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

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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 was then used to convert these molecules into piperidines, which are important structural components of numerous pharmaceuticals.

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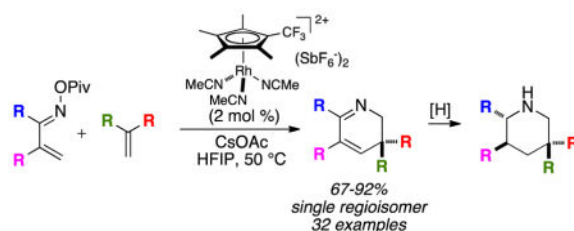
Nitrogen heterocycles are among the most abundant structural components of pharmaceuticals.[1] Due to their omnipresence in biologically active molecules, the synthesis of nitrogen heterocycles has attracted considerable attention in the synthetic community. Pyridines represent one of the most prevalent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

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 have recently demonstrated that high regioselectivities are obtainable when electronically-biased alkenes are used in place of alkynes as coupling partners (Scheme 1, eq 1).[11a] Furthermore, substituted acrylic acids were shown to give the complementary regioisomer of the pyridine products, where the carboxylate acts as a traceless directing group (eq 2).[11b] In a conceptually distinct approach, Bergman and Ellman have shown that a Rh(I) catalyst can couple unsaturated imines with internal alkynes followed by imminium formation and reduction to deliver complementary tetrahydropyridines depending on nature of the acid (eq 3).[11c] This latter reaction was proposed to proceed through dihydropyridine intermediates.

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 rapid *in situ* oxidation to the pyridine was faster than the initial annulation.[12] We speculated 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 HFIP at 60 °C (Table 1). As can be seen from the Table, replacing the Cp* ligand (**A₁**) with its more sterically congested *tert*-butyl-substituted congener (**A₂**) increases the yield of the 2,3-dihydropyridine product (**3aa**) from 81% to 91%. Product yield is further enhanced when electron-deficient Cp-ligand **A₃** bearing a trifluoromethyl[10b] substituent is used. Provided that CsOAc was employed as an additive, product **3aa** was isolated in 99% yield when 5 mol % of **A₃** was used.

The use of Rh(III) diacetates is problematic for some Cp-ligands due to their hygroscopicity. Fortunately, use of the more easily handled cationic tris(acetonitrile) Rh(III) precatalyst **B₃**, bearing a trifluoromethyl-substituted Cp*-ligand, did not deteriorate the yield of the 2,3-dihydropyridine. Interestingly, the dinuclear [Cp*RhCl₂]₂ complex did not promote the title transformation with either CsOAc or AgOAc as additives.

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

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**) are tolerated. With methylene cyclopentanes and cyclohexanes as substrates, *spiro*-bicyclic 2,3-dihydropyridines are obtained in good yields (**3dj**-**3ao**). Finally, *exo*-methylene cyclohexanes 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).

To demonstrate the synthetic utility of the 2,3-dihydropyridines, we turned our attention to derivation of the products. Stimulated by the wide abundance of piperidines in biologically active copounds,[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 (Scheme 4) to deliver high overall yield of piperidine products. Surprisingly, the major diastereomer formed proved to have the trans relationship between the substituents at the 2 and 3 positions, although the level of selectivity seems to be modestly substrate dependent (compare **6mi** *vs* **6hi**). The relative configuration of products **6am** and **6ao** was 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 explained by evoking a reversible C-H activation event and incorporation of deuterium from solvent rather than a direct indicator of 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 for olefin insertion being the slow step.[13] A large and negative value of the reaction constant ($\rho = -1.2$) 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 rate on both catalyst and oxime. Furthermore, first order dependence on alkene was also seen at low concentrations; higher concentrations demonstrated some evidence of an inhibitory effect.[14]

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 metallation 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 semi-saturated nitrogen heterocycles. A significant ligand effect on reactivity was observed, the electron-deficient trifluoromethyl-substituted Cp*[CF3] 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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12. Neely, JM. PhD Dissertation. Colorado State University; Fort Collins, CO: 2014. Subjection of **1a** and methyl acrylate to our optimized reaction conditions (see Scheme 2) delivered only pyridine adduct in 38% yield. No trace of 2,3-dihydropyridine was observed

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14. See the Supporting Information section for details regarding X-ray crystal structures and mechanistic studies.

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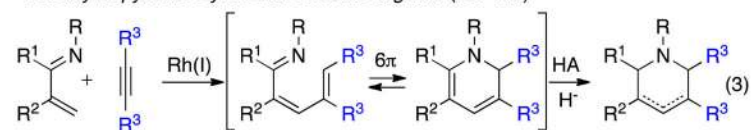16. Terminal alkenes afford pyridine adducts in low yield. Internal alkenes are not suitable partners.
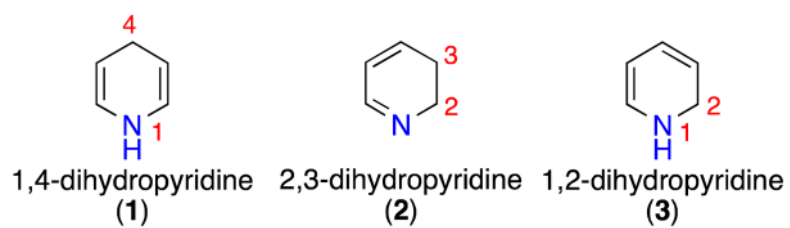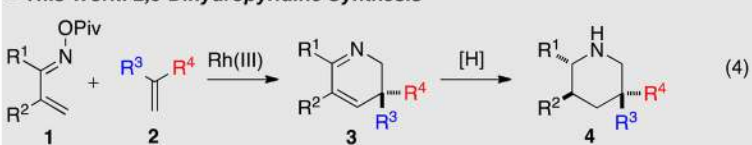
Figure 1.
Structures of Dihydropyridines

• **Previous Work:**

• *Pyridine Synthesis: Rovis (refs. 11a,b)*

>20:1 regioselectivity (1)
R^3 = EWG, Ar

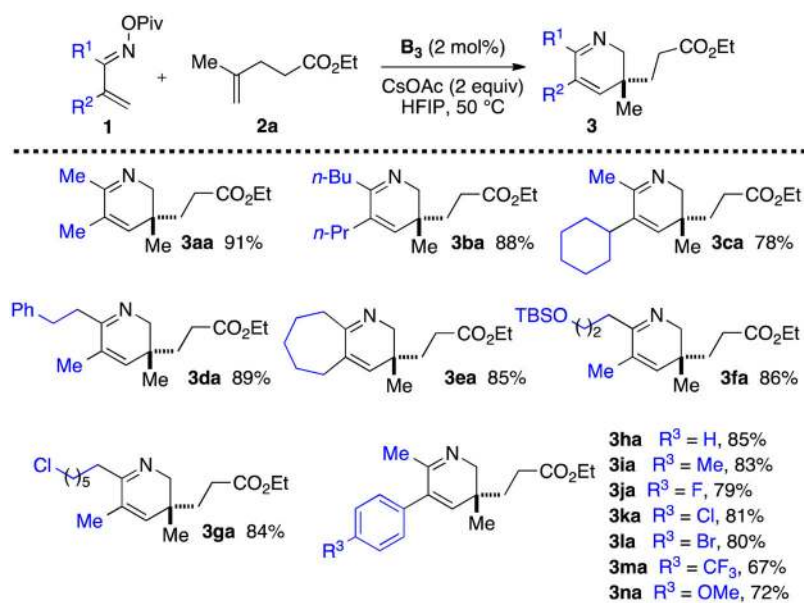>20:1 regioselectivity (2)
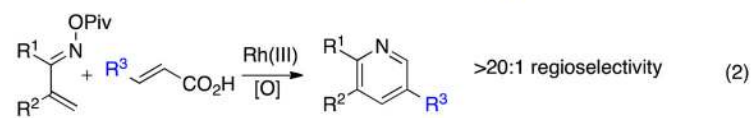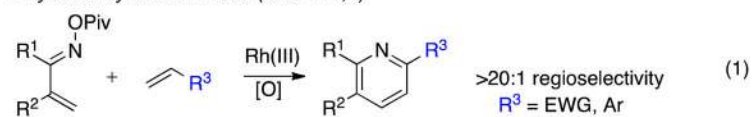
• *Tetrahydropyridine Synthesis: Ellman/Bergman (ref. 11c)*
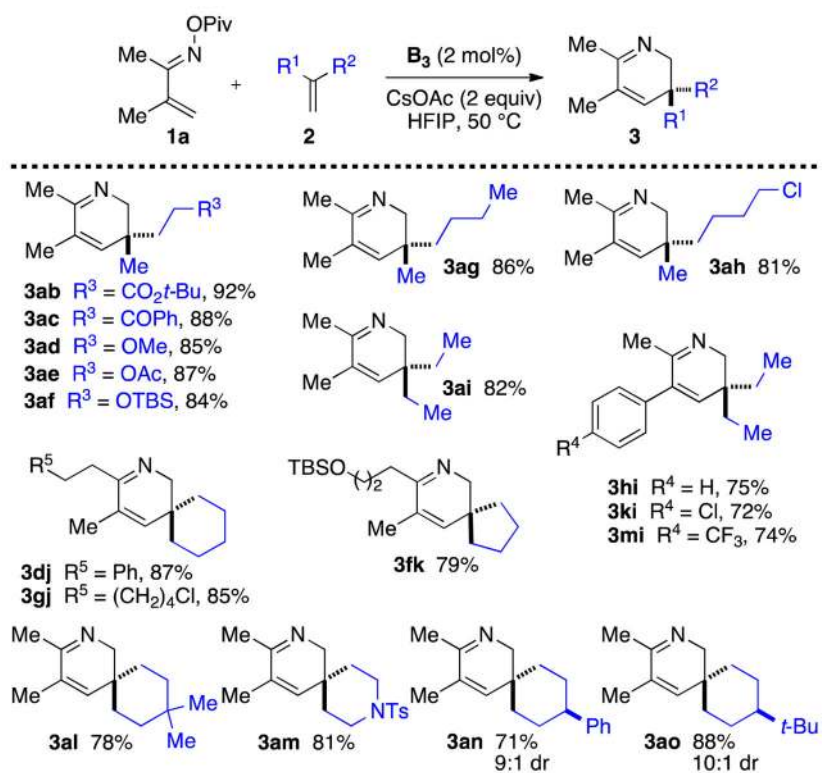

(3)

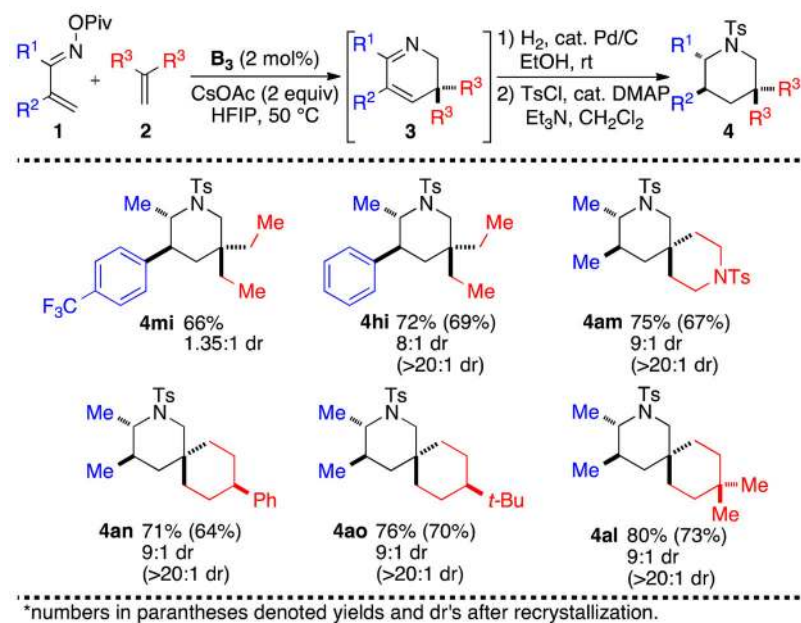• **This Work: 2,3-Dihydropyridine Synthesis**

(4)

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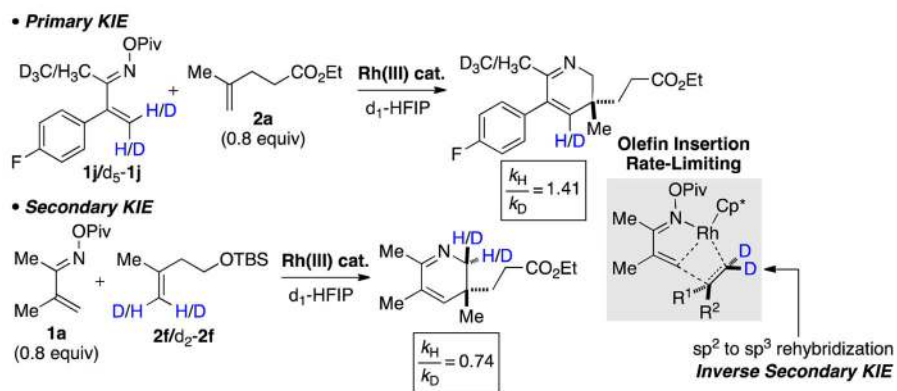Rh(III)-Catalyzed Synthesis of 2,3-Dihydropyridines

Scheme 2.
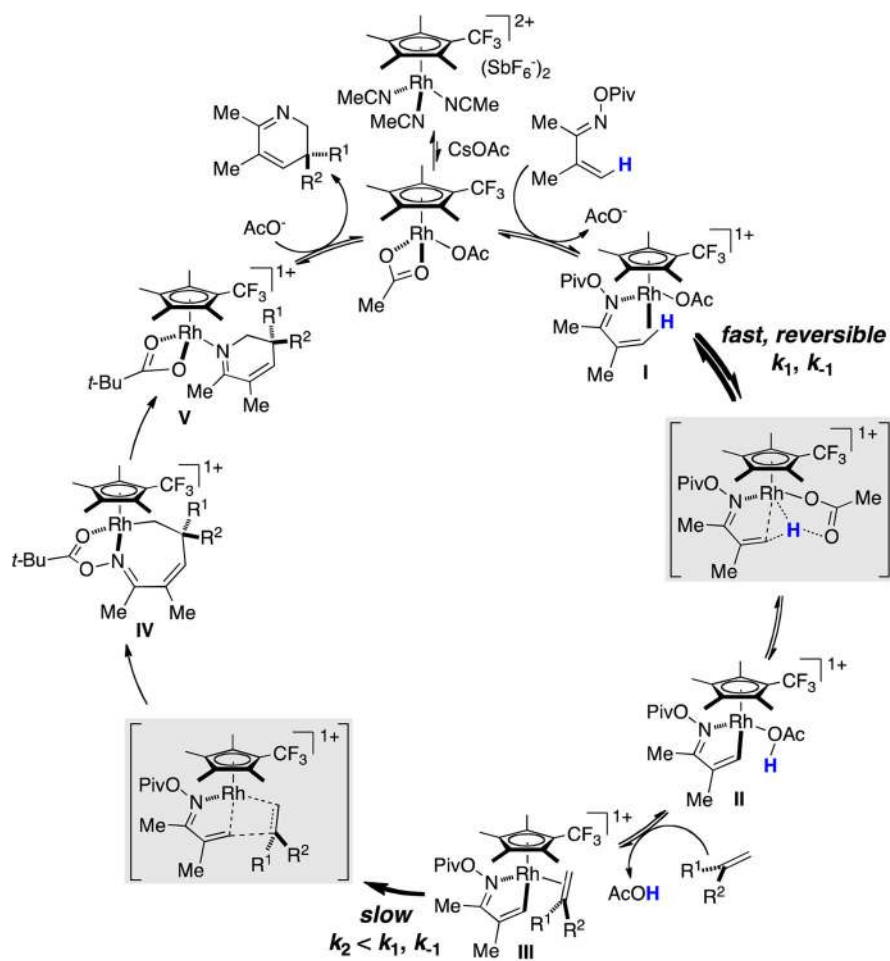α,β-Unsaturated Oxime Pivalate Scope

Scheme 3.
Alkene Scope

Scheme 4. One-Pot Synthesis of Piperidines
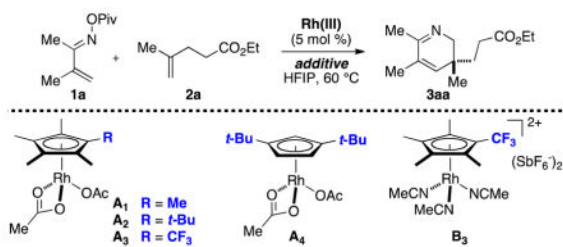*numbers in parantheses denoted yields and dr's after recrystallization.

Scheme 5.
Observation of KIE Effects

Scheme 6.
Postulated Catalytic Cycle

Table 1

Optimization of the Reaction Conditions[a]

entry	Rh(III)	additive	yield (%)[d]
1	[Cp*RhCl₂]₂	AgOAc[b]	<12[c]
2	A₁	none	55
3	A₁	p-TsOH[b]	72
4	A₁	CsOAc	81
5	A₂	CsOAc	91
6	A₃	CsOAc	99
7	A₄	CsOAc	92
8	B₃	CsOAc	99
9[e]	B₃	CsOAc	99

[a]Reaction Conditions: **1a** (1.0 equiv), **2a** (1.2 equiv), additive (2.0 equiv), Rh(III) catalyst (5 mol %) in HFIP (0.3 M), at 60 °C for 16 h.

[b]10 mol % of additive was used.

[c]Determined by ^{1}H NMR.

[d]Yield of isolated product.

[e]Catalyst loading was decreased to 2 mol %, reaction temperature was decreased to 50 °C.