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

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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 developing methods to access this motif.² Limitations associated with more established carbonyl condensation³ and [2+2+2] cycloaddition⁴ strategies have inspired new approaches to the pyridine core, and several elegant reports demonstrate the recent progress in this field.⁵

Previous work (Cheng,^{6a,b} Chiba,^{6c} Rovis^{6d}):

(1)

Bergman and Ellman^{6e}:

(2)

This work:

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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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(3)

Rhodium-catalyzed coupling of α,β -unsaturated oximes and alkynes represents a particularly useful contribution to pyridine synthesis (eq 1, 2).^{6,7} In a recent report, Cheng demonstrated the Rh(I)-catalyzed synthesis of polysubstituted pyridines from α,β -unsaturated oximes and internal, symmetrical alkynes.^{6a} Several terminal alkynes, historically avoided due to their propensity to side reactions,⁸ were reported by Bergman and Ellman to be competent substrates with a Rh(I)/phosphite system (eq 2).^{6c} The reactions with internal, unsymmetrical and terminal alkynes, however, suffer from low regioselectivities. Investigations by our group found that a bulky *tert*-butyl cyclopentadienyl ligand allowed for enhanced selectivity with internal, unsymmetrical alkynes.^{6d}

Despite these advances, inconsistent regioselectivities and a restricted terminal alkyne scope still limit this methodology. We envisioned that use of an alkene in the 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 in the presence of $[\text{RhCp}^*\text{Cl}_2]_2$ (Cp^* = pentamethylcyclopentadienyl) in 2,2,2-trifluoroethanol (TFE) (Table 1). With silver(I) acetate as an oxidant, the parent oxime affords none of the desired pyridine **3aa**, and instead undergoes intramolecular cyclization to isoxazole **4** (entry 1). Isoxazole formation is similarly observed with the *O*-acetyl oxime ester of **1a** (entry 2). The *O*-pivaloyl derivative ($\text{Piv} = \text{C}(\text{O})t\text{Bu}$), on the other hand, furnishes the desired pyridine **3aa** in 30% yield (entry 3). Importantly, the 6-substituted pyridine is formed as a single regioisomer. An extensive screen of reaction conditions (see Supporting Information) revealed a 0.3 M solution of dichloroethane (DCE): acetic acid (AcOH) (2:1) to be optimal, providing pyridine **3aa** in 65% yield (entry 5).

With these optimized conditions in hand, we examined the reaction of various *O*-pivaloyl ketoximes **1** and ethyl acrylate (Chart 1).¹¹ The oxime ester substrates are accessed easily from the corresponding ketones, hydroxylamine hydrochloride and pivaloyl chloride. Reactivity dramatically increases when the oxime ester (**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 the disubstituted pyridine **3ha**, but in lower yield. Notably, the 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 reaction of oxime **1g** with various substituted styrenes provides the 2-aryl pyridines (**3**) as single regioisomers.

(4)

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); 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 regiocontrol.

β -Substituted acrylates (**6**) also participate as the alkene component (Table 3). Both (*Z*)- and (*E*)-isomers of **6** react with **1c** to afford the tetrasubstituted pyridines in similar yields. The reaction is selective for 2-picolinate products (**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 electrocyclicization and elimination of PivOH furnishes **3**. Such Rh-catalyzed C-H alkenylations have been demonstrated with various directing groups,^{10b,12,15,16,17} including oxime ethers.¹⁸ Moreover, 6π -electrocyclization of an azatriene intermediate¹⁹ is 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 forming/N-O bond cleaving event that is followed by oxidative aromatization to **3**. This type of process is 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 demonstrates that the product of the reaction of *N*-oxybenzamides and alkenes hinges upon the *O*-substituent.^{10b} Namely, *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 Particularly, when the reaction is performed with AcOD to approximately 50% conversion, deuterium incorporation is observed at the β -position of **1c** and at the 2-methyl and 5-H of **3ca**. The observed deuteration at the β -position of **1c** implies that C-H activation is reversible. Near complete deuterium incorporation at the 2-methyl of **3ca** signals a deprotonation step; since there is 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 2. After generation of acetate catalyst **I**, reversible C-H activation forms rhodacycle **II**. Dissociation of an acetate ligand leads to cationic complex **III** that 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 due to coordinative saturation.²³ Instead, a C-N bond forming/N-O bond cleaving 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 pyridine synthesis 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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*see Supporting Information

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21. See Supporting Information for further details.
22. Additionally, no deuterium incorporation of **3ca** occurs when it is subjected to the reaction of **1c** and methyl crotonate with AcOD; see Supporting Information.
23. See ref 20. A similar argument is proposed for the formation of tetrahydroisoquinolones in the reaction of *N*-pivaloxybenzamides and alkenes; see ref 10b.
24. The order of deprotonation, C-N formation/N-O cleavage and tautomerization could certainly be different. Presuming the C-N formation/N-O cleavage to be the slowest of these steps, however, the proposed sequence seems logical given the extent of deuteration at the 2-methyl (88%) and 5-H (12%) positions.
25. ^1H NMR data indicates that a Rh-H species is present after a stoichiometric reaction; see Supporting Information. Its relevance to the catalytic cycle is currently under investigation.

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

Scheme 1.
Proposed Reaction Mechanism

n=2: **3aa**, 55% yield
 n=1: **3ba**, 44% yield

3ca, 92% yield

X=Me: **3da**, 91% yield
 X=Cl: **3ea**, 65% yield^b

3fa, 95% yield

3ga, 96% yield

3ha, 33% yield

Chart 1. Oxime Ester Scope^a

^aConditions: **1** (0.21 mmol), **2a** (0.25 mmol), $[\text{RhCp}^*\text{Cl}_2]_2$ (0.005 mmol) and AgOAc (0.44 mmol) in 0.7 mL DCE/AcOH (2:1) for 14h. ^b0.12 mmol scale.

Chart 2. Activated Alkene Scope^a

^aConditions: see Chart 1. For **1g**: 1.05 equiv **2**. ^b1.2 equiv **1c**. ^c75 °C.

Table 1

Reaction Optimization^a

entry	R	solvent	temp. (°C)	yield 3aa (%) ^b	yield 4 (%) ^b
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 **2a**, 0.15 M solution.^b Determined by ¹H NMR.^c Formed as a ~4:1 mixture of Et and CH₂CF₃ esters.^d 0.3 M solution.

Table 2

Alkyl Alkene Scope^a

entry	alkene	R	3:5 ^b	yield (%)
1	2m	CH ₂ OPh	2.2:1	66
2	2n	<i>n</i> Hex	1:1.3	72
3	2o	Cyp	1.3:1	67
4	2p	Cy	7.2:1	69
5	2q	<i>s</i> Bu	3.4:1	50 ^c
6	2r	<i>t</i> Bu	<1:20	17 ^{c,d}

^aConditions: see Chart 1.^bDetermined by ¹H NMR.^c5 equiv **2**.^d0.54 mmol scale.

Table 3

Internal Alkene Scope^a

entry	alkene	CO ₂ R	R	7:8 ^b	yield (%)
1	(<i>Z</i>)- 6a	CO ₂ Me	CO ₂ Me	n/a	71
2	(<i>E</i>)- 6a	CO ₂ Me	CO ₂ Me	n/a	54
3 ^c	(<i>Z</i>)- 6b	CO ₂ Et	Me	>20:1	47
4 ^c	(<i>E</i>)- 6b	CO ₂ Et	Me	>20:1	51
5	(<i>E</i>)- 6c	CO ₂ Me	C(O)Me	4.7:1	41

^aConditions: see Chart 1.^bDetermined by ¹H NMR.^c5 mol % [RhCp*Cl₂]₂.