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Expedient Access to 2,3-Dihydropyridines from Unsaturated Oximes by Rh(III)-Catalyzed C−H Activation

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Supporting Information

ABSTRACT: α,β-Unsaturated oxime pivalates are proposed to undergo reversible C(sp^2)−H insertion with cationic Rh(III) complexes to furnish five-membered metallacycles. In the presence of 1,1-disubstituted olefins, these species participate in irreversible migratory insertion to give, after reductive elimination, 2,3-dihydropyridine products in good yields. Catalytic hydrogenation can then be used to convert these molecules into piperidines, which are important structural components of numerous pharmaceuticals.

Nitrogen heterocycles are among the most abundant structural components of pharmaceuticals.[1] Because of their omnipresence in biologically active molecules, the synthesis of nitrogen heterocycles has attracted considerable attention in the synthetic community. Pyridines represent one of the most prevalent scaffolds encountered in medicinal chemistry.[1b,c] Removal of one unsaturation from a pyridine ring affords a dihydropyridine.[2] Dihydropyridines come as three double-bond isomers: 1,4-dihydropyridine (**1**), 2,3-dihydropyridine (**2**), and 1,2-dihydropyridine (**3**) (Figure 1). The first

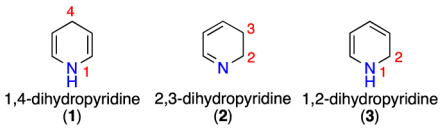


Figure 1. Structures of dihydropyridines.

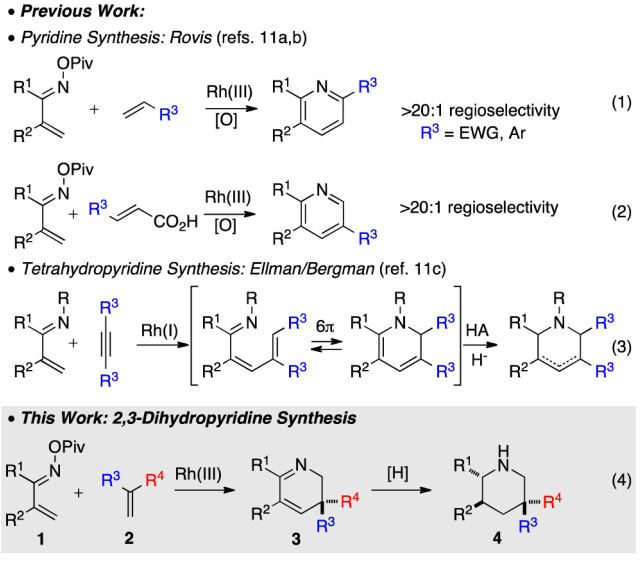
synthesis of a 1,4-dihydropyridine is attributed to Arthur Hantzsch for work done over a century ago.[3] The importance of this motif is highlighted by its presence in nicotinamide adenine dinucleotide (NADH), a universal biological reducing agent. Interest in 1,4-dihydropyridines has been further stimulated after their incorporation into calcium channel blockers.[4]

In stark contrast to 1,4-dihydropyridines, which are stable structures, the 2,3- and 1,2-congeners are kinetically labile and thus are not found in bioactive molecules as such. Nevertheless, they have been implicated as versatile intermediates in biosynthetic pathways leading to alkaloid natural products. Recent examples include the proposed biosynthesis of the marine natural product symbioimine[5] as well as the isoquinuclidine alkaloids keramaphidin B and manzamine A.[6]

While *N*-alkyl-2,3-dihydropyridinium salts are well-documented and even isolable,[7] there is scarce information on the synthesis of N-unprotected 2,3-dihydropyridines.[8] This constitutes a handicap to the synthetic community, given the potential number of transformations in which such intermediates can engage.

In recent years, Rh(III)-catalyzed C−H activation has become a method of choice for constructing nitrogen heterocycles.[9,10] In particular, coupling of α,β-unsaturated imines and oximes with alkynes represents a useful approach to pyridines.[11] We recently demonstrated that high regioselectivities are obtainable when electronically biased alkenes are used in place of alkynes as coupling partners (Scheme 1, eq

Scheme 1. Rh(III)-Catalyzed Synthesis of 2,3-Dihydropyridines



1).[11a] Furthermore, substituted acrylic acids were shown to give the complementary regioisomers of the pyridine products, where the carboxylate acts as a traceless directing group (eq 2).[11b] In a conceptually distinct approach, Bergman and Ellman showed that Rh(I)-catalyzed coupling of unsaturated imines with internal alkynes followed by iminium formation and reduction can deliver complementary tetrahydropyridines depending on nature of the acid (eq 3).[11c] This latter reaction was proposed to proceed through dihydropyridine intermediates.

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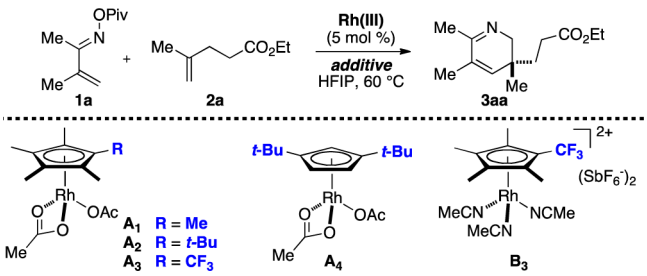
In our initial work (eq 1), we never observed the presumed intermediate dihydropyridine adducts even in the absence of external oxidants. We speculated that the instability of the 2,3-dihydropyridine was responsible and that rapid in situ oxidation to the pyridine was faster than the initial annulation.[12] We envisioned that the use of 1,1-disubstituted alkenes would prevent oxidation and deliver 2,3-dihydropyridines as isolable outcomes of the reaction (eq 4). Herein we disclose our results.

We commenced our investigation by subjecting α,β-unsaturated oxime pivalate **1a** and alkene **2a** to catalytic amounts of various CpRh(III) diacetates[13] in hexafluoroisopropanol (HFIP) at 60 °C (Table 1). As can be seen from the table, replacing the Cp* ligand ($\mathbf{A_1}$) with its more sterically congested *tert*-butyl-substituted congener ($\mathbf{A_2}$) increased the yield of the 2,3-dihydropyridine product (**3aa**) from 81% to 91%. The product yield was further enhanced when electron-deficient Cp ligand $\mathbf{A_3}$ bearing a trifluoromethyl[10b] substituent was used. When CsOAc was employed as an additive, product **3aa** was isolated in 99% yield when 5 mol % $\mathbf{A_3}$ was used.

Table 1. Optimization of the Reaction Conditions[a]

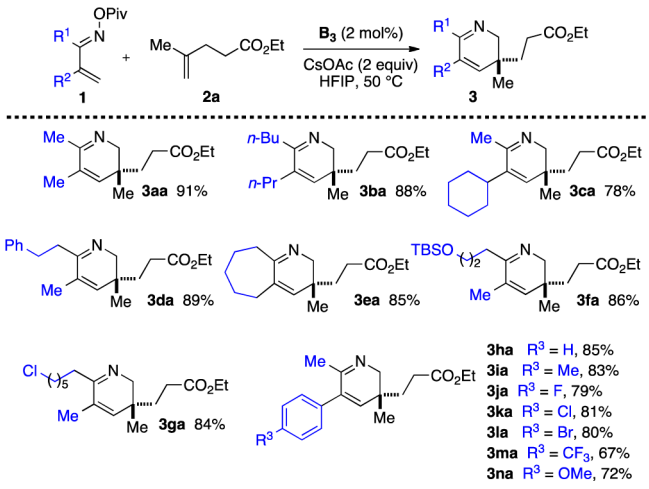


entry	Rh(III)	additive	yield (%)[d]
1	$[Cp^*RhCl_2]_2$	AgOAc[b]	<12[c]
2	$\mathbf{A_1}$	none	55
3	$\mathbf{A_1}$	p-TsOH[b]	72
4	$\mathbf{A_1}$	CsOAc	81
5	$\mathbf{A_2}$	CsOAc	91
6	$\mathbf{A_3}$	CsOAc	99
7	$\mathbf{A_4}$	CsOAc	92
8	$\mathbf{B_3}$	CsOAc	99
9[e]	$\mathbf{B_3}$	CsOAc	99

[a]Reaction conditions: **1a** (1.0 equiv), **2a** (1.2 equiv), additive (2.0 equiv), and Rh(III) catalyst (5 mol %) in HFIP (0.3 M) at 60 °C for 16 h. [b]10 mol % additive was used. [c]Determined by ^{1}H NMR spectroscopy. [d]Yields of isolated products. [e]The catalyst loading was decreased to 2 mol %, and the reaction temperature was decreased to 50 °C.

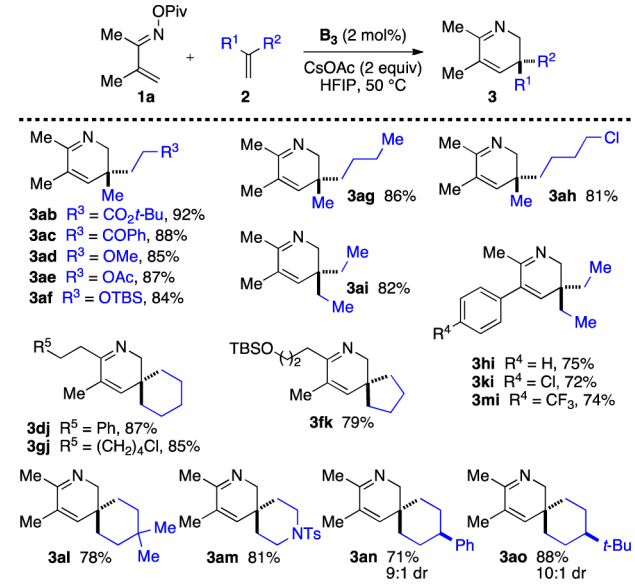
With the optimal conditions in hand, we examined the scope of the reaction (Scheme 2). α,β-Unsaturated oxime pivalates **1** bearing various linear or branched alkyl substituents at positions 2 and 3 were tolerated (**3aa**−**3da**). Substrates bearing an aromatic ring at position 3 were also competent (**3ha**−**3na**), as well as functional groups such as silylated alcohols (**3fa**) and halides (**3ga** and **3la**).

Scheme 2. α,β-Unsaturated Oxime Pivalate Scope



Turning our attention to the scope of the alkenes, we found that various 1,1-disubstituted olefins are competent substrates for 2,3-dihydropyridine synthesis (Scheme 3). Functional groups including esters (**3ab**), ketones (**3ac**), ethers (**3ad**), and protected amines (**3am**) were tolerated. With methylenecyclopentanes and cyclohexanes as substrates, *spiro*-bicyclic 2,3-dihydropyridines were obtained in good yields (**3dj**−**3ao**). Finally, *exo*-methylenecyclohexanes bearing a prostereogenic carbon at the 4-position furnished the corresponding 2,3-dihydropyridines (**3an** and **3ao**) with high levels of diastereocontrol (up to 10:1 dr).

Scheme 3. Alkene Scope



To demonstrate the synthetic utility of the 2,3-dihydropyridines, we turned our attention to derivatization of the products. Stimulated by the wide abundance of piperidines in biologically active compounds,[1a] attention was placed on the reduction of C−C and C−N double bonds. We successfully developed a single-pot protocol wherein the Rh(III)-catalyzed coupling of imines and alkenes was sequenced with Pd-catalyzed hydrogenation to deliver high overall yields of piperidine products (Scheme 4). Surprisingly, the major

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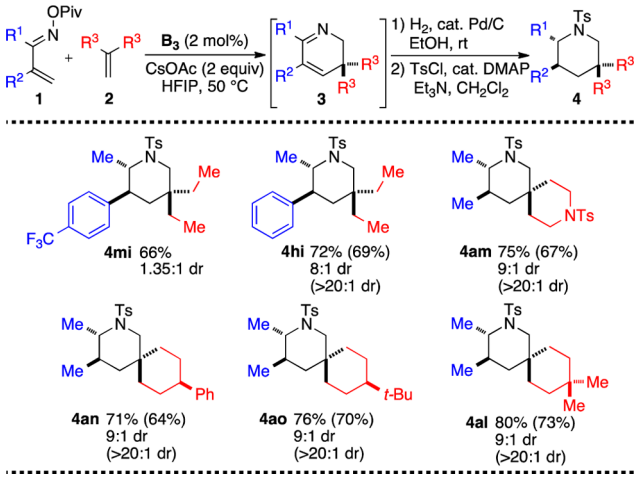
Scheme 4. One-Pot Synthesis of Piperidines[a]

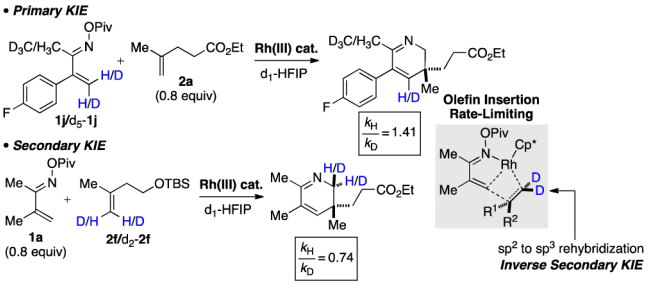


[a]Values in parentheses denote yields and diastereomeric ratios after recrystallization.

diastereomer formed proved to have the trans relationship between the substituents at the 2 and 3 positions, although the level of selectivity seemed to be modestly substrate-dependent (compare **6mi** vs **6hi**). The relative configurations of products **6am** and **6ao** were unambiguously assigned by X-ray crystallography.[13]

Labeling studies provided valuable insight into the mechanism of the reaction. A small primary kinetic isotopic effect (KIE = 1.41) was observed when deuterated oxime pivalate d_5-**1j** was used (Scheme 5). This observation may be

Scheme 5. Observation of Kinetic Isotope Effects

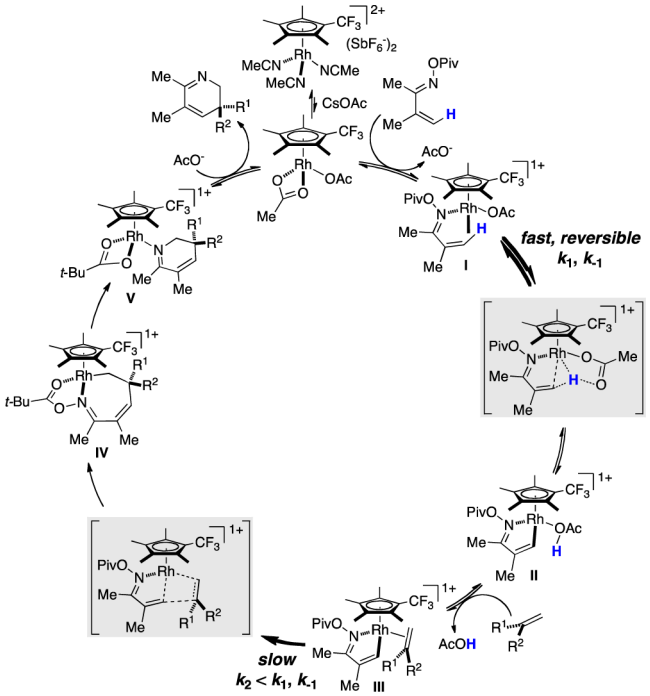


explained by evoking a reversible C−H activation event and incorporation of deuterium from solvent rather than as a direct indicator of a rate difference.[14] A rather large inverse KIE (0.74) was observed with deuterated alkene d_2-**2f**, which is consistent with rate-determining olefin insertion.

A Hammett study provided further support that olefin insertion is the slow step.[13] A large and negative value of the reaction constant (ρ = −1.2) indicates that positive charge builds up at the reaction site during the rate-limiting step. Preliminary kinetic analysis[15] of the reaction revealed a first-order dependence of the rate on both the catalyst and the oxime. Furthermore, a first-order dependence on the alkene was also seen at low concentrations; higher concentrations demonstrated some evidence of an inhibitory effect.[13]

In order to account for the observed mechanistic data, the following catalytic cycle is proposed (Scheme 6). Following the formation of the active Rh(III) diacetate complex, C−H activation takes place reversibly through a concerted metal-

Scheme 6. Postulated Catalytic Cycle



ation−deprotonation mechanism. The resultant five-membered metallacycle **II** then undergoes rate-limiting migratory insertion to give the seven-membered metallacycle **IV**. Reductive elimination/N−O bond cleavage furnishes the 2,3-dihydropyridine and regenerates the catalyst.

In conclusion, we have described an efficient Rh(III)-catalyzed synthesis of semisaturated nitrogen heterocycles. A significant effect of the ligand on the reactivity was observed, with the electron-deficient trifluoromethyl-substituted Cp*^{CF_3} ligand being optimal. The scope of the transformation is large,[16] and many of the obtained 2,3-dihydropyridines were successfully reduced to piperidines with good levels of diastereocontrol. Mechanistically, it was established that the reaction follows overall second-order kinetics, migratory insertion being the turnover-limiting step.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic characterization of compounds, X-ray crystal structures (CIF), and detailed mechanistic studies. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04946.

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Notes

The authors declare no competing financial interest.

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spectroscopy, Brian Newell (CSU) for solving X-ray crystal structures, and Maria Romanova-Michaelides (University of Geneva) for assistance with mathematical analysis.

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(16) Terminal alkenes afford pyridine adducts in low yields. Internal alkenes are not suitable reaction partners.

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