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Rh(III)-Catalyzed Regioselective Synthesis of Pyridines from Alkenes and α,β-Unsaturated Oxime Esters

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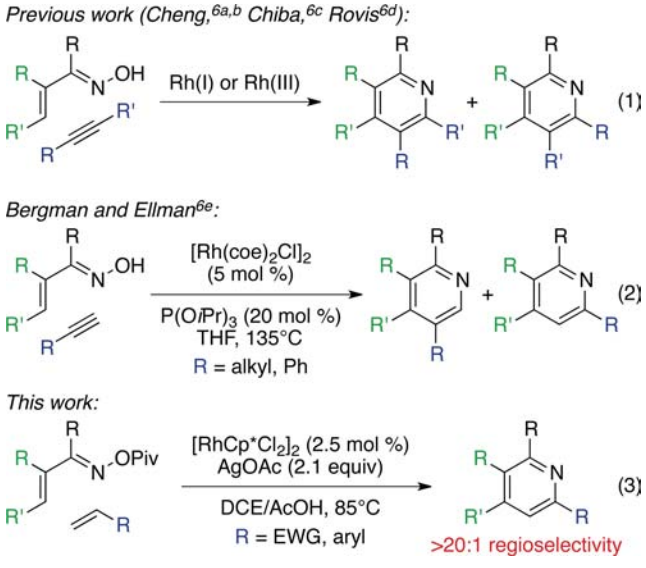
Supporting Information

ABSTRACT: α,β-Unsaturated *O*-pivaloyl oximes are coupled to alkenes by Rh(III) catalysis to afford substituted pyridines. The reaction with activated alkenes is exceptionally regioselective and high-yielding. Mechanistic studies suggest that heterocycle formation proceeds via reversible C−H activation, alkene insertion, and a C−N bond formation/N−O bond cleavage process.

Substituted pyridines are the most abundant heteroaromatic structures in medicinal chemistry.[1] Consequently, extensive research has focused on the development of methods to access this motif.[2] Limitations associated with more established carbonyl condensation[3] and [2 + 2 + 2] cycloaddition[4] strategies have inspired new approaches to the pyridine core, and several elegant reports demonstrate the recent progress in this field.[5]

Rhodium-catalyzed coupling of α,β-unsaturated oximes and alkynes (eqs 1 and 2) represents a particularly useful

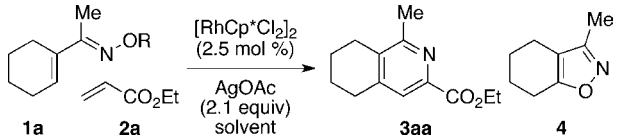


contribution to pyridine synthesis.[6,7] In a recent report, Cheng demonstrated the Rh(I)-catalyzed synthesis of polysubstituted pyridines from α,β-unsaturated oximes and symmetrical internal alkynes.[6a] Several terminal alkynes, historically avoided because of their propensity to undergo side reactions,[8] were reported by Bergman and Ellman to be competent substrates with a Rh(I)/phosphite system (eq 2).[6e] The reactions with terminal and unsymmetrical internal alkynes, however, suffer from low regioselectivities. Investigations by our group found that a bulky *tert*-butylcyclopentadienyl ligand allowed for enhanced selectivity with unsymmetrical internal alkynes.[6d]

Despite these advances, inconsistent regioselectivities and restricted terminal alkyne scope still limit this methodology. We envisioned that the use of an alkene in place of the alkyne, with an external oxidant in addition to the N−O bond internal oxidant,[9,10] could potentially address these problems and provide a complementary method for pyridine synthesis (eq 3).

We chose to examine the reaction of oxime derivatives of 1-acetyl-1-cyclohexene (**1a**) with ethyl acrylate (**2a**) in the presence of $[RhCp^*Cl_2]_2$ (Cp* = pentamethylcyclopentadienyl) in 2,2,2-trifluoroethanol (TFE) (Table 1). With silver(I)

Table 1. Reaction Optimization[a]



1a 2a 3aa 4

entry	R	solvent	T (°C)	yield (%)[b] 3aa	4
1	H	TFE	74	0	35
2	Ac	TFE	74	0	35
3	Piv	TFE	74	30[c]	0
4	Piv	DCE/AcOH	85	45	0
5[d]	Piv	DCE/AcOH	85	65	0

[a]1.2 equiv of **2a**, 0.15 M solution. [b]Determined by ^{1}H NMR analysis. [c]Formed as a ∼4:1 mixture of Et and CF_3CH_2 esters. [d]0.3 M solution.

acetate as an oxidant, the parent oxime afforded none of the desired pyridine **3aa**, instead undergoing intramolecular cyclization to give isoxazole **4** (entry 1). Isoxazole formation was similarly observed with the *O*-acetyl oxime ester of **1a** (entry 2). On the other hand, the *O*-pivaloyl derivative [Piv = C(O)*t*Bu] furnished the desired pyridine **3aa** in 30% yield (entry 3). Importantly, the 6-substituted pyridine was formed as a single regioisomer. An extensive screen of reaction conditions (see the Supporting Information) revealed a 0.3 M solution in 2:1 dichloroethane (DCE)/acetic acid (AcOH) to be optimal, providing **3aa** in 65% yield (entry 5).

With these optimized conditions in hand, we examined the reactions of various *O*-pivaloyl ketoximes **1** with **2a** (Chart 1).[11]

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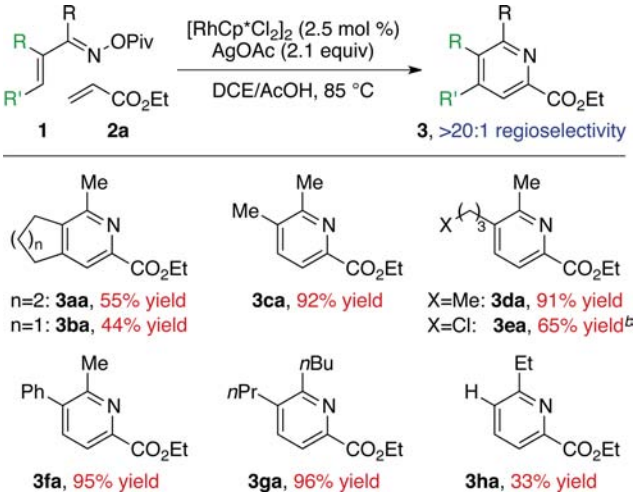
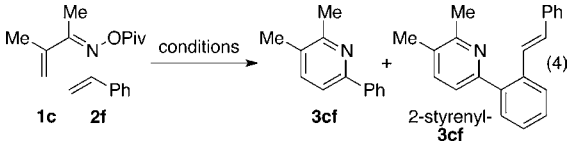
Chart 1. Oxime Ester Scope[a]



[a]Conditions: **1** (0.21 mmol), **2a** (0.25 mmol), $[RhCp^*Cl_2]_2$ (0.005 mmol), and AgOAc (0.44 mmol) in 0.7 mL of 2:1 DCE/AcOH for 14 h. [b]0.12 mmol scale.

The oxime ester substrates were accessed easily from the corresponding ketones, hydroxylamine hydrochloride, and pivaloyl chloride. The reactivity dramatically increases when **1** lacks substitution at the β-position. α-Alkyl and α-aryl substrates afford the 2,3,6-trisubstituted pyridines in excellent yields. Vinyl oxime ester **1h** delivers disubstituted pyridine **3ha**, but in lower yield. Notably, primary alkyl chloride **1e** is tolerated in the presence of the Ag(I) oxidant, giving **3ea** in good yield. In all cases, 6-substituted pyridines are formed with complete selectivity.

We next investigated the alkene component of the reaction (Chart 2). Electron-deficient alkenes afford the desired products in excellent yields as single regioisomers. The reaction of **1c** and styrene is also completely regioselective; however, the 6-phenylpyridine product **3cf** undergoes a second C−H activation event,[12] resulting in a mixture of **3cf** and 2-styrenyl-**3cf** (eq 4). On the other hand, product alkenylation



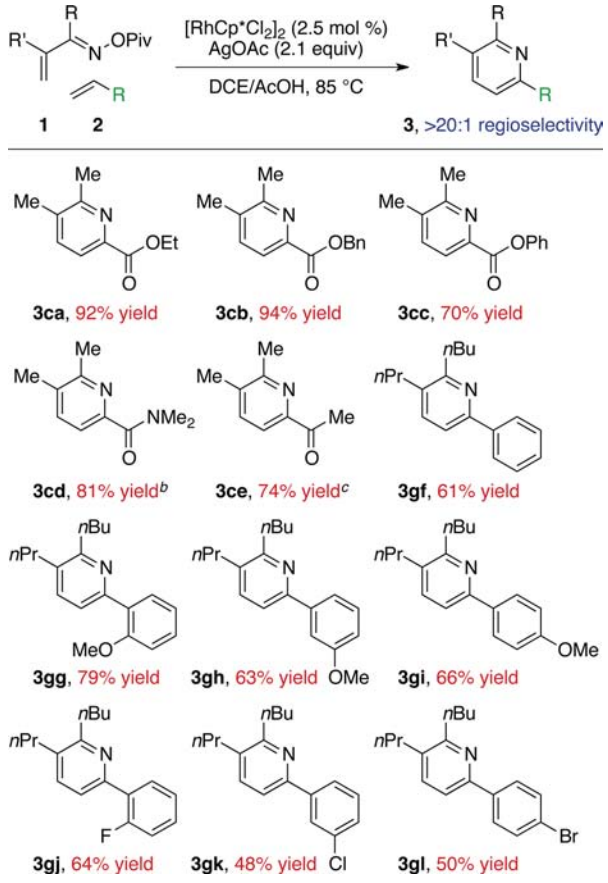
is not observed with oxime ester **1g**. Presumably, the slightly larger ortho substituent in **3gf** discourages alkenylation.[13] The reactions of oxime **1g** with various substituted styrenes provides the corresponding 2-arylpyridines as single regioisomers.

Alkyl alkenes are also competent coupling partners but produce separable mixtures of the 6- and 5-substituted pyridines **3** and **5** (Table 2).[14] Surprisingly, the reaction with vinylcyclohexane (**2p**) is significantly more selective for **3** than that with vinylcyclopentane (**2o**; Cyp = cyclopentyl), while intermediate selectivity is observed with 3-methylpentene (**2q**) (entries 3−5). The reason for this anomaly is currently under investigation. Notably, the reaction of 3,3-dimethylbutene (**2r**) affords the 5-substituted product **5cr** exclusively, albeit in low yield, suggesting that there is a steric component to the control of regioselectivity.

β-Substituted acrylates **6** could also participate as the alkene component (Table 3). The *Z* and *E* isomers of **6** both react with **1c** to afford the corresponding tetrasubstituted pyridine in similar yields. The reaction is selective for the 2-picolinate product (**7**) even when the β-substituent of the alkene is a ketone (**6c**; entry 5).

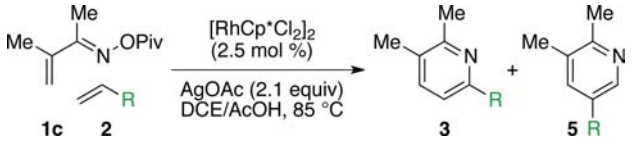
Contemplating the mechanism of the reaction, we considered two general pathways for C−N bond formation from rhodacycle **A** (Figure 1). In pathway A, β-hydride elimination generates azatriene **B**, and subsequent electrocyclization and elimination of PivOH furnishes **3**. Such Rh-catalyzed C−H alkenylations have been demonstrated with various directing groups,[10b,12,15−17] including oxime ethers.[18]

Chart 2. Activated Alkene Scope[a]



[a]Conditions: see Chart 1. For **1g**, 1.05 equiv of **2** was used. [b]1.2 equiv of **1c**. [c]75 °C.

Table 2. Alkyl Alkene Scope[a]



entry	alkene	R	3:5[b]	yield (%)
1	**2m**	CH_2OPh	2.2:1	66
2	**2n**	*n*Hex	1:1.3	72
3	**2o**	Cyp	1.3:1	67
4	**2p**	Cy	7.2:1	69
5	**2q**	*s*Bu	3.4:1	50[c]
6	**2r**	*t*Bu	<1:20	17[c,d]

[a]Conditions: see Chart 1. [b]Determined by ^1H NMR analysis. [c]5 equiv of **2** was used. [d]0.54 mmol scale.

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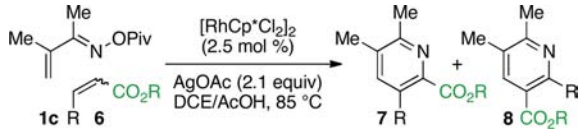
Table 3. Internal Alkene Scope[a]



entry	alkene	CO_2R	R	7:8[b]	yield (%)
1	(*Z*)-**6a**	CO_2Me	CO_2Me	n/a	71
2	(*E*)-**6a**	CO_2Me	CO_2Me	n/a	54
3[c]	(*Z*)-**6b**	CO_2Et	Me	>20:1	47
4[c]	(*E*)-**6b**	CO_2Et	Me	>20:1	51
5	(*E*)-**6c**	CO_2Me	C(O)Me	4.7:1	41

[a]Conditions: see Chart 1. [b]Determined by ^1H NMR analysis. [c]5 mol % $[RhCp^*Cl_2]_2$.

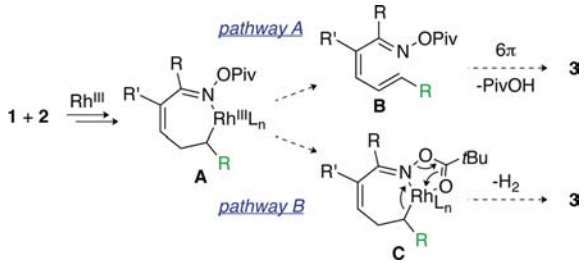
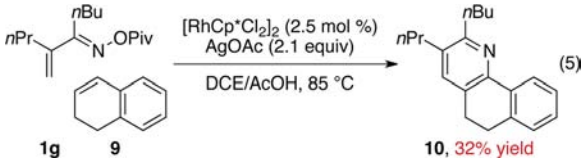


Figure 1. Two possible pathways for C−N bond formation.

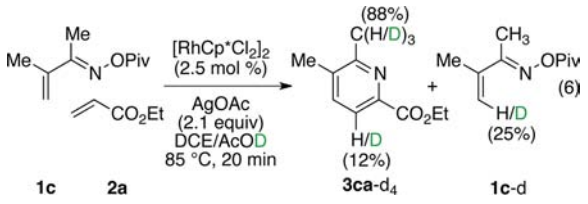
Moreover, 6π-electrocyclization of an azatriene intermediate[19] has been proposed in the Rh(I)-catalyzed reaction of oximes and alkynes.[6a,b,e] To probe the possibility of pathway A, we used cis-fused 1,2-dihydronaphthalene as our alkene component (eq 5). If pathway A were operational, no product would



be expected, since a trans relationship between rhodium and the β-hydride in intermediate **A** would preclude β-hydride elimination.[20] In fact, tricyclic product **10** is formed in 32% yield, implicating an alternate pathway for C−N bond formation.

Pathway B in Figure 1 depicts a C−N bond formation/N−O bond cleavage event that is followed by oxidative aromatization to give **3**. This type of process has been invoked in the Rh(III)-catalyzed synthesis of pyridines from oximes and alkynes[6c,d] and analogous reactions of hydroxamic acid derivatives.[10] In particular, Glorius demonstrated that the product of the reaction of *N*-oxybenzamides and alkenes hinges upon the O substituent.[10b] Specifically, *N*-methoxybenzamides afford olefinated products while *N*-pivaloxybenzamides form tetrahydroisoquinolones, presumably via pathways analogous to A and B, respectively. Accordingly, the *O*-methyl derivative of **1a** does not afford the pyridine product under our conditions.

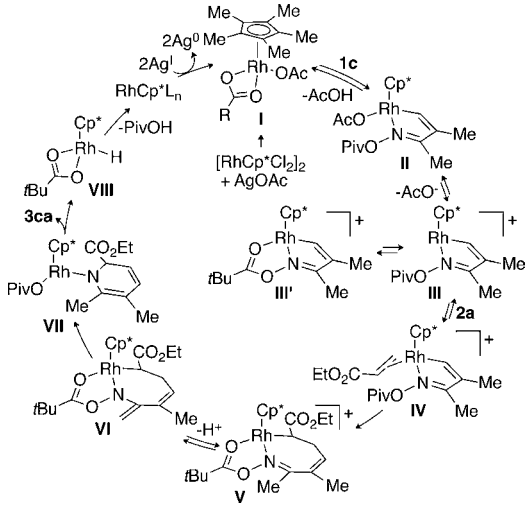
Isotope experiments provided further insight into the mechanism of pyridine formation.[21] In particular, when the reaction was performed with AcOD to ~50% conversion, deuterium incorporation was observed at the β-position of **1c** and the 2-methyl and 5-H of **3ca** (eq 6). The observed deuteration at the β-position of **1c** implies that C−H activation is reversible. Nearly complete deuterium incorporation at the 2-



methyl of **3ca** signals a deprotonation step; since there was no deuteration at the same position of **1c**, the deprotonation most likely occurs after the first irreversible step of the reaction.[22]

With these observations in mind, we propose the reaction mechanism in Scheme 1. After generation of acetate catalyst **I**,

Scheme 1. Proposed Reaction Mechanism



reversible C−H activation forms rhodacycle **II**. Dissociation of an acetate ligand leads to cationic complex **III**, which may be in equilibrium with chelated complex **III′**. Alkene coordination and presumed irreversible migratory insertion provides rhodacycle **V**, and deprotonation at the α-position gives neutral complex **VI**. It is possible that chelation of the *O*-pivalate substituent prevents β-hydride elimination at this stage as a result of coordinative saturation.[23] Instead, a C−N bond formation/N−O bond cleavage event provides complex **VII** after tautomerization.[24] Final β-hydride elimination furnishes the pyridine product. Reductive elimination of complex **VIII** followed by oxidation of the Rh(I) species regenerates the active catalyst.[25]

In conclusion, we have developed a novel synthesis of pyridines from α,β-unsaturated *O*-pivaloyl oximes and alkenes. The reaction is general, efficient, and highly regioselective with activated alkenes. Mechanistic studies support a pathway that proceeds by reversible C−H activation, alkene insertion, and a C−N bond formation/N−O bond cleavage process.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, compound characterization, and additional experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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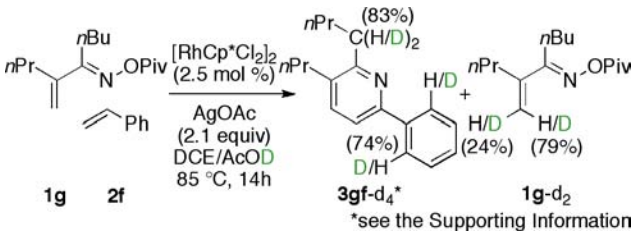
(13) Isotope experiments suggested that C−H activation of **3gf** still occurs:



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(14) Aspects of the terminal alkyne methodology (ref 6e) should be noted for comparison. Namely, the alkyne scope consists of alkyl acetylenes and phenylacetylene, and 5-substituted products are formed with regioselectivities of 1.6:1 to >20:1.

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(21) See the Supporting Information for further details.

(22) Additionally, no deuterium incorporation of **3ca** occurred when it was subjected to the reaction of **1c** and methyl crotonate with AcOD (see the Supporting Information).

(23) See ref 20. A similar argument for the formation of tetrahydroisoquinolones in the reaction of *N*-pivaloxybenzamides and alkenes has been proposed (see ref 10b).

(24) The order of deprotonation, C−N formation/N−O cleavage, and tautomerization could certainly be different. However, if it is presumed that the C−N formation/N−O cleavage is the slowest of these steps, the proposed sequence seems logical given the extent of deuteration at the 2-methyl (88%) and 5-H (12%) positions.

(25) ^{1}H NMR data indicated that a Rh−H species was present after a stoichiometric reaction (see the Supporting Information). Its relevance to the catalytic cycle is currently under investigation.