

#### Letter

# Palladium(II)-Catalyzed Substituted Pyridine Synthesis from $\alpha,\beta$ -Unsaturated Oxime Ethers via a C–H Alkenylation/Aza-6 $\pi$ -Electrocyclization Approach

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pyridines with complete regioselectivity. The usefulness of this methodology was showcased by the synthesis of 4-aryl-substituted pyridine derivatives, which are difficult to access with previously reported Rh-catalyzed approaches with alkenes.

C ubstituted pyridine scaffolds are widely encountered in  $\bigcirc$  medicinal chemistry,<sup>1</sup> and several approaches are available to obtain pyridines with different substitution patterns.<sup>2</sup> The Rh-catalyzed approaches are particularly useful<sup>3</sup> and can provide access to multisubstituted pyridines from  $\alpha_{,\beta}$ unsaturated oximes and symmetrical internal alkynes (Scheme 1a).<sup>3a-d</sup> However, the reactions with terminal and unsymmetrical internal alkynes suffer from low regioselectivity. Rovis's group reported that Rh(III)-catalyzed coupling of  $\alpha_{\beta}$ -unsaturated oximes with activated alkenes is a useful approach to synthesize substituted pyridines with good regioselectivity (Scheme 1b).<sup>3e</sup> Interestingly, this reaction involves a 7-membered rhodacycle intermediate, which undergoes C-N bond formation/N-O bond cleavage to furnish the pyridine product. Unfortunately, high yields are obtained only with  $\beta$ -unsubstituted  $\alpha$ , $\beta$ -unsaturated oximes.<sup>3e,f</sup> Therefore, there remains a need for a versatile and efficient approach to synthesize multisubstituted pyridines from readily accessible  $\beta$ -aryl-substituted  $\alpha_{\beta}$ -unsaturated oximes with high regioselective control.

We have already reported the Pd-catalyzed  $\beta$ -selective C–H arylation of  $\alpha$ , $\beta$ -unsaturated oxime ethers with arylboronic acids, featuring the use of cationic Pd(II) catalyst.<sup>4</sup> We envisioned that the use of alkenes in place of arylboronic acids might provide 1-azatrienes, which would undergo aza- $6\pi$ -electrocyclization and subsequent aromatization via the release of alcohol along with N–O bond cleavage to furnish the desired pyridine products.<sup>5</sup> Herein, we report the results of this new approach for the synthesis of multisubstituted pyridines via Pd-catalyzed C–H alkenylation of  $\alpha$ , $\beta$ -unsaturated oximes followed by aza- $6\pi$ -electrocyclization. A key feature of our

# Scheme 1. Transition-Metal-Catalyzed Substituted Pyridine Synthesis from $\alpha,\beta$ -Unsaturated Oximes

(a) Rh-catalyzed pyridine synthesis with alkynes



(b) Rh-catalyzed pyridine synthesis with alkenes







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method is the use of a general  $Pd(OAc)_2$  catalyst to obtain 4substituted pyridine derivatives, which are difficult to synthesize with Rh-catalyzed methodology. This work complements previously reported pyridine synthetic methods, since 4unsubstituted pyridines can already be easily prepared with alkenes by using a commercially available Rh-catalyst (Scheme 1b vs 1c).

We first examined the reaction between symmetrical  $\alpha_{,\beta}$ unsaturated O-methyl oxime 1a (Me) and methyl acrylate (2a) in the presence of Pd(OAc)<sub>2</sub> as a catalyst.<sup>6</sup> With AgTFA as an oxidant and dioxane as a solvent, the desired pyridine 3aa was obtained in 17% yield, and no  $\beta$ -alkenylation product was observed.

Based on our experience in the development of Pd-catalyzed  $\beta$ -selective C–H functionalization of  $\alpha,\beta$ -unsaturated oximes,<sup>4</sup> we expected that the identification of a suitable catalyst ligand would be the key to establish the optimal protocol. We chose to examine the effect of pyridine derivatives, since they are known to be useful ligands for Pd-catalyzed C–H alkenylation of oxime derivatives (Table 1).<sup>7</sup> Although simple organic





<sup>a</sup>Reaction conditions: 1a (Me) (0.2 mmol, 1.0 equiv), 2a (3.0 equiv), Pd(OAc)<sub>2</sub> (10 mol %), ligand (30 mol %), AgTFA (2.5 equiv), dioxane (2.0 mL), 90 °C, 24 h. Isolated yield.

bases, pyridine  $(L1)^{7a,b}$  and 2,6-lutidine (L2), inhibited the reaction, 2,6-dimethoxypyridine  $(L3)^{7c}$  slightly improved the reactivity and afforded the desired pyridine in 29% yield. Interestingly, more sterically hindered 2,6-di-*tert*-butylpyridine (L4) significantly increased the reactivity and 3aa was obtained in 47% yield. Next, we tested a series of 2-alkoxylquinoline derivatives (L5-L8), which are more electron-rich than the pyridine series ligands (L1-L4). The use of 2-methoxyquino-line (L5) did not improve the reactivity, but the product yield was increased when a quinoline ligand bearing a bulkier side chain, *tert*-butoxy (L6) or 1-adamantyloxy (L7), was used. This substituent effect suggests that steric hindrance around the nitrogen atom of the quinoline ligand is crucial for high

reactivity. Tricyclic quinoline-derived ligand L8 and acridine (L9), developed by Yu and co-workers,<sup>8</sup> led to loss of reactivity. Anticipating a positive effect of a bulkier ligand, we prepared L10 in one step from 2,6-difluoropyridine and 1-adamantanol. To our delight, the use of L10 significantly improved the reactivity and afforded 3aa in 50% yield. The yield could not be further improved despite extensive ligand screening with substrate 1a (Me).

Having identified two suitable ligands L4 and L10, we turned our attention to exploring the structure-reactivity relationship of the oxime ether moiety. Although various oximes 1a bearing O-acetyl, O-pivaloyl, O-silyl, and O-SEM<sup>4</sup> groups were examined, the reaction did not proceed at all (see the Supporting Information). Indeed, with the highly sterically hindered O-tert-butyl oxime 1a (<sup>t</sup>Bu), only the starting material was recovered (Table 2, entry 2). However, O-isopropyl oxime

#### Table 2. Reaction Optimization<sup>a</sup>

	N_OR	Pd	CO2Me 2a (OAc)2 (10 m gand (30 mo AgTFA (x equ dioxane 90 °C, 24	h	
entry	R	1a	ligand	AgTFA (x equiv)	yield (%)
1	Me	1a (Me)	L4	2.5	47
2	<sup>t</sup> Bu	1a ( <sup>t</sup> Bu)	L4	2.5	0
3	<sup>i</sup> Pr	1a ( <sup>i</sup> Pr)	L4	2.5	69
4	<sup>i</sup> Pr	1a ( <sup>i</sup> Pr)	L10	2.5	76
5	<sup>i</sup> Pr	1a ( <sup><i>i</i></sup> Pr)	L10	5.0	85

"Reaction conditions: 1a (0.2 mmol, 1.0 equiv), 2a (3.0 equiv), Pd(OAc)<sub>2</sub> (10 mol %), ligand (30 mol %), AgTFA (x equiv), dioxane (2.0 mL), 90 °C, 24 h. Isolated yield.

1a (<sup>i</sup>Pr) improved the reactivity and the yield increased to 69% (entry 3). To our delight, the use of the ligand L10 in place of L4 further improved the yield from 69% to 76% (entry 4). Finally, further screening of reaction conditions revealed that 5.0 equiv of AgTFA was optimal, affording 3aa in 85% yield (entry 5).

With the optimal oxime moiety as well as reaction conditions in hand, we surveyed the generality of this multisubstituted pyridine synthesis by examining the reaction of various  $\alpha_{,\beta}$ -unsaturated oximes with methyl acrylate (2a) (Table 3). Symmetrical oximes bearing an electron-donating group (1b and 1c), halogens (1d and 1e) and an electronwithdrawing  $CF_3$  group (1f) at the para position of the phenyl ring afforded the expected 2-allylpyridines (3ba-3fa) in good yields (65-91%). Notably, unsymmetrical ketoximes were available, affording the pyridines (3ga-3ka) in good yields (64-80%). Oximes with heteroaromatics such as dibenzothiophene (11) and carbazole (1m) were also acceptable and furnished the desired pyridines 3la and 3ma in 48% and 55% yields, respectively. This reaction also worked well with cyclized oximes derived from benzylidene cyclopentanone derivatives (1n-1p), giving the desired 2,3,4,6-tetrasubstituted pyridines (3na-3pa) in good yields. Unfortunately, with the exception of the cyclized oximes (1n-1p), neither  $\alpha$ substituents nor  $\beta$ -alkyl substituents were generally tolerated (see the Supporting Information).

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<sup>a</sup>Reaction conditions: 1 (0.2 mmol, 1.0 equiv), 2a (3.0 equiv), Pd(OAc)<sub>2</sub> (10 mol %), L10 (30 mol %), AgTFA (5.0 equiv), dioxane (2.0 mL), 90 °C, 24 h. Isolated yield.

Next, we examined the scope with respect to the partner olefins (Table 4). Acrylates bearing ethyl (2b), benzyl (2c), and methoxy ethyl (2d) substituents were found to react smoothly, giving the expected 2-phenylethenylpyridines (3bb-3bd) in 86%, 79%, and 93% yields, respectively. Unsymmetrical ketoximes with various acrylates were also compatible,

Table 4. Scope of Various Alkenes<sup>a</sup>

and the corresponding pyridines (3hb-3hd) were obtained in good yields. Notably, acrylates bearing sterically bulky alkyl groups, such as isopropyl (2e), cyclohexyl (2f), and 1adamantyl (2g) groups, worked well, affording the desired products (3he-3hg) in excellent yields. Unexpectedly, the use of phenyl acrylate (2h) as a partner olefin gave not pyridine 3hh but pyridine with an isopropyl ester 3he as the major product. This product was probably produced by ester exchange reaction between the corresponding pyridine 3hh and *in situ* generated 2-propanol.

Other acrylate derivatives such as acrylamides were also tolerated and provided the corresponding pyridines in moderate yields (3hi and 3ji). To our surprise, cyclized oximes 10 and 1p reacted efficiently with N,N-dimethyl acrylamide (2i), giving the desired tetrasubstituted pyridines 30i and 3pi in excellent yields. To demonstrate the generality and utility of this multisubstituted pyridine synthesis, the reactions of cyclized oximes 10 and 1p with other unsaturated olefins were also tested. Various acrylamide derivatives such as phenyl acrylamide (2i), n-butyl acrylamide (2k), and 4acryloylmorpholine (21) were found to be suitable coupling partners, giving the desired products (30i-30l) in 58%, 84%, and 90% yields, respectively. Weinreb amide-derived acrylamide 2m was also tolerated, giving the corresponding pyridine 3om in moderate yield. Various styrene derivatives containing electron-withdrawing groups such as nitro and ester were also tolerated and afforded the expected pyridines (3on-3or) in moderate to excellent yields. Notably, 4-trifluoromethylstyrene (2q) and pentafluorostyrene (2r) reacted smoothly with cyclized oximes, providing the corresponding pyridines 30q, 3or, and 3pr in excellent yields. Further, this pyridine synthesis is effective not only for monosubstituted olefins but also for disubstituted olefins. Oxime 10 with dimethyl maleate (2s)and N-methyl maleimide (2t) were successfully converted into the corresponding pentasubstituted pyridines (3os and 3ot) in 36% and 52% yields, respectively.



<sup>a</sup>Reaction conditions: 1 (0.1–0.2 mmol, 1.0 equiv), alkene 2 (1.5 equiv), Pd(OAc)<sub>2</sub> (10 mol %), L10 (30 mol %), AgTFA (5.0 equiv), dioxane (2.0 mL), 90 °C, 24 h. Isolated yield. <sup>b</sup>3.0 equiv of alkene was used. <sup>c</sup>3he was obtained in 48% yield.

To gain insight into the mechanism of this pyridine formation, additional experiments were conducted (Table 5).

# Table 5. Reaction of $\beta$ -Unsubstituted $\alpha_{,\beta}$ -Unsaturated Oxime with Alkene<sup>*a*</sup>



When the reaction was performed with  $\beta$ -unsubstituted oxime **1q** and ethyl acrylate (**2b**) under the same reaction conditions for 4 h, 1-azatriene **4qb** was obtained in 36% yield as a 1.3:1 mixture of E/Z isomers, but the expected pyridine was not detected (Table 5, entry 1). However, when the reaction time was extended to 36 h, the pyridine **3qb** was obtained in 28% yield along with 1-azatriene **4qb** in 11% yield (Table 5, entry 2). It should be noted that only (E)-**4qb** was recovered, suggesting that (Z)-**4qb** undergoes much faster electrocyclization than (E)-**4qb**. To confirm this, (Z)-**4qb** was stirred in dioxane at 90 °C for 36 h. As expected, the corresponding pyridine **3qb** was obtained in 84% yield and a small amount of E/Z mixture of **4qb** was recovered (Scheme 2, eq 1). In

### Scheme 2. Mechanistic Experiment



contrast, similar treatment of (E)-4qb gave 3qb in only 18% yield and most of the (E)-4qb was recovered (Scheme 2, eq 2). These results clearly indicate that pyridines 3 were formed from 1-azatriene intermediates via aza- $6\pi$ -electrocyclization. Considering that pyridine 3qb was also formed from the *E*-isomer of 4qb to some extent, E/Z isomerization of 1-azatriene appears to proceed to some extent under these reaction conditions.

Based on these observations and the results of our previous investigation of Pd-catalyzed electrophilic C–H activation,<sup>4,9</sup> a

plausible mechanism for this reaction is depicted in Scheme 3. After the generation of palladium trifluoroacetate *in situ*,





electrophilic C–H activation with  $\alpha,\beta$ -unsaturated oxime 1 forms  $\beta$ -palladated intermediate **A**. Olefin coordination and 1,2-migratory insertion provides intermediate **C**, which undergoes  $\beta$ -hydride elimination and reductive elimination to form the 1-azatriene **4** with liberation of trifluoroacetic acid and Pd(0) species. The formed Pd(0) is oxidized to Pd(II) by Ag oxidant to complete the catalytic cycle. Then, aza- $6\pi$ electrocyclization and subsequent aromatization proceed rapidly to furnish the pyridine **3**. The C4-substituent of 1azatriene intermediate **4** may contribute to the acceleration of this aza- $6\pi$ -electrocyclization step.

In conclusion, we have developed an efficient Pd-catalyzed synthesis of 4-aryl-substituted pyridines from  $\beta$ -aryl-substituted  $\alpha,\beta$ -unsaturated oxime ethers. The catalyst ligand significantly affected the reactivity, with the sterically hindered pyridine-based ligand L10 being optimal. Various olefins could be utilized to synthesize multisubstituted pyridines with complete regioselectivity. Mechanistic studies indicate that the pyridine formation proceeds via aza- $6\pi$ -electrocyclization of  $\beta$ -alkeny-lated  $\alpha,\beta$ -unsaturated oximes. Considering the difficulties inherent in the synthesis of 4-aryl-substituted pyridines with previously developed Rh-catalyzed approaches with alkenes, we believe this transformation will prove useful as a complementary synthetic method.

## ASSOCIATED CONTENT

# **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00061.

Experimental procedures, characterization data for all new compounds, additional experiments, and spectral data (PDF)

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#### Notes

The authors declare no competing financial interest.

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