] Conversion of nitriles determined by GC using benzene as an internal standard. [c] Isolated yields after column chromatography. [d] Using 2 mol % catalyst and 4 mol % base. [e] Reaction time of 24 h. [f] Reaction performed with 0.25 mmol of nitrile and 0.5 mmol of cyclohexanol using 3 mol % catalyst **1** and 6 mol % base.

from very simple and readily available starting materials with liberated dihydrogen and water as the only byproducts.

Mechanistic Investigations. GC monitoring of the progress of the catalytic α-olefination reaction of phenylacetonitrile using cyclohexanol catalyzed by **1** indicated that the reaction follows first-order kinetics with respect to phenylacetonitrile (Figure 1). Over time, decreasing the concentration of phenylacetonitrile (black line) can be corroborated with increasing concentrations of product **2a** (red line). While nearly 1.5 equiv of cyclohexanol (green line) was consumed in the reaction, the intermediate cyclohexanone (magenta line) was only short-lived as it undergoes rapid condensation with phenylacetonitrile.

A plausible mechanism for the α-olefination of nitriles using secondary alcohols catalyzed by **1** is depicted in Scheme 2. Our previous work with catalyst **1** established facile O−H, N−H,

Table 3. Ruthenium-Catalyzed α-Olefination of Nitriles Using Secondary Alcohols[a]



3a, 75% (>99%)
3b, 93% (>99%)
3c, 80% (88%)
3d, 60% (89%)
3e, 86% (>99%)
3f, 70% (78%)
3g, 66% (85%)[c]
3h, 69% (90%)[b]
3i, 58% (99%)[b,d]
3j, 48% (65%)[c,d]
3k, 58% (99%)[c,d,e]
3l, 20% (40%)[c,d,e]
3m, 20% (40%)[c,d,e]

[a] Reaction conditions: nitrile (1 mmol), alcohol (2 mmol), toluene (1.5 mL) catalyst **1** (1 mol %), and KO^{t}Bu (2 mol %) heated at 135 °C under open conditions with an argon flow. Reported yields correspond to isolated pure compounds. Conversion of nitriles is given within parentheses and determined by GC analysis using benzene as an internal standard. [b] Using 2 mol % catalyst **1** and 4 mol % base. [c] Reaction performed with 0.25 mmol of nitrile and 0.5 mmol of secondary alcohol using 5 mol % catalyst **1** and 10 mol % base. [d] Reaction time of 24 h. [e] Isolated as an *E*/*Z* mixture.

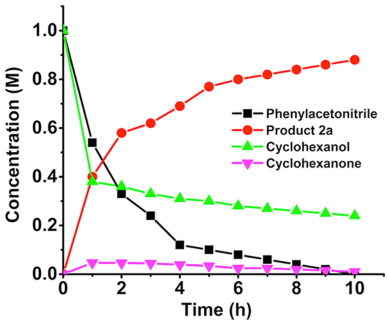
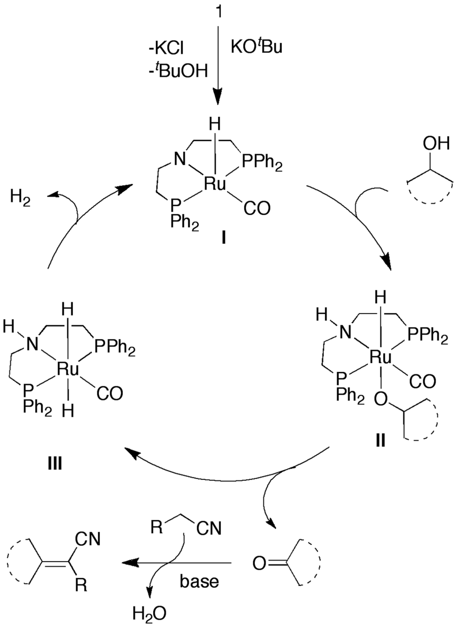


Figure 1. Monitoring the progress of the reaction by GC. Concentrations of phenylacetonitrile (black line), cyclohexanol (green line), product **2a** (red line), and the intermediate cyclohexanone (magenta line) in the catalytic α-olefination of nitriles.

and spC–H bond activation reactions.[16,18] Catalyst **1** reacts with a base to generate a coordinatively unsaturated reactive intermediate **I** (under similar conditions, the formation of **I** from catalyst **1** in the reaction mixture was previously established by us),[18a] which further reacts with secondary alcohols to provide an alkoxy ligand-coordinated intermediate **II** (such an alkoxy complex coordinated with benzyloxy ligand was characterized in situ by us)[18c] upon O–H activation of secondary alcohol.[18c] The amide donor present in unsaturated intermediate **I** accepts the proton upon activation of the O–H bond and becomes the amine donor in **II**. In concert with the metal center, the ligand motif participates in bond formation and bond breaking and hence displays metal–ligand cooperation. At this point, a dehydrogenation reaction takes place by a β-hydride elimination reaction (perhaps via decoordination of one of the donor atoms), which releases the ketone and generates a ruthenium dihydride complex **III**. However,

Scheme 2. Proposed Mechanism for the Ruthenium-Catalyzed α-Olefination of Nitriles Using Secondary Alcohols



although such a mechanism is often invoked to explain the apparent β-hydride elimination reaction (which requires coordinative unsaturation) in transition metal alkoxo-ligated pincer complexes,[14e,f,19] the involvement of other mechanistic pathway cannot be ruled out.[20] In addition, complex **III** liberates dihydrogen to regenerate the catalytically active intermediate **I**. Finally, the Knoevenagel condensation between in situ-formed ketones and nitriles provides β-disubstituted vinyl nitriles by elimination of a water molecule.

CONCLUSION

In conclusion, we have presented an unprecedented transition metal-catalyzed α-olefination of nitriles using secondary alcohols, which resulted in β-disubstituted vinyl nitriles. Notably, arylmethyl nitriles, heteroarylmethyl nitriles, and aliphatic nitriles were amenable to this catalytic transformation. Similarly, cyclic and acyclic secondary alcohols as well as symmetrical and unsymmetrical secondary alcohols were also employed in this reaction, which resulted in an assortment of α-vinyl nitrile products. The acceptorless dehydrogenative coupling of nitriles and alcohols proceeds via amine−amide metal−ligand cooperation that occurs in the activated complex of **1**. Remarkably, dihydrogen and water are the only byproducts in this catalytic olefination reaction, which make this method highly attractive for the synthesis of different kinds of fine and bulk chemicals.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.7b04013.

Experimental procedures, spectral data, and copies of ^{1}H and ^{13}C NMR spectra of the products (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank SERB New Delhi (EMR/2016/002517), DAE, and NISER for financial support. S.T. thanks UGC for a research fellowship.

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