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Rh(III)-Catalyzed Aryl and Alkenyl C−H Bond Addition to Diverse Nitroalkenes

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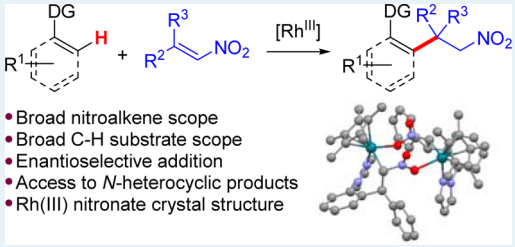
Supporting Information

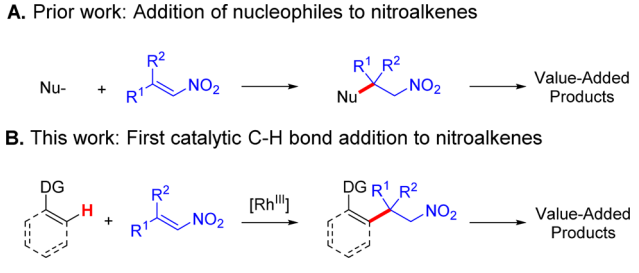
ABSTRACT: The transition-metal-catalyzed C−H bond addition to nitroalkenes has been developed. Very broad nitroalkene scope was observed for this Rh(III)-catalyzed method, including for aliphatic, aromatic, and *β*,*β*-disubstituted derivatives. Additionally, various directing groups and both aromatic and alkenyl C−H bonds were effective in this transformation. Representative nitroalkane products were converted to dihydroisoquinolones and dihydropyridones in a single step and in high yield by iron-mediated reduction and in situ cyclization. Moreover, preliminary success in enantioselective Rh(III)-catalyzed C−H bond addition to nitroalkenes was achieved as was X-ray structural characterization of a nitronate intermediate.



KEYWORDS: *C−H functionalization, Rh(III) catalysis, nitroalkene, enantioselective catalysis, dihydroisoquinolone*

Nitroalkenes are valued and extensively employed electrophiles for the addition of a broad range of different nucleophiles to give nitroalkanes, which are versatile intermediates to amines, carbonyl compounds, and other useful chemotypes (Scheme 1A).[1] Many heteroatom and carbon nucleophiles have been added to nitroalkenes, including additions catalyzed by Lewis acids and organocatalysts. Nitroalkenes have also been used as Michael acceptors in Rh- and Pd-catalyzed additions of stable organometallic reagents such as aryl boronic acids.[2] However, despite dramatic recent advances in C−H bond functionalization, to our knowledge,[3−5] transition-metal-catalyzed C−H bond additions to nitroalkenes have not been reported.

Scheme 1. Nitroalkenes as Versatile Electrophiles



Herein, we report on the Rh(III)-catalyzed addition of aryl and alkenyl C(sp^2)-H bonds to nitroalkenes (Scheme 1B). A broad range of C−H functionalization substrates with different directing groups as well as branched and unbranched aliphatic and aromatic nitroalkenes are effective inputs. Moreover, *β*,*β*-disubstituted nitroalkenes also coupled efficiently and represent the first examples of Rh(III)-catalyzed intermolecular C−H bond additions to trisubstituted alkenes.[6] The utility of representative products was demonstrated by their conversion in a single step and in high yield to dihydroisoquinolones and dihydropyridones that cannot be accessed by alternative Rh(III)-catalyzed methods. Finally, promising initial results for enantioselective catalytic C−H bond addition to nitroalkenes was accomplished.

After evaluating a number of reaction parameters for coupling pyrrolidine benzamide **1a** and nitroalkene **2a**, optimal conditions were identified to be $[Cp^*RhCl_2]_2$ as the pre-catalyst, $AgSbF_6$ as the chloride abstractor, dichloroethane as the solvent, and an 80 °C reaction temperature (entry 1, Table 1). Importantly, product **3a** was obtained in high yield without the formation of any bis-addition byproduct.[7] Both $[Cp^*RhCl_2]_2$ and $AgSbF_6$ are essential as is apparent by the complete absence of product obtained when either is excluded (entries 2 and 3). Replacing $AgSbF_6$ with the less-coordinating $AgB(C_6F_5)_4$ did not improve the yield of the reaction (entry 4).[8] The addition of 20 mol % of AgOAc, an additive that has been reported to be successful for other Rh(III)-catalyzed transformations,[9] decreased the yield to 65% for this reaction (entry 5). However, this additive was found to be beneficial for other C−H functionalization substrates (vide infra). The reaction proceeded equally well in 1,4-dioxane as solvent (entry 6), but a significantly lower yield was observed in AcOH despite its previous use as solvent in other Rh(III)-catalyzed additions to Michael acceptors.[10,11] When the reaction was performed at room temperature, a slightly diminished yield was observed (entry 8). Because 80 °C proved to be the optimal temperature for more challenging C−H functionalization substrate/nitroalkene pairs, this reaction temperature was chosen for evaluating substrate scope. Use of the bench-stable

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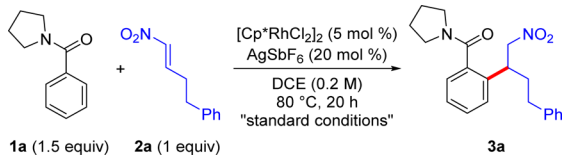
Table 1. Control Reactions



1a (1.5 equiv) **2a** (1 equiv) **3a**

entry[a]	variation from the standard conditions	yield **3a** (%)[b]
1	**none**	**84**
2	no $[Cp^*RhCl_2]_2$	0
3	no $AgSbF_6$	0
4	$AgB(C_6F_5)_4$ instead of $AgSbF_6$	71
5	with 20 mol % AgOAc	65
6	in 1,4-dioxane	82
7	in AcOH	14
8	room temperature instead of 80 °C	66
9	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$ instead of $[Cp^*RhCl_2]_2$	80
10[c]	$Cp^*Rh(CH_3CN)_3(SbF_6)_2$ instead of $[Cp^*RhCl_2]_2$	78
11	$[Cp^*IrCl_2]_2$ instead of $[Cp^*RhCl_2]_2$	53
12	$[RuCl_2(p\text{-cymene})]_2$ instead of $[Cp^*RhCl_2]_2$	62
13	$[Cp^*CoCl_2]_2$ instead of $[Cp^*RhCl_2]_2$	0

[a]Standard conditions: 0.15 mmol of **1a**, 0.10 mmol of **2a** with $[Cp^*RhCl_2]_2$, $AgSbF_6$ in dichloroethane at 80 °C for 20 h. [b]Yields determined by ^1H NMR spectroscopic analysis relative to $SiMe_3Ph$ as an external standard. [c]Reaction conducted on the benchtop.

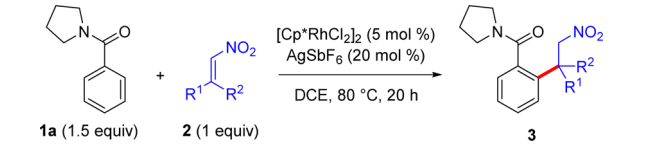
preformed catalyst $Cp^*Rh(CH_3CN)_3(SbF_6)_2$ resulted in a comparable yield of 80% (entry 9), and when the reaction was performed on the benchtop with the preformed catalyst, a 78% yield was observed (entry 10). While not as effective as $[Cp^*RhCl_2]_2$, $[Cp^*IrCl_2]_2$ and $[RuCl_2(p\text{-cymene})]_2$ precatalysts did afford product **3a** in 53% and 62% yield, respectively (entries 11 and 12). No conversion was observed for the cobalt precatalyst $[Cp^*CoCl_2]_2$ under these conditions (entry 13).

Very broad scope for the nitroalkene coupling partner was observed (Table 2). Product **3a** was isolated by silica gel chromatography in 85% yield, and when the reaction was conducted on the benchtop with the preformed catalyst $Cp^*Rh(CH_3CN)_3(SbF_6)_2$, **3a** was isolated in 75% yield. This result highlights the tolerance of this reaction to air and ambient conditions. Additional branched and unbranched aliphatic nitroalkenes afforded products **3b**, **3c**, and **3d** in high yields. A broad range of aromatic *β*-nitrostyrenes were also effective coupling partners (**3e**–**3h**), including electron-rich (**3f**), electron-poor (**3g**), and ortho-substituted (**3h**) derivatives. Nitroalkenes containing indole (**3i**) and furan (**3j**) heterocycles also coupled in acceptable yields.

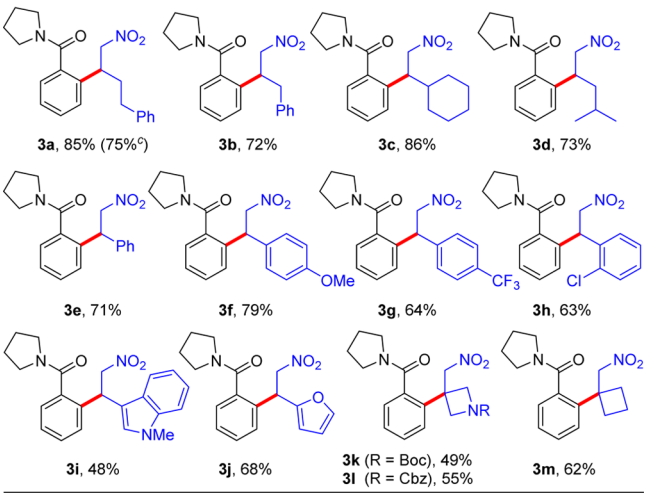
We next explored *β*,*β*-disubstituted nitroalkenes. Although acyclic 2-methyl-1-nitroprop-1-ene and *trans*-*α*-methyl-*β*-nitrostyrene did not couple under these reaction conditions, we were pleased to find modest to good yields of the coupled products when employing azetidine (**3k** and **3l**) and cyclobutane (**3m**) nitroalkenes. Significantly, these products represent the first examples of a Rh(III)-catalyzed intermolecular C–H bond addition to trisubstituted alkenes.[6]

After establishing broad nitroalkene scope, we next explored the scope of the C–H functionalization substrate (Table 3). In addition to pyrrolidine benzamide, other amide directing groups such as *N*,*N*-diisopropylbenzamide (**3n**) and *N*-methylbenzamide (**3o**) were also successful in this reaction. Electron-rich (**3p** and **q**) and electron-poor (**3s**) substituents on the C–H bond functionalization substrate were well tolerated, and when the substituents were placed at the

Table 2. Nitroalkene Scope[a,b]



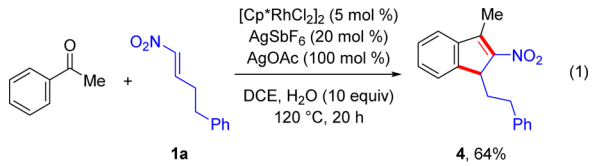
1a (1.5 equiv) **2** (1 equiv) **3**



[a]Conditions: 0.30 mmol of **1a**, 0.20 mmol of **2a** with $[Cp^*RhCl_2]_2$, $AgSbF_6$ in dichloroethane at 80 °C for 20 h. [b]Isolated yields after silica gel chromatography. [c]Reaction conducted on the benchtop using 10 mol % of $Cp^*Rh(CH_3CN)_3(SbF_6)_2$.

meta-position, high regioselectivity was observed for the least hindered site (**3q**–**3s**). Heteroaromatic C–H bond activation substrates such as thiophene (**3t**), furan (**3u**), and indoles (**3v** and **3w**) afforded the addition products in good to excellent yields. In addition to aryl substrates, alkenyl amides were also effective C–H bond substrates with products **3x**, **3y**, and **3z** obtained in good yields. We also expanded the scope of the directing group beyond amides. The electron rich urea directing group afforded product **3aa** in a high yield. Additionally, N-heterocyclic directing groups such as pyrazole (**3ab**), triazole (**3ac**), and tetrazole (**3ad**) provided the addition products in good yields. Surprisingly, 2-phenylpyridine resulted in <5% of the desired addition product **3ae**, instead giving multiple unassigned decomposition products. The poor results obtained for the archetypal 2-pyridyl directing group, which is more basic than all of the other directing groups used, perhaps clarify why C–H bond additions to nitroalkenes had not previously been reported.

The weakly coordinating acetophenone C–H functionalization substrate was also evaluated, and it required more forcing conditions similar to those reported for the Rh(III)-catalyzed synthesis of indenes from acetophenones and enones.[9] Under these conditions, addition and cyclization with concomitant loss of water afforded nitroindene **4** (eq 1).



1a **4**, 64% (1)

To demonstrate the utility of the nitroalkene addition products **3**, representative derivatives were subjected to a single-step iron-mediated nitro group reduction/cyclization

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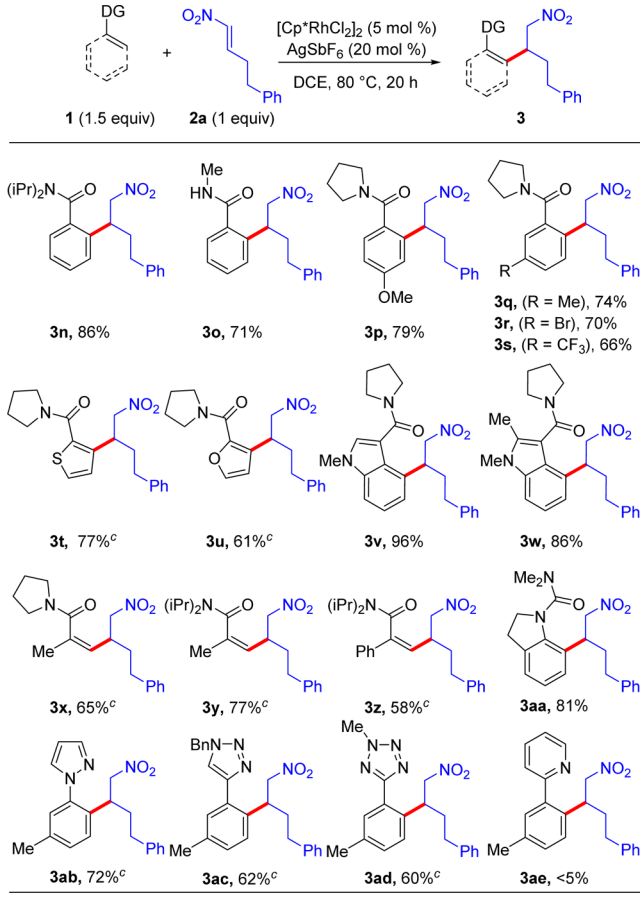
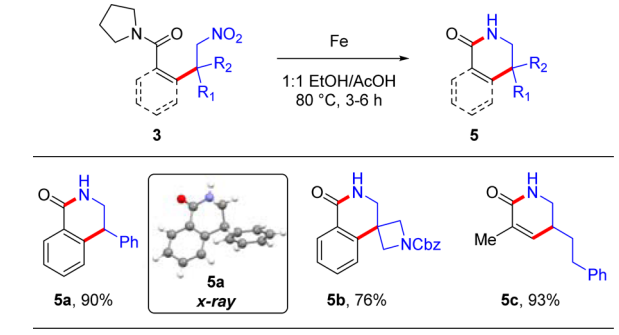
Table 3. C−H Functionalization Substrate Scope[a,b]



[a]Conditions: 0.30 mmol of **1a**, 0.20 mmol of **2a** with $[Cp^*RhCl_2]_2$, $AgSbF_6$ in dichloroethane at 80 °C for 20 h. [b]Isolated yields after silica gel chromatography. [c]20 mol % of AgOAc was added.

sequence (Table 4). Dihydroisoquinolones have previously been synthesized by Rh(III)-catalyzed annulations of *O*-pivaloyl or *O*-Boc benzhydroxamic acids and alkenes, but controlling selectivity is often a challenge, and a mixture of isomers is typically observed.[12] Dihydroisoquinolone **5a** was obtained in high yield with the structure confirmed by X-ray crystallographic analysis. This is a different isomer than that obtained by the Rh(III)-catalyzed annulation of *O*-Boc benzhydroxamic acid and styrene.[13] Moreover, both dihydroisoquinolone **5b** and dihydropyridone **5c** were also obtained in good yields as single

Table 4. Product Reduction and Cyclization[a,b]

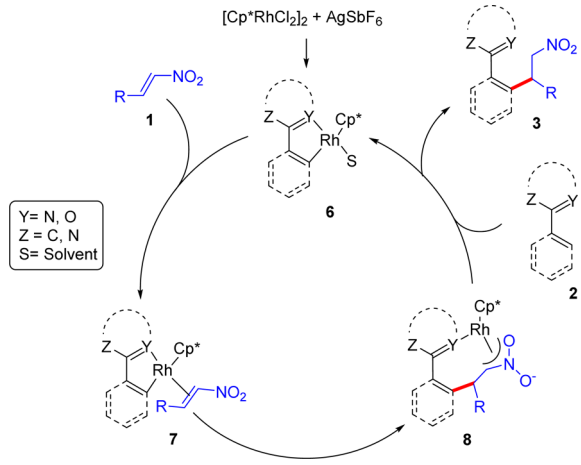


[a]Conditions: **3** (1 equiv), Fe (6 equiv) in 1:1 EtOH/AcOH (0.2 M) at 80 °C for 3−6 h. [b]Isolated yields after aqueous workup.

isomers and they represent structural types that have not previously been prepared by Rh(III)-catalyzed alkene annulation approaches and would likely be very difficult to access.

A plausible mechanism for the Rh(III)-catalyzed C−H bond addition to nitroalkenes is shown in Scheme 2. Concerted

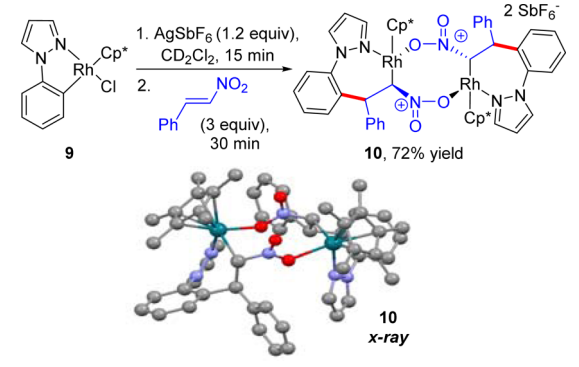
Scheme 2. Proposed Mechanism for the Transformation



metalation/deprotonation of **2** generates the well-documented rhodacycle **6**.[14] Coordination of the nitroalkene **1** provides complex **7**, which upon insertion to the nitroalkene provides the Rh(III) nitronate **8**. Coordination of **2** followed by concerted metalation/deprotonation then concomitantly releases product **3** and regenerates rhodacycle **6**.

To investigate the mechanism of this transformation, we sought to characterize the proposed Rh(III) nitronate intermediate by X-ray crystallography (Scheme 3). Subjecting

Scheme 3. Preparation of a Rh(III) Nitronate



the preformed rhodacycle **9** to stoichiometric $AgSbF_6$ followed by excess *β*-nitrostyrene gave the Rh(III) nitronate **10** in 72% yield after trituration. The structure of **10** was rigorously characterized by X-ray crystallographic analysis as a C-bound nitronate dimer and to our knowledge represents the first X-ray structure of a rhodium nitronate.[15] While **10** exists as the η^1-C-bound rhodacycle nitronate dimer in crystal form, it is possible that an η^3-bound monomer exists in solution.[16]

Finally, in preliminary results using the Rh-diiodo dimer **11** employing Cramer's elegantly designed chiral ligand,[17] we observed promising selectivities in the catalytic enantioselective synthesis of various alkyl (**3a**) and aromatic (**3e**, **3f**, **3g**) nitroalkene addition products (eq 2). Notably, electron-poor,

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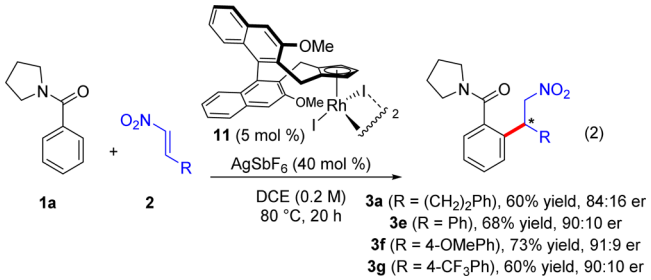

-neutral, and -rich aromatic nitroalkenes all coupled with ≥90:10 er. These results suggests a new general strategy for catalytic asymmetric additions to nitroalkenes.[1b]

In conclusion, we have developed the first transition-metal-catalyzed C−H bond addition to nitroalkenes. Broad substrate scope was realized for both the C−H bond and nitroalkene coupling partners. Representative addition products were converted to dihydroisoquinolone and dihydropyridone heterocycles in a single step and in high yield by iron-mediated reduction/cyclization. Additionally, preliminary success with the catalytic enantioselective addition of C−H bonds to nitroalkenes was achieved as was X-ray structural characterization of a Rh(III) nitronate intermediate.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b03217.

Procedures and spectral data (PDF)
Crystal data for **5a** (CIF)
Crystal data for **10** (CIF)

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Notes

The authors declare no competing financial interest.

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(13) Although compound **5a** was reported to be the product of Rh(III)-catalyzed annulation using styrene,[12c] our spectral data for **5a**, whose structure was rigorously confirmed by X-ray crystallographic analysis, is very different than the reported data. We conclude that the previously reported compound was incorrectly assigned.

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