Palladium-Catalyzed Ligand-Directed Oxidative Functionalization of Cyclopropanes

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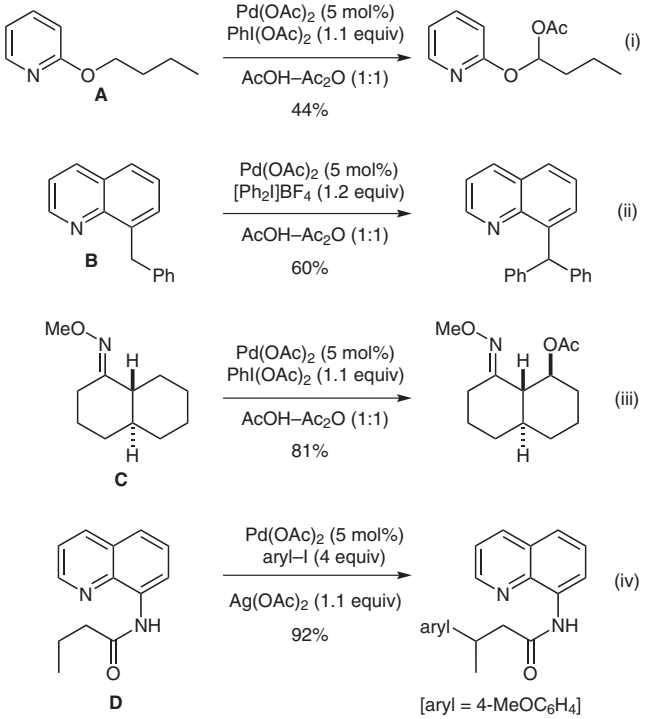
Abstract: This report describes the palladium-catalyzed functionalization of cyclopropanes containing oxazoline, oxime ether, and pyridine directing groups. Three different oxidants were examined in these studies: IOAc, $PhI(OAc)_2$, and benzoquinone. The reactions yielded products derived from 2° sp^3 C–H functionalization and/or C–C activation of the cyclopropane ring. The outcome and the product distributions were highly dependent on the structure of the substrate and the nature of the oxidant.

Key words: cyclopropane, C–H functionalization, palladium, cleavage, homogeneous catalysis

Transition-metal-catalyzed reactions for the direct functionalization of C–H bonds serve as atom economical methods for the synthesis of diverse organic molecules.[1] Research in this area has expanded dramatically over the past decade, and palladium-catalyzed ligand-directed C–H functionalization has become a particularly active subfield.[2] Numerous palladium-catalyzed methods have been developed for transforming C–H bonds into C–O, C–halogen, C–S, C–N, and C–C linkages.[2] Furthermore, these reactions have been applied to the functionalization of diverse aromatic, olefinic, and 1° sp^3 C–H bonds.[2]

In marked contrast, the palladium-catalyzed functionalization at 2° sp^3 C–H sites remains a significant challenge. Sporadic examples of this type of reactivity have been reported. However, as shown in Scheme 1, the vast majority of these require the presence of an electronically and/or sterically biasing element within the substrate. For example, substrates **A** and **B** are activated by the presence of α-heteroatoms and α-aryl groups adjacent to the site of 2° C–H functionalization (Scheme 1, i and ii).[3,4] The rigid structure of substrate **C** provides a conformational bias for 2° sp^3 C–H functionalization (Scheme 1, iii).[3] Finally, substrate **D** can participate in two-point binding to the palladium catalyst (through the quinoline and amide nitrogens), and this facilitates cleavage of an unactivated 2° sp^3 C–H bond (Scheme 1, iv).[5]

Cyclopropanes have also been successfully utilized as substrates for palladium-catalyzed 2° sp^3 C–H functionalization. For example, recent reports have described the palladium-catalyzed ligand-directed C–H halogenation,[6] arylation,[7] alkylation,[8] and olefination[9,10] of various substituted cyclopropanes. Interestingly, the C–H bonds of cyclopropanes are not particularly activated towards either homolytic nor heterolytic cleavage (BDE = 106 kcal/mol; $pK_a = 46$).[11] Nonetheless, in many of these examples, the cyclopropane C–H bonds are cleaved selectively in lieu of adjacent sp^2 and/or 1° sp^3 C–H bonds.



Scheme 1 Examples of 2° sp^3 C–H activation/acetoxylation

The reactions in Scheme 2 are of particular interest because substituted cyclopropanes serve as versatile intermediates for further synthetic manipulations.[12] In addition, studies of the scope and limitations of such transformations could provide valuable insights for the development of more general palladium-catalyzed reactions for 2° sp^3 C–H functionalization. However, to date, these cyclopropane C–H functionalization reactions remain isolated examples, and have not been subject to systematic investigation.

To address this gap in knowledge, we have conducted a detailed study of the palladium-catalyzed ligand-directed oxidation of cyclopropane derivatives. This paper describes the palladium-catalyzed reactions of cyclopropyl oxazolines, oxime ethers, and pyridines with three differ-

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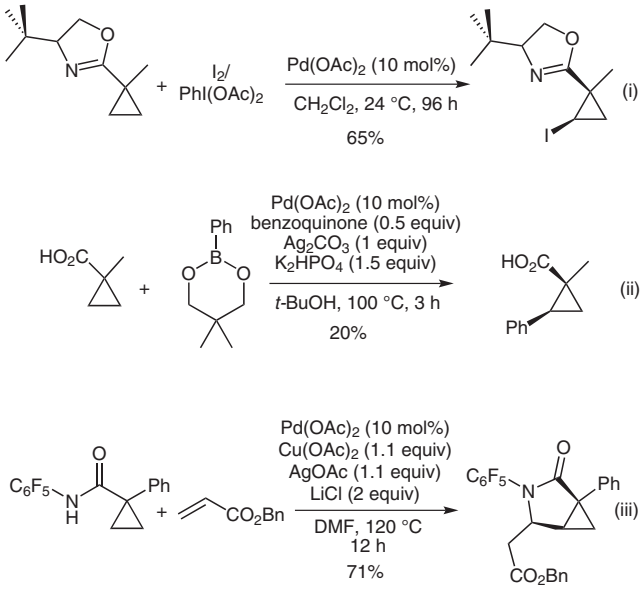
ent oxidants: IOAc, $PhI(OAc)_2$, and benzoquinone (BQ). We demonstrate that these reactions are remarkably sensitive to subtle changes in the directing group and reaction conditions. Minor perturbations of both variables often lead to competing C–C bond activation of the cyclopropane to afford ring opened products.

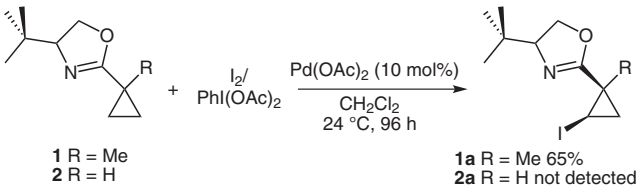
Three different oxidants were utilized for all of the substrates discussed in this manuscript. First, the oxidant IOAc [generated in situ from $PhI(OAc)_2$ and I_2] was examined, since this reagent was shown to be effective for the C–H iodination of cyclopropyl oxazoline **1** (Scheme 2, i).[6] Second, $PhI(OAc)_2$ was used as an oxidant, since our group[13] and others[14] have demonstrated that this is a highly effective reagent for the palladium(II/IV)-catalyzed C–H acetoxylation of diverse substrates. Finally, benzoquinone was employed in conjunction with acetic acid as an external nucleophile. Benzoquinone is a much weaker oxidant than $PhI(OAc)_2$, and is frequently used to mediate palladium(II/0) catalytic cycles. Most relevant to the current manuscript, Yudin has demonstrated the $PdCl_2$-catalyzed oxidative C–C activation of arylcyclopropanes using benzoquinone as a terminal oxidant.[15]



Scheme 2 Examples of ligand-directed C–H functionalization of cyclopropane derivatives

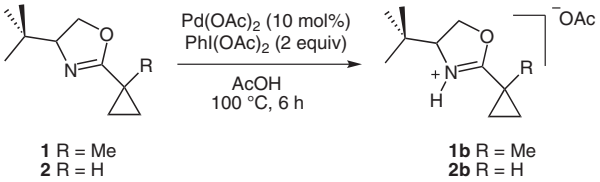
Oxazoline Substrates

Our initial studies focused on the oxazoline substrates **1** and **2**. These were selected based on Yu's report that **1** participates in 2° sp^3 C–H iodination at room temperature using IOAc.[6] However, interestingly, under analogous conditions compound **2** was completely unreactive towards C–H iodination (Scheme 3). After 96 hours at 25 °C, the starting material remained in nearly quantitative yield (99%), as determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. This result demonstrates that the C–H iodination reaction is extremely sensitive to the steric/electronic environment around the directing group.



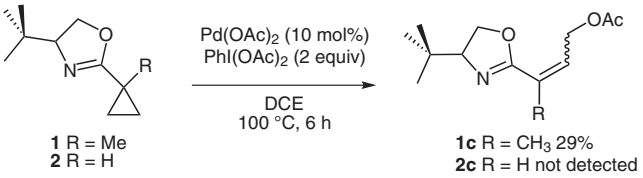
Scheme 3 Oxazoline-directed C–H iodination

The palladium-catalyzed oxidation of **1** and **2** was next examined using $PhI(OAc)_2$. Under standard conditions for palladium-catalyzed sp^3 C–H acetoxylation [10 mol% $Pd(OAc)_2$, 2 equiv $PhI(OAc)_2$ in AcOH at 100 °C],[3,13,14] the major observable products were oxazolium acetate salts **1b** (19%) and **2b** (29%) (Scheme 4). C–H acetoxylation products were not detected by ^1H NMR spectroscopy or by mass spectrometric analysis. The protonated oxazolines **1b** and **2b** were also formed (in 59% and 62% yield) when **1** and **2** were heated in acetic acid at 100 °C for six hours in the absence of palladium and oxidant.



Scheme 4 Oxazolium acetate salt formation

In an effort to limit this undesired acid/base chemistry, we switched the solvent for this reaction from acetic acid to dichloroethane (DCE). Under these conditions, substrate **1** underwent cyclopropane C–C bond activation to generate olefin **1c** in modest 29% yield as a mixture of *E*- and *Z*-isomers (Scheme 5). Notably, similar reactivity was observed at room temperature (with **1c** formed in 12% yield). In contrast, substrate **2** did not yield any detectable acetoxylated products under any conditions examined.



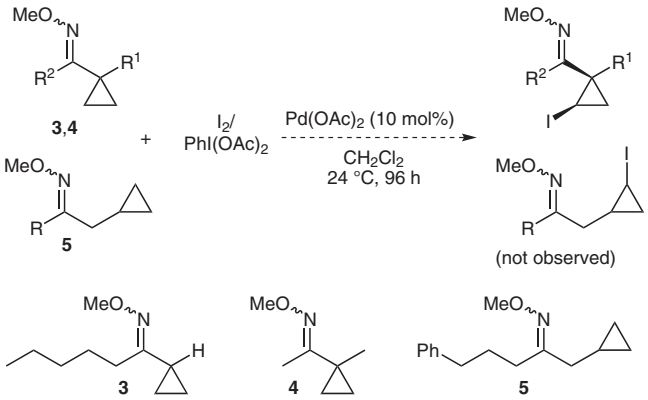
Scheme 5 Oxazoline-directed acetoxylation

Finally, oxazolines **1** and **2** were subjected to benzoquinone in acetic acid [10 mol% $Pd(OAc)_2$, 2 equiv BQ in AcOH at 100 °C]. The major observable products under these conditions were also the oxazolium acetate salts [**1b** (<10%) and **2b** (25%), respectively], and no acetoxylated products were observed upon analysis of the crude reaction mixtures by NMR or electrospray mass spectrometry.

Oxime Ether Substrates

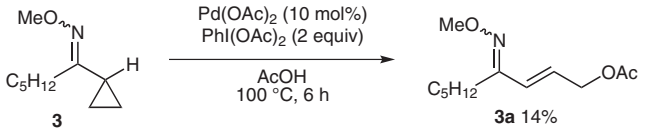
Several reports by our group have shown that oxime derivatives are versatile directing groups for palladium-cat-

alyzed sp^3 C–H functionalization.[3,13c,f] As such, oxime ether derivatives **3**–**5** were examined next. These substrates were prepared by oximation of the corresponding ketones and isolated in 68–91% yields as clear oils. Subjecting **3**–**5** to Yu's conditions[6] for palladium-catalyzed C–H iodination [10 mol% $Pd(OAc)_2$, 1 equiv $PhI(OAc)_2$, 1 equiv I_2 in CH_2Cl_2 at r.t.] did not produce the desired iodinated products (Scheme 6). In all cases, ^1H NMR spectroscopic analysis of the crude reaction mixtures showed that significant quantities of starting material remained after 96 hours (22–68%). Complex mixtures of minor products were also observed; however, electrospray mass spectrometry did not show any signals associated with the expected monoiodinated cyclopropane.



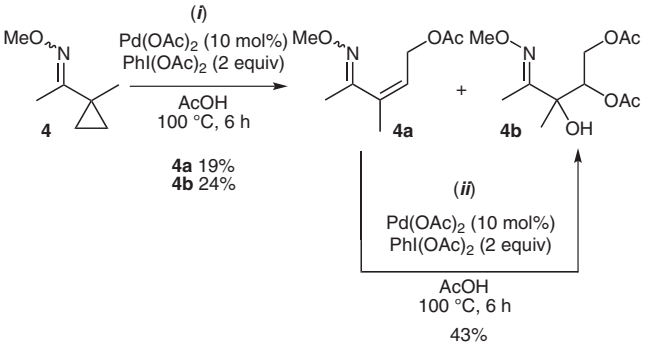
Scheme 6 Attempted iodination of oxime ether derivatives

The palladium-catalyzed reactions of oxime ethers **3**–**5** with 2 equivalents of $PhI(OAc)_2$ in the presence of 10 mol% of $Pd(OAc)_2$ in acetic acid at 100 °C were studied next. With all three substrates, C–C activation and ring opening of the cyclopropane ring were observed. As shown in Scheme 7, substrate **3** formed the α,β-unsaturated allylic acetate **3a** in low (14%) yield. The mass balance was poor in this reaction; the starting material was completely consumed, and a complex and undecipherable mixture of other by-products was formed. This suggested to us that the product might be unstable under the reaction conditions. Indeed, resubjecting an isolated sample of **3a** to $Pd(OAc)_2/PhI(OAc)_2$/AcOH showed that only 6% of **3a** remained after six hours at 100 °C.



Scheme 7 Acetoxylation of **3** with $Pd(OAc)_2/PhI(OAc)_2$

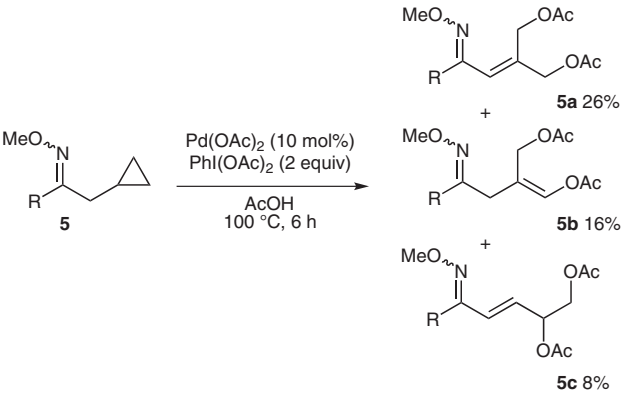
Substrate **4** showed somewhat different reactivity with $Pd(OAc)_2/PhI(OAc)_2$. Under analogous conditions, it formed a mixture of monoacetoxylated product **4a** and trioxygenated **4b** in 19% and 24% yield, respectively (Scheme 8, i). We hypothesized that **4b** might be generated from **4a** via in situ palladium-catalyzed olefin dioxygenation. Consistent with this proposal, subjecting an isolated sample of **4a** to the reaction conditions led to formation of **4b** in 43% yield (Scheme 8, ii). Notably, similar palladium-catalyzed olefin dioxygenation reactions have been reported in the literature.[16]



Scheme 8 Acetoxylation of **4** with $Pd(OAc)_2/PhI(OAc)_2$

Treatment of substrate **5** with $Pd(OAc)_2/PhI(OAc)_2$ resulted in cyclopropane ring opening to form diacetoxylated branched products **5a** and **5b** along with linear product **5c** (Scheme 9). The ratio of these three isomers was highly temperature dependent. At 60 °C, **5a** was the major product (45% yield) and **5b** was not detected (Table 1, entry 1). In contrast, at 120 °C, the yield of **5a** was only 9% and **5b** was formed in 10% yield (Table 1, entry 4).

We reasoned that the strong temperature dependence of the **5a**/**5b** ratio might indicate that **5a** is kinetically favored, while **5b** is the thermodynamic product. Indeed,



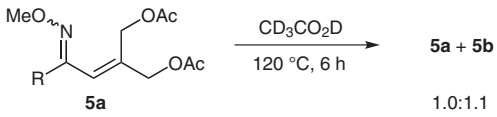
Scheme 9 Acetoxylation of **5** with $Pd(OAc)_2/PhI(OAc)_2$

Table 1 Product Distribution as a Function of Temperature

Entry	Temp (°C)	Yield (%) of **5a**	Yield (%) of **5b**	Yield (%) of **5c**	Yield (%) of **5**
1	60	45	n.d.[a]	7	3
2	80	44	n.d.[a]	8	6
3	100	26	16	8	3
4	120	9	10	9	3

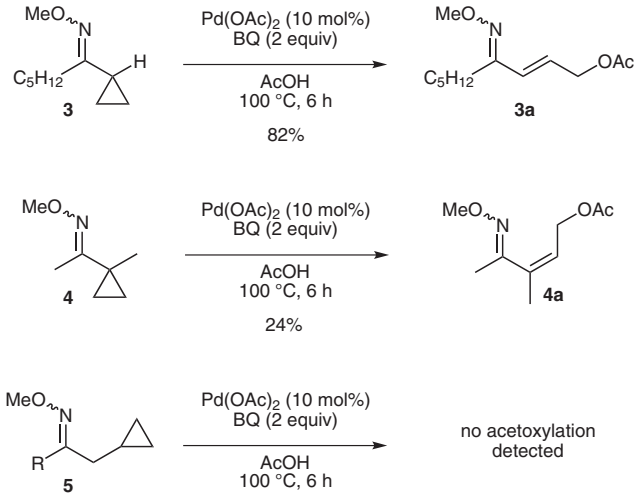
[a] n.d. = not detected.

heating a pure sample of **5a** in CD_3CO_2D for six hours at 120 °C produced a 1.0:1.1 mixture of **5a/5b**, implicating isomerization under the reaction conditions (Scheme 10). Collectively these results suggest that isomerization of **5a** is likely a major pathway to **5b**.



Scheme 10 Isomerization of **5a** at 120 °C in CD_3CO_2D

Finally, the use of benzoquinone in acetic acid for the palladium-catalyzed oxime ether directed functionalization of **3**–**5** was examined. As shown in Scheme 11, substrates **3** and **4** underwent ring opening to generate **3a** and **4a**, respectively. In contrast, no acetoxylated products were detected when substrate **5** was subjected to benzoquinone in acetic acid.



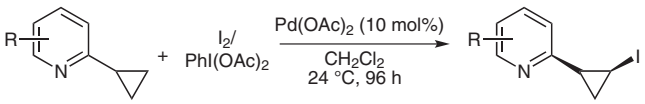
Scheme 11 Reaction of substrates **3**–**5** with benzoquinone/acetic acid

Pyridine Substrates

Pyridine derivatives have proven to be highly effective directing groups for palladium-catalyzed ligand-directed C–H functionalization reactions.[3,4,13d] As such, our final set of studies focused on evaluating 2-cyclopropylpyridines **6**–**10** as substrates for the palladium-catalyzed oxidation of cyclopropanes. Compounds **6**–**10** were prepared via Suzuki coupling between cyclopropyl boronic acid and the appropriate 2-bromopyridines.[17]

In general, the reactivity of substrates **6**–**10** was extremely sensitive to the substitution pattern on the pyridine ring. For example, the $Pd(OAc)_2$-catalyzed reactions of **6** and **7** with IOAc did not yield any monoiodinated products, as determined by ^1H NMR and electrospray mass spectrometric analysis of the crude reaction mixtures (Table 2, entries 1 and 2). In contrast, when the pyridine methyl substituent was moved to the 3-position (substrate **8**), the *cis*-iodinated product **8a** was formed in 19% yield (entry 3). The 3-ethyl- and 3-methoxy-substituted derivatives showed similar modest reactivity towards C–H iodination (entries 4 and 5). Notably, attempts to further optimize these reactions by varying the reaction time, temperature, and screening iodine salt additives did not lead to significant improvements in yield for any of these transformations.

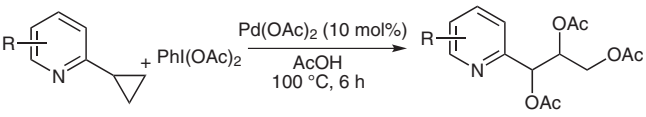
Table 2 C–H Iodination of 2-Cyclopropylpyridines with $Pd(OAc)_2$/IOAc



Entry	R	Yield (%)
1	4-Me (**6**)	n.d.
2	6-Me (**7**)	n.d.
3	3-Me (**8**)	19
4	3-Et (**9**)	21
5	3-MeO (**10**)	19

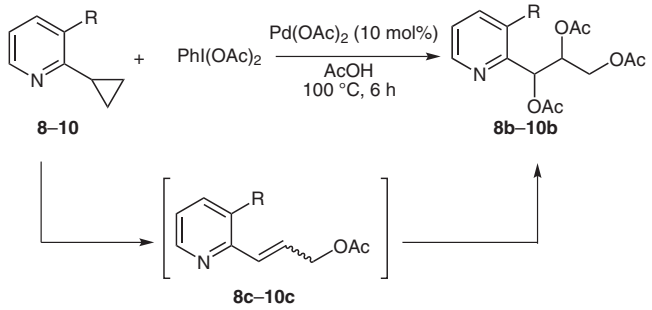
The reactions of 2-cyclopropylpyridines with $Pd(OAc)_2$/$PhI(OAc)_2$ were similarly sensitive to pyridine substitution patterns (Table 3). The 4- and 6-methyl substrates did not yield detectable acetoxylated products (Table 3, entries 1 and 2). However, the 3-substituted derivatives **8**–**10** all underwent ring opening triacetoxylation to afford moderate yields (21–34%) of **8b**–**10b** as mixtures of diastereomers (entries 3–5).

Table 3 C–C Activation of 2-Cyclopropylpyridines with $Pd(OAc)_2$/$PhI(OAc)_2$



Entry	R	Yield (%)
1	4-Me (**6**)	n.d.
2	6-Me (**7**)	n.d.
3	3-Me (**8**)	29
4	3-Et (**9**)	21
5	3-MeO (**10**)	34

The trioxygenated products **8b**–**10b** are structurally similar to oxime ether **4b**. As such, we hypothesized that they likely derive from a similar pathway involving initial cyclopropane ring opening followed by palladium-catalyzed dioxygenation of allylic acetate intermediates **8c**–**10c** (Scheme 12).[16] Consistent with this possibility, when an independently synthesized sample of **8c** was subjected to



Scheme 12 Plausible pathway to triacetoxylated product

$Pd(OAc)_2$/$PhI(OAc)_2$, product **8b** was observed, albeit in modest (17%) yield.

Finally, cyclopropyl pyridines **8–10** were subjected to 10 mol% $Pd(OAc)_2$ and 2 equivalents of benzoquinone at 100 °C in acetic acid. Interestingly, these substrates did not undergo ring opening or C–H acetoxylation under these conditions. In all cases, the major organic compound at the end of the reaction was the starting material (55–81%). Furthermore, ^{1}H NMR spectroscopic analysis and electrospray mass spectrometric analysis of the crude reaction mixtures did not show detectable quantities of monoacetoxylated products.

The results reported herein show that cyclopropanes are not very general substrates for ligand-directed 2° sp^3 C–H activation/functionalization. Under certain conditions, cyclopropane C–H functionalization was observed. For example, iodinated cyclopropyl oxazolines and pyridines could be isolated using IOAc as the oxidant. However, the yields of these transformations were typically modest, and the reactions were extremely sensitive to the substitution patterns of the substrate.

Under most conditions that are commonly used for palladium-catalyzed C–H functionalization, C–C activation of the cyclopropane was observed. These ring-opening reactions proceeded with concomitant incorporation of an acetate nucleophile derived from the solvent and/or the oxidant. While the detailed mechanism of cyclopropane ring opening has not been elucidated in the current systems, it is likely to be initiated by nucleopalladation of the cyclopropane. Such reactions have significant precedent in the organopalladium(II) literature. For example, Backvall has shown the stoichiometric acetoxypalladation and methoxypalladation of vinylcyclopropanes in acetic acid and methanol solvent, respectively.[18] A similar mechanism has also been proposed by Yudin in the catalytic conversion of substituted cyclopropanes into heterocycles.[15]

In summary, this paper describes studies of the ligand-directed oxidative functionalization of cyclopropane derivatives. In certain cases, these substrates undergo 2° sp^3 C–H oxidation reactions. However, relatively minor perturbations of the substrate structure, oxidant, and/or reaction conditions can lead to oxidative ring opening of the cyclopropane moiety. As a result, it is likely to be hard to extrapolate the reactivity of cyclopropanes to the functionalization of other substrates containing 2° sp^3 C–H sites. Furthermore, future efforts to achieve palladium-catalyzed C–H and/or C–C activation of cyclopropane derivatives should take into account the possibility of generating products derived from these two different pathways.

NMR spectra were obtained on a Varian Inova 500 (499.90 MHz for ^{1}H; 125.70 MHz for ^{13}C), a Varian Inova 400 (399.96 MHz for ^{1}H; 100.57 MHz for ^{13}C), or a MR400 (400.53 MHz for ^{1}H; 100.71 MHz for ^{13}C) spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. Standard abbreviations are used to describe the signal multiplicity. Flash chromatography was performed on EM Science silica gel 60 (0.040–0.063 mm particle size, 230–400 mesh) and TLC was performed on Merck TLC plates precoated with silica gel 60 F254. HPLC was performed on a Varian ProStar 210 HPLC using Waters SunFire Prep Silica 5 μm (19 × 150 mm) column. IR spectra were obtained on a Perkin-Elmer Spectrum BX FT-IR spectrometer. HRMS were obtained on a Micromass AutoSpec Ultima Magnetic sector mass spectrometer.

All reagents mentioned below were obtained from commercial sources and used as received unless noted otherwise. Petroleum ether (PE) used refers to the fraction boiling in the range 36–60 °C. Benzoquinone (BQ) was obtained from Acros and sublimed prior to use. The parent ketone of **3** was synthesized from oct-1-en-3-ol via Simmons–Smith cyclopropanation followed by oxidation of the alcohol.[19] The parent ketone of **5** was synthesized by the addition of allylmagnesium bromide to 4-phenylbutanal, Simmons–Smith cyclopropanation, and oxidation of the alcohol.[19,20]

Substrates 1 and 2

Substrates **1** and **2** were synthesized according to the reported procedure[6] by converting cyclopropanecarboxylic acid into its acid chloride and coupling with (*S*)-*tert*-leucinol. The coupled product was then cyclized using Ph_3P.

4-*tert*-Butyl-2-(1-methylcyclopropyl)-4,5-dihydrooxazole (1)

The three-step synthesis[6] from 1-methylcyclopropanecarboxylic acid (320 mg, 3.2 mmol, 1.0 equiv) afforded substrate **1** as a clear oil after purification by chromatography on silica gel using PE–Et_2O (80:20); yield: 349 mg (60% yield over 3 steps); R_f = 0.31 (hexanes–EtOAc, 85:15).

IR (film): 3008, 1663 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.06 (dd, *J* = 9.6, 8.8 Hz, 1 H), 3.99 (dd, *J* = 8.8, 6.8 Hz, 1 H), 3.78 (dd, *J* = 9.6, 6.8 Hz, 1 H), 1.34 (s, 3 H), 1.12 (m, 1 H), 1.06 (m, 1 H), 0.86 (s, 9 H), 0.59 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.00, 75.68, 68.52, 33.82, 25.64, 20.94, 14.80, 14.58, 14.01.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{20}NO$: 182.1539; found: 182.1536.

4-*tert*-Butyl-2-cyclopropyl-4,5-dihydrooxazole (2)

The three-step synthesis[6] from cyclopropanecarboxylic acid (2.0 g, 23.2 mmol, 1.0 equiv) afforded substrate **2** as a clear oil after purification by chromatography on silica gel using PE–Et_2O (80:20); yield: 1.7 g (43% yield over 3 steps); R_f = 0.24 (hexanes–EtOAc, 80:20).

IR (film): 3015, 1669 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.06 (dd, *J* = 8.0, 6.8 Hz, 1 H), 3.94 (dd, *J* = 6.8, 6.0 Hz, 1 H), 3.75 (dd, *J* = 8.0, 6.0 Hz, 1 H), 1.62 (dddd, *J* = 6.8, 6.8, 4.0, 4.0 Hz, 1 H), 0.90 (m, 1 H), 0.87 (m, 1 H), 0.87 (s, 9 H), 0.79 (m, 1 H), 0.78 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.01, 75.57, 68.28, 33.60, 25.71, 8.43, 6.75, 6.34.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{18}NO$: 168.1383; found: 168.1377.

Oxime Substrates 3–5; Representative Procedure (for Substrate 3)

The corresponding ketone (7.6 mmol, 1.0 equiv) and $NH_2OMe{\cdot}HCl$ (10.3 mmol, 1.35 equiv) were combined in pyridine (2.7 M). The resulting solution was stirred at 80 °C for 15 min and then at r.t. overnight. The reaction mixture was diluted with Et_2O (10 mL) and washed with H_2O containing a few drops of glacial AcOH (5 × 20 mL), H_2O (20 mL), sat. aq $NaHCO_3$ (20 mL), and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum.

1-Cyclopropylhexan-1-one *O*-Methyl Oxime (3)

Substrate **3** was obtained as a 2.3:1 mixture of oxime isomers as a clear oil (1.18 g, 91%). Purification by column chromatography was not necessary.

IR (film, mixture of oxime isomers): 3088, 1621 cm^{-1}.

HRMS (mixture of oxime isomers, EI): *m*/*z* $[M]^+$ calcd for $C_{10}H_{19}NO$: 169.1467; found: 169.1467.

Major Oxime Isomer

R_f = 0.53 (hexanes–EtOAc, 90:10).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.76 (s, 3 H), 2.13 (dd, *J* = 8.0, 7.5 Hz, 2 H), 1.53–1.44 (multiple peaks, 3 H), 1.36–1.25 (multiple peaks, 4 H), 0.94–0.87 (multiple peaks, 5 H), 0.70 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.99, 61.07, 32.05, 27.35, 25.96, 22.39, 13.98, 13.96, 5.02.

Minor Oxime Isomer

R_f = 0.28 (hexanes–EtOAc, 90:10).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.85 (s, 3 H), 2.19 (dddd, *J* = 11.0, 11.0, 5.5, 5.5 Hz, 1 H), 1.76 (dd, *J* = 8.0, 8.0 Hz, 2 H), 1.48 (m, 2 H), 1.36–1.25 (multiple peaks, 4 H), 0.82 (m, 2 H), 0.71–0.66 (multiple peaks, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.12, 61.26, 31.71, 28.98, 27.30, 22.42, 14.03, 8.64, 5.06.

1-(1-Methylcyclopropyl)ethanone *O*-Methyl Oxime (4)

Methyl 1-methylcyclopropyl ketone (1.0 g, 10.2 mmol) reacted to form **4** as a single detectable oxime isomer as a clear oil (0.88 g, 68%). Purification by column chromatography was not necessary.

IR (film): 3084, 1613 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.82 (s, 3 H), 1.72 (s, 3 H), 1.24 (s, 3 H), 0.85 (m, 2 H), 0.51 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.06, 61.13, 21.78, 20.13, 12.51, 11.29.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_7H_{13}NO$: 127.0997; found: 127.0999.

1-Cyclopropyl-5-phenylpentan-2-one *O*-Methyl Oxime (5)

Reaction with 1-cyclopropyl-5-phenylpentan-2-one (1.27 g, 6.3 mmol) afforded **5** as 1:1 mixture of oxime isomers as a clear oil after purification by chromatography on silica gel using hexanes–EtOAc (95:5); yield: 1.41 g (97%).

IR (film, mixture of oxime isomers): 3079 cm^{-1}.

HRMS (mixture of oxime isomers, EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{21}NO$: 231.1631; found: 231.1625.

Oxime Isomer 1

R_f = 0.52 (hexanes–EtOAc, 90:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (m, 2 H), 7.20–7.16 (multiple peaks, 3 H), 3.81 (s, 3 H), 2.65 (dd, *J* = 7.6, 7.6 Hz, 2 H), 2.30 (dd, *J* = 8.0, 7.6 Hz, 2 H), 2.20 (d, *J* = 6.8 Hz, 2 H), 1.86 (m, 2 H), 0.84 (m, 1 H), 0.45 (m, 2 H), 0.10 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.58, 142.01, 128.43, 128.28, 125.77, 61.04, 35.53, 33.53, 32.27, 28.39, 7.68, 4.70.

Oxime Isomer 2

R_f = 0.48 (hexanes–EtOAc, 90:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (m, 2 H), 7.20–7.17 (multiple peaks, 3 H), 3.81 (s, 3 H), 2.64 (dd, *J* = 7.6, 7.6 Hz, 2 H), 2.41 (dd, *J* = 8.0, 8.0 Hz, 2 H), 2.04 (d, *J* = 7.2 Hz, 2 H), 1.83 (m, 2 H), 0.81 (m, 1 H), 0.46 (m, 2 H), 0.11 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.01, 141.90, 128.36, 128.28, 125.82, 61.01, 38.84, 36.03, 27.56, 27.51, 8.55, 4.63.

Pyridine Substrates 6–8 and 10; Representative Procedure (for Substrate 6)

The corresponding 2-bromopyridine (5.8 mmol, 1.0 equiv) and cyclopropylboronic acid (2.0 equiv) were reacted via a modification of a literature procedure.[17] The reaction was run overnight and then cooled to r.t. A 3 M aq solution of HCl (10 mL) was added, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The EtOAc extracts were discarded, the aqueous layer was made basic with 3 M aq NaOH, and the product was extracted with Et_2O (3 × 20 mL). The Et_2O extracts were dried over $MgSO_4$, filtered, and concentrated under vacuum.

2-Cyclopropyl-4-methylpyridine (6)

Substrate **6** was obtained as a clear oil after purification by chromatography on silica gel using hexanes–EtOAc (90:10); yield: 310 mg (40%); R_f = 0.22 (hexanes–EtOAc, 90:10).

IR (film): 3089 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 5.2 Hz, 1 H), 6.94 (m, 1 H), 6.84 (m, 1 H), 2.29 (s, 3 H), 1.98 (dddd, *J* = 8.0, 8.0, 5.2, 5.2 Hz, 1 H), 0.98–0.96 (multiple peaks, 3 H), 0.95 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.56, 148.97, 146.75, 122.03, 121.46, 20.90, 16.94, 9.49.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_9H_{12}N$: 134.0964; found: 134.0964.

2-Cyclopropyl-6-methylpyridine (7)

2-Bromo-6-methylpyridine (344 mg, 2.0 mmol) reacted to afford substrate **7** as a clear oil after purification by chromatography on silica gel using PE–Et_2O (90:10); yield: 168 mg (63%); R_f = 0.41 (hexanes–EtOAc, 90:10).

IR (film): 3064 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (t, *J* = 7.6 Hz, 1 H), 6.88 (d, *J* = 7.6 Hz, 1 H), 6.83 (d, *J* = 7.6 Hz, 1 H), 2.47 (s, 3 H), 2.02 (m, 1 H), 0.96 (m, 2 H), 0.94 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.18, 157.66, 136.06, 119.79, 117.09, 24.57, 17.25, 9.45.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_9H_{12}N$: 132.0964; found: 132.0965.

2-Cyclopropyl-3-methylpyridine (8)

2-Bromo-3-methylpyridine (5.0 g, 29.1 mmol) reacted to afford substrate **8** as a clear oil after purification by chromatography on silica gel using PE–Et_2O (90:10); yield: 3.1 g (80%); R_f = 0.28 (hexanes–EtOAc, 90:10).

IR (film): 3087 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 4.8 Hz, 1 H), 7.36 (m, 1 H), 6.93 (dd, *J* = 7.6, 4.8 Hz, 1 H), 2.41 (s, 3 H), 2.08 (dddd, *J* = 9.6, 9.6, 5.2, 5.2 Hz, 1 H), 1.06 (m, 2 H), 0.95 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.45, 146.56, 136.75, 130.98, 120.07, 18.83, 13.54, 8.76.

HRMS (EI): *m*/*z* $[M - H]^+$ calcd for $C_9H_{10}N$: 132.0813; found: 132.0816.

2-Cyclopropyl-3-methoypyridine (10)

2-Bromo-3-methoxypyridine (1.0 g, 5.3 mmol) afforded substrate **10** as a clear oil after purification by chromatography on silica gel using PE–Et_2O (90:10); yield: 590 mg (74%); R_f = 0.36 (hexanes–EtOAc, 85:15).

IR (film): 3063, 1430 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.03 (dd, *J* = 4.8, 1.2 Hz, 1 H), 7.05 (dd, *J* = 8.4, 1.2 Hz, 1 H), 6.93 (dd, *J* = 8.4, 4.8 Hz, 1 H), 3.86 (s, 3 H), 2.47 (dddd, *J* = 10.0, 10.0, 4.8, 4.8 Hz, 1 H), 1.05 (m, 2 H), 0.95 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.68, 152.55, 140.57, 120.28, 116.05, 55.37, 10.24, 9.01.

HRMS (EI): *m*/*z* $[M - H]^+$ calcd for $C_9H_{10}NO$; 148.0762; found: 148.0766.

Substrate 9

2-Cyclopropyl-3-ethylpyridine (9)

A solution of **8** (1.0 g, 7.5 mmol, 1.0 equiv) in THF (1.5 mL) was added to a solution of LDA (1.5 equiv) in THF (23 mL) at –40 °C under N_2. The reaction mixture was stirred for 30 min and then cooled to –78 °C. MeI (5.3 g, 37.5 mmol, 5.0 equiv) was added, and the resulting solution was stirred for 2 h at –78 °C. The reaction was quenched with H_2O (15 mL) at –78 °C and then slowly warmed to r.t. The product was obtained using the same workup procedure as that for the synthesis of substrates **6**, **7**, and **10**. Compound **9** was obtained as a clear oil after purification by chromatography on silica gel using PE–Et_2O (97.5:2.5); yield: 1.1 g (98%); R_f = 0.23 (hexanes–EtOAc, 95:5).

IR (film): 3051, 1586, 1572 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 4.8 Hz, 1 H), 7.37 (d, *J* = 7.6 Hz, 1 H), 6.97 (dd, *J* = 7.6, 4.8 Hz, 1 H), 2.79 (q, *J* = 7.6 Hz, 2 H), 2.13 (dddd, *J* = 9.6, 9.6, 4.8, 4.8 Hz, 1 H), 1.27 (t, *J* = 7.6 Hz, 3 H), 1.08 (m, 2 H), 0.95 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.90, 146.53, 136.76, 135.17, 120.22, 25.49, 14.55, 13.09, 9.03.

HRMS (EI): *m*/*z* $[M - H]^+$ calcd for $C_{10}H_{12}N$: 146.0970; found: 146.0971.

Oxazolium Acetate Salts 1b, 2b

The appropriate substrate (0.1 mmol, 1.0 equiv) was weighed into a scintillation vial containing a stir bar. AcOH (0.12 M) was added, and the vial was sealed with a Teflon-lined cap. The resulting solution was stirred at 100 °C for 12 h. The reaction mixture was concentrated under vacuum, and the product was recovered as a white solid.

4-*tert*-Butyl-2-(1-methylcyclopropyl)-4,5-dihydrooxazol-3-ium Acetate Salt (1b)

Substrate **1** (100 mg, 0.55 mmol, 1.0 equiv) yielded **1b** as a white solid; yield: 82 mg (62%); mp 92.8–93.7 °C; R_f = 0.48 (hexanes–EtOAc, 50:50).

IR (thin film with CH_2Cl_2): 3310, 3002, 1739, 1632 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.70 (d, *J* = 9.2 Hz, 1 H), 4.28 (m, 1 H), 4.11–4.05 (multiple peaks, 2 H), 2.03 (s, 3 H), 1.31 (s, 3 H), 1.18 (dd, *J* = 3.2, 9.6 Hz, 1 H), 1.12 (dd, *J* = 3.2, 9.6 Hz, 1 H), 0.95 (s, 9 H), 0.56 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.79, 171.42, 63.54, 55.85, 33.94, 26.69, 20.91, 19.59, 19.10, 15.82, 15.74.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{23}NO$ + Na: 264.1570; found: 264.1565.

4-*tert*-Butyl-2-cyclopropyl-4,5-dihydrooxazol-3-ium Acetate Salt (2b)

Substrate **2** (100 mg, 0.60 mmol, 1.0 equiv) yielded **2b** as a white solid; yield: 80 mg (59%); mp 53.8–54.9 °C; R_f = 0.31 (hexanes–EtOAc, 50:50).

IR (thin film with CH_2Cl_2): 3301, 3010, 1739, 1645 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.64 (d, *J* = 9.6 Hz, 1 H), 4.22 (dd, *J* = 11.6, 8.8 Hz, 1 H), 4.13–4.05 (multiple peaks, 2 H), 2.02 (s, 3 H), 1.62 (dddd, *J* = 8.0, 8.0, 4.4, 4.4 Hz, 1 H), 0.95 (s, 9 H), 0.93 (m, 2 H), 0.71 (dd, *J* = 8.0, 2.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.54, 171.38, 63.68, 55.80, 33.85, 26.67, 20.89, 14.79, 7.01, 6.97.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{21}NO_3$ + Na: 250.1414; found: 250.1412.

Iodination of 2-Cyclopropyl-Substituted Pyridines; Representative Procedure (for Iodination of 8)

The pyridine substrate (0.45 mmol, 1.0 equiv), $Pd(OAc)_2$ (10 mol%), $PhI(OAc)_2$ (1.0 equiv), and I_2 (1.0 equiv) were weighed into a scintillation vial containing a stir bar. CH_2Cl_2 was added to make a 0.2 M solution (in substrate), and the vial was sealed with a Teflon-lined cap. The reaction was stirred at r.t. for 96 h. The reaction mixture was washed with sat. aq $Na_2S_2O_3$ (3 × 3 mL). The organic layer was collected, the solvent was removed under vacuum, NO_2Ph (0.25 equiv, ^1H NMR resonance at 8.2 ppm) was added as an internal standard, and the crude mixture was analyzed by ^1H NMR spectroscopy.

2-(*cis*-2-Iodocyclopropyl)-3-methylpyridine (8a)

^1H NMR spectroscopic analysis of the crude reaction mixture after 96 h at r.t. showed that substrate **8** reacted to form **8a** in 19% yield. To isolate **8a**, substrate **8** (60 mg, 0.45 mmol) was stirred for 96 h under the reaction conditions. Product **8a** was purified by chromatography on silica gel using CH_2Cl_2–EtOAc (90:10) and was isolated as a white solid; yield: 19 mg (16%); R_f = 0.42 (CH_2Cl_2–EtOAc, 90:10).

IR (thin film with CH_2Cl_2): 3051 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.40 (m, 1 H), 7.48 (m, 1 H), 7.12 (dd, *J* = 7.6, 4.8 Hz, 1 H), 3.02 (td, *J* = 7.6, 5.6 Hz, 1 H), 2.38 (s, 3 H), 2.25 (td, *J* = 8.0, 7.6 Hz, 1 H), 1.98 (td, *J* = 6.4, 5.6 Hz, 1 H), 1.65 (ddd, *J* = 8.8, 7.6, 6.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.67, 146.11, 137.31, 133.27, 121.94, 21.07, 18.70, 13.54, –7.97.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_9H_{11}IN$: 259.9936; found: 259.9936.

2-(*cis*-2-Iodocyclopropyl)-3-ethylpyridine (9a)

^1H NMR spectroscopic analysis of the crude reaction mixture after 96 h at r.t. showed that substrate **9** reacted to form **9a** in 21% yield. To isolate **9a**, substrate **9** (50 mg, 0.34 mmol) was stirred for 60 h under the reaction conditions. Product **9a** was purified by chromatography on silica gel using hexanes–EtOAc (85:15) and was isolated as a yellow oil; yield: 15 mg (16%); R_f = 0.32 (hexanes–EtOAc, 85:15).

IR (film): 3049 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.41 (dd, *J* = 4.8,1.2 Hz, 1 H), 7.52 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.15 (dd, *J* = 7.6, 5.2 Hz, 1 H), 3.02 (td, *J* = 7.6, 5.6 Hz, 1 H), 2.76 (q, *J* = 3.6 Hz, 2 H), 2.08 (td, *J* = 7.6, 7.6 Hz, 1 H), 1.98 (td, *J* = 6.4, 6.4 Hz, 1 H), 1.64 (td, *J* = 8.0, 6.4 Hz, 1 H), 1.31 (t, *J* = 3.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.94, 145.93, 138.75, 135.32, 122.05, 24.76, 20.29, 13.70, 13.52, –7.04.

HRMS (EI): *m/z* $[M + H]^+$ calcd for $C_{10}H_{13}IN$: 274.0087; found: 274.0085.

2-(*cis*-2-Iodocyclopropyl)-3-methoxypyridine (10a)

^1H NMR spectroscopic analysis of the crude reaction mixture after 96 h at r.t. showed that substrate **10** reacted to form **10a** in 19% yield. To isolate **10a**, substrate **10** (50 mg, 0.34 mmol) was stirred for 45 h under the reaction conditions. Product **10a** was purified by chromatography on silica gel using hexanes–EtOAc (85:15) and was isolated as a yellow oil; yield: 14 mg (15%); R_f = 0.21 (hexanes–EtOAc, 85:15).

IR (film): 3058, 1435 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.16 (dd, *J* = 4.0, 2.0 Hz, 1 H), 7.19–7.13 (multiple peaks, 2 H), 3.89 (s, 3 H), 3.01 (td, *J* = 8.0, 5.6 Hz, 1 H), 2.48 (td, *J* = 8.0, 7.2 Hz, 1 H), 1.90 (td, *J* = 7.2, 5.6 Hz, 1 H), 1.59 (td, *J* = 8.0, 6.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.97, 148.38, 139.98, 122.34, 116.68, 55.45, 17.93, 13.29, –6.87.

HRMS (EI): *m/z* $[M + H]^+$ calcd for $C_9H_{11}INO$: 275.9880; found: 275.9881.

Acetoxylation with $PhI(OAc)_2$ or Benzoquinone; Representative Procedure (for Acetoxylation of 3)

Substrate (0.34 mmol, 1.0 equiv), $Pd(OAc)_2$ (10 mol%), and $PhI(OAc)_2$ (2.0 equiv) or benzoquinone (2.0 equiv) were weighed into a scintillation vial containing a stir bar. Solvent was added to make a 0.12 M solution (in substrate), and the vial was sealed with a Teflon-lined cap. The reaction was stirred at 100 °C for 12 h. The reaction mixture was filtered through Celite, and the Celite was washed with Et_2O (5 mL). The solvent was removed under vacuum, NO_2Ph (0.25–0.5 equiv, ^1H NMR resonance at 8.2 ppm) was added as an internal standard, and the crude mixture was analyzed by ^1H NMR spectroscopy.

3-(4-*tert*-Butyl-4,5-dihydrooxazol-2-yl)but-2-en-1-yl Acetate (1c)

^1H NMR spectroscopic analysis of the crude reaction mixture after 6 h at 100 °C showed that substrate **1** (50 mg, 0.28 mmol) reacted with $PhI(OAc)_2$ in DCE to form **1c** in 29% yield as a 2.6:1 mixture of *E*/*Z*-isomers. The products were purified by chromatography on silica gel using CH_2Cl_2–EtOAc (90:10) and were isolated as clear oils.

(*E*)-1c

Yield: 12 mg (18%); R_f = 0.16 (hexanes–EtOAc, 85:15).

IR (film): 1741 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.41 (t, *J* = 6.4 Hz, 1 H), 4.74 (d, *J* = 6.4 Hz, 2 H), 4.20 (dd, *J* = 9.6, 8.8 Hz, 1 H), 4.10 (dd, *J* = 8.8, 8.0 Hz, 1 H), 3.93 (dd, *J* = 9.6, 8.0 Hz, 1 H), 2.08 (s, 3 H), 1.99 (br s, 3 H), 0.89 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.79, 164.03, 129.95, 128.09, 76.13, 68.47, 60.96, 33.93, 25.79, 20.86, 13.70.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{22}NO_3$: 240.1594; found: 240.1586.

(*Z*)-1c

Yield: 5 mg (8%); R_f = 0.25 (hexanes–EtOAc, 85:15).

IR (film): 1744 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.85 (t, *J* = 6.0 Hz, 1 H), 5.03 (dd, *J* = 15.2, 6.0 Hz, 1 H), 4.96 (dd, *J* = 15.2, 6.0 Hz, 1 H), 4.20 (dd, *J* = 10.0, 8.4 Hz, 1 H), 4.08 (dd, *J* = 8.4, 8.0 Hz, 1 H), 3.93 (dd, *J* = 10.0, 8.0 Hz, 1 H), 2.07 (s, 3 H), 1.98 (br s, 3 H), 0.90 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.87, 163.17, 132.60, 126.33, 75.88, 68.27, 62.91, 33.81, 25.82, 21.08, 20.99.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{22}NO_3$; 240.1594; found: 240.1586.

(2*E*)-4-(Methoxyimino)non-2-en-1-yl Acetate (3a)

^1H NMR spectroscopic analysis of the crude reaction mixture after 6 h at 100 °C showed that substrate **3** reacted with benzoquinone to afford **3a** in 82% yield. To isolate **3a**, substrate **3** (50 mg, 0.30 mmol) was heated for 12 h under the reaction conditions. Product **3a** was purified by chromatography on silica gel using hexanes–EtOAc (95:5) and was isolated as a 3.0:1.0 mixture of oxime isomers as a clear oil; yield: 44 mg (66%).

IR (film, mixture of isomers): 1741 cm^{-1}.

HRMS (mixture of isomers, ESI): *m/z* $[M + Na]^+$ calcd for $C_{12}H_{21}NO_3$ + Na: 250.1419; found: 250.1417.

Major Oxime Isomer

R_f = 0.40 (hexanes–EtOAc, 85:15).

^1H NMR (400 MHz, $CDCl_3$): δ = 6.26 (dt, *J* = 16.0, 1.6 Hz, 1 H), 6.06 (dt, *J* = 16.0, 6.0 Hz, 1 H), 4.68 (dd, *J* = 6.0, 1.6 Hz, 2 H), 3.89 (s, 3 H), 2.42 (m, 2 H), 2.09 (s, 3 H), 1.46 (m, 2 H), 1.35–1.29 (multiple peaks, 4 H), 0.89 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.66, 158.51, 129.93, 127.48, 64.29, 61.81, 31.96, 26.22, 24.64, 22.38, 20.89, 13.94.

Minor Oxime Isomer

R_f = 0.47 (hexanes–EtOAc, 85:15).

^1H NMR (400 MHz, $CDCl_3$): δ = 6.87 (dt, *J* = 16.4, 1.6 Hz, 1 H), 6.15 (dt, *J* = 16.4, 5.6 Hz, 1 H), 4.69 (dd, *J* = 5.6, 1.6 Hz, 2 H), 3.87 (s, 3 H), 2.34 (m, 2 H), 2.10 (s, 3 H), 1.54 (m, 2 H), 1.34–1.29 (multiple peaks, 4 H), 0.89 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.61, 154.67, 131.08, 121.41, 64.30, 61.60, 31.63, 30.95, 27.42, 22.38, 20.88, 13.99.

4-(Methoxyimino)-3-methylpent-2-en-1-yl Acetate (4a)

^1H NMR spectroscopic analysis of the crude reaction mixture after 6 h at 100 °C showed that substrate **4** reacted with benzoquinone to afford **4a** in 24% yield. To isolate **4a**, substrate **4** (60 mg, 0.47 mmol) was heated for 12 h under the reaction conditions. Product **4a** was purified by chromatography on silica gel using hexanes–EtOAc (90:10) and was isolated as a 7.0:1.0 mixture of oxime isomers as a clear oil; yield: 29 mg (33%).

Major Oxime Isomer

R_f = 0.42 (hexanes–EtOAc, 85:15).

IR (film, major oxime isomer): 1589, 1739 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.90 (t, *J* = 6.8 Hz, 1 H), 4.76 (d, *J* = 6.8 Hz, 2 H), 3.92 (s, 3 H), 2.08 (s, 3 H), 1.96 (s, 3 H), 1.91 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.93, 155.64, 137.14, 124.61, 61.83, 61.37, 20.94, 12.86, 10.55.

HRMS (for *E*-isomer, ESI): *m/z* $[M + Na]^+$ calcd for $C_9H_{15}NO_3$ + Na: 208.0950; found: 208.0947.

Minor Oxime Isomer
R_f = 0.35 (hexanes–EtOAc, 85:15).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.56 (t, *J* = 6.4 Hz, 1 H), 4.70 (d, *J* = 6.4 Hz, 2 H), 3.89 (s, 3 H), 2.05 (s, 3 H), 1.92 (s, 3 H), 1.90 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.83, 155.43, 136.22, 124.92, 62.23, 61.74, 21.37, 20.98, 13.44.

3-Hydroxy-4-(methoxyimino)-3-methylpentane-1,2-diyl Diacetate (4b)
^{1}H NMR spectroscopic analysis of the crude reaction mixture after 6 h at 100 °C showed that substrate **4** reacted with $PhI(OAc)_2$ to afford **4a** in 19% and **4b** in 24% yield. To isolate **4b**, substrate **4** (100 mg, 0.79 mmol) was heated for 12 h under the reaction conditions. Product **4b** was purified by chromatography on silica gel using hexanes–EtOAc (80:20) and was isolated as a 1.7:1.0 mixture of diastereomers as a yellow oil; yield: 83 mg (40%).

Major Diastereomer
R_f = 0.17 (hexanes–EtOAc, 80:20).

IR (film): 3481, 1744 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.21 (dd, *J* = 8.0, 2.8 Hz, 1 H), 4.51 (dd, *J* = 12.0, 2.8 Hz, 1 H), 4.16 (dd, *J* = 12.0, 8.0 Hz, 1 H), 4.03 (s, 1 H), 3.87 (s, 3 H), 2.07 (s, 3 H), 2.02 (s, 3 H), 1.82 (s, 3 H), 1.38 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.75, 170.03, 156.93, 74.64, 74.18, 62.41, 62.08, 23.10, 20.78, 20.74, 10.93.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{19}NO_6$ + Na: 284.1105; found: 284.1100.

Minor Diastereomer
R_f = 0.12 (hexanes–EtOAc, 80:20).

IR (film): 3475, 1744 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.27 (dd, *J* = 8.4, 3.6 Hz, 1 H), 4.49 (dd, *J* = 12.0, 3.6 Hz, 1 H), 4.02 (s, 1 H), 4.01 (dd, *J* = 12.0, 8.4 Hz, 1 H), 3.86 (s, 3 H), 2.14 (s, 3 H), 1.98 (s, 3 H), 1.90 (s, 3 H), 1.29 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.71, 170.65, 156.90, 74.89, 73.80, 62.71, 62.18, 23.32, 20.88, 20.69, 11.13.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{19}NO_6$ + Na: 284.1105; found: 284.1099.

Acetoxylation of Substrate 5
^{1}H NMR spectroscopic analysis of the crude reaction mixture after 6 h at 100 °C showed that substrate **5** (200 mg, 0.87 mmol) reacted with $PhI(OAc)_2$ to form **5a** (26% yield as a 2.3:1.0 mixture of oxime isomers), **5b** (16% yield as a 3.0:1.0 mixture of oxime isomers), and **5c** (8% yield as a single detectable oxime isomer). The products were purified by chromatography on silica gel using hexanes–EtOAc (gradient 90:10 to 80:20). The mixture of isomers **5a–c** was isolated as a yellow oil (145 mg, 48% total yield). Each isomer was separated and isolated using HPLC (hexanes–EtOAc, 93:7, 22 mL/min, Waters SunFire Prep Silica 5 μm).

2-[2-(Methoxyimino)-5-phenylpentylidene]propane-1,3-diyl Diacetate (5a)
Major Oxime Isomer
R_f = 0.47 (hexanes–EtOAc, 70:30).

IR (film): 1742 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (m, 2 H), 7.20–7.16 (multiple peaks, 3 H), 6.00 (s, 1 H), 4.96 (s, 2 H), 4.67 (s, 2 H), 3.90 (s, 3 H), 2.62 (t, *J* = 7.6 Hz, 2 H), 2.42 (t, *J* = 7.6 Hz, 2 H), 2.08 (s, 3 H), 2.06 (s, 3 H), 1.78 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.52, 170.43, 155.77, 141.64, 135.75, 128.35, 128.30, 126.21, 125.88, 65.22, 62.99, 61.45, 35.66, 28.66, 27.51, 20.85, 20.79.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{25}NO_5$ + Na: 370.1630; found: 370.1621.

Minor Oxime Isomer
R_f = 0.42 (hexanes–EtOAc, 70:30).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (m, 2 H), 7.18–7.16 (multiple peaks, 3 H), 5.94 (s, 1 H), 4.64 (s, 2 H), 4.50 (s, 2 H), 3.84 (s, 3 H), 2.62 (t, *J* = 7.6 Hz, 2 H), 2.29 (t, *J* = 7.6 Hz, 2 H), 2.10 (s, 3 H), 2.03 (s, 3 H), 1.81 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.46, 170.39, 154.08, 141.69, 135.36, 128.42, 128.33, 125.88, 122.73, 64.51, 62.01, 61.63, 35.35, 33.97, 28.39, 20.84, 20.68.

(*Z*)-2-[2-(Methoxyimino)-5-phenylpentyl]prop-1-ene-1,3-diyl Diacetate (5b)
Major Oxime Isomer
R_f = 0.47 (hexanes–EtOAc, 70:30).

IR (film): 1761, 1740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (m, 2 H), 7.20–7.16 (multiple peaks, 3 H), 7.08 (s, 1 H), 4.65 (s, 2 H), 3.81 (s, 3 H), 3.06 (s, 2 H), 2.63 (t, *J* = 7.6 Hz, 2 H), 2.19 (t, *J* = 7.6 Hz, 2 H), 2.16 (s, 3 H), 2.04 (s, 3 H), 1.84 (quint, *J* = 7.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.80, 167.30, 156.51, 141.82, 135.25, 128.44, 128.34, 125.85, 115.03, 61.30, 59.80, 35.41, 33.10, 29.69, 28.14, 20.77, 20.65.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{25}NO_5$ + Na: 370.1630; found: 370.1640.

Minor Oxime Isomer
R_f = 0.41 (hexanes–EtOAc, 70:30).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (m, 2 H), 7.20–7.16 (multiple peaks, 3 H), 7.11 (s, 1 H), 4.70 (s, 2 H), 3.81 (s, 3 H), 2.89 (s, 2 H), 2.61 (t, *J* = 7.6 Hz, 2 H), 2.29 (t, *J* = 7.6 Hz, 2 H), 2.17 (s, 3 H), 2.03 (s, 3 H), 1.77 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.80, 167.36, 157.57, 135.26, 128.45, 128.33, 126.23, 125.89, 115.78, 61.33, 59.27, 36.38, 35.83, 34.88, 27.27, 20.82, 20.67.

(3*E*)-5-(Methoxyimino)-8-phenyloct-3-ene-1,2-diyl Diacetate (5c)
^{1}H NMR analysis of the crude reaction mixture showed a single oxime isomer of **5c**. However, this compound underwent isomerization to a mixture of oxime isomers during chromatographic purification on silica gel.

Major Oxime Isomer
R_f = 0.43 (hexanes–EtOAc, 70:30).

IR (film): 1744 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (m, 2 H), 7.21–7.17 (multiple peaks, 3 H), 6.27 (dd, *J* = 16.4, 1.6 Hz, 1 H), 5.75 (dd, *J* = 16.4, 6.0 Hz, 1 H), 5.57 (m, 1 H), 4.24 (dd, *J* = 12.0, 4.0 Hz, 1 H), 4.08 (dd, *J* = 12.0, 6.8 Hz, 1 H), 3.90 (s, 3 H), 2.64 (t, *J* = 7.6 Hz, 2 H), 2.45 (t, *J* = 7.6 Hz, 2 H), 2.10 (s, 3 H), 2.05 (s, 3 H), 1.77 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.59, 169.89, 157.81, 141.67, 129.94, 128.40, 128.34, 127.56, 125.94, 71.15, 64.58, 61.92, 35.75, 27.87, 24.10, 21.02, 20.74.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{25}NO_5$ + Na: 370.1625; found: 370.1622.

Minor Oxime Isomer
R_f = 0.45 (hexanes–EtOAc, 70:30).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (m, 2 H), 7.21–7.17 (multiple peaks, 3 H), 6.89 (dd, *J* = 16.4, 1.6 Hz, 1 H), 5.90 (dd, *J* = 16.4, 6.0 Hz, 1 H), 5.57 (m, 1 H), 4.27 (dd, *J* = 12.0, 4.0 Hz, 1 H), 4.10 (dd, *J* = 11.6, 6.8 Hz, 1 H), 3.88 (s, 3 H), 2.64 (t, *J* = 7.6 Hz, 2 H), 2.36 (t, *J* = 7.6 Hz, 2 H), 2.11 (s, 3 H), 2.05 (s, 3 H), 1.77 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.57, 169.88, 153.68, 141.82, 130.95, 128.48, 128.35, 125.89, 121.72, 71.33, 64.49, 61.72, 35.42, 30.20, 29.06, 21.01, 20.72.

1-(3-Methylpyridin-2-yl)propane-1,2,3-triyl Triacetate (8b)
^{1}H NMR spectroscopic analysis of the crude reaction mixture after 6 h at 100 °C showed that substrate **8** reacted with $PhI(OAc)_2$ to afford **8b** in 29% yield. To isolate **8b**, substrate **8** (20 mg, 0.15 mmol) was heated for 12 h under the reaction conditions. Product **8b** was purified by chromatography on silica gel using hexanes–EtOAc (50:50) and was isolated as a 2.6:1.0 mixture of diastereomers as a yellow oil; yield: 17 mg (37%). Pure samples of each diastereomer were obtained from individual column fractions.

IR (film, mixture of diastereomers): 1739 cm^{-1}.

Major Diastereomer
R_f = 0.30 (EtOAc–hexanes, 60:40).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (m, 1 H), 7.46 (m, 1 H), 7.13 (m, 1 H), 6.15 (d, *J* = 6.4 Hz, 1 H), 5.52 (td, *J* = 6.4, 2.4 Hz, 1 H), 4.60 (dd, *J* = 12.0, 2.4 Hz, 1 H), 4.46 (dd, *J* = 12.0, 6.4 Hz, 1 H), 2.48 (s, 3 H), 2.13 (s, 3 H), 2.05 (s, 3 H), 1.93 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.63, 170.03, 169.65, 153.25, 147.20, 138.25, 132.40, 123.29, 72.23, 70.24, 62.02, 20.84, 20.74, 20.68, 18.08.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{19}NO_6$ + Na: 332.1110; found: 332.1106.

Minor Diastereomer
R_f = 0.27 (EtOAc–hexanes, 60:40).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (m, 1 H), 7.48 (m, 1 H), 7.16 (m, 1 H), 6.25 (d, *J* = 8.0 Hz, 1 H), 5.82 (ddd, *J* = 8.0, 4.8, 3.2 Hz, 1 H), 4.38 (dd, *J* = 12.0, 3.2 Hz, 1 H), 3.74 (dd, *J* = 12.0, 4.8 Hz, 1 H), 2.49 (s, 3 H), 2.08 (s, 3 H), 2.07 (s, 3 H), 2.05 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.35, 170.26, 169.98, 152.78, 147.44, 138.70, 132.57, 123.63, 71.85, 70.82, 62.43, 20.82, 20.73, 20.67, 18.11.

1-(3-Ethylpyridin-2-yl)propane-1,2,3-triyl Triacetate (9b)
^{1}H NMR spectroscopic analysis of the crude reaction mixture after 6 h at 100 °C showed that substrate **9** reacted with $PhI(OAc)_2$ to afford **9b** in 21% yield. To isolate **9b**, substrate **9** (50 mg, 0.34 mmol) was heated for 12 h under the reaction conditions. Product **9b** was purified by chromatography on silica gel using hexanes–EtOAc (50:50) and was isolated as a 3.2:1.0 mixture of diastereomers as a yellow oil; yield: 23 mg (21%). Pure samples of each diastereomer were obtained from individual column fractions.

Major Diastereomer
IR (film): 1741 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (m, 1 H), 7.51 (m, 1 H), 7.18 (m, 1 H), 6.24 (d, *J* = 6.8 Hz, 1 H), 5.55 (ddd, *J* = 6.8, 6.0, 2.4 Hz, 1 H), 4.61 (dd, *J* = 12.4, 2.4 Hz, 1 H), 4.46 (dd, *J* = 12.4, 6.0 Hz, 1 H), 2.86 (m, 2 H), 2.12 (s, 3 H), 2.06 (s, 3 H), 1.91 (s, 3 H), 1.23 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.65, 170.04, 169.61, 152.55, 147.18, 138.26, 136.62, 123.56, 72.34, 69.64, 62.03, 24.27, 20.92, 20.76, 20.68, 14.68.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{22}NO_6$: 324.1442; found: 324.1443.

Minor Diastereomer
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (m, 1 H), 7.54 (m, 1 H), 7.22 (m, 1 H), 6.37 (d, *J* = 7.6 Hz, 1 H), 5.85 (ddd, *J* = 7.6, 4.8, 3.2 Hz, 1 H), 4.36 (dd, *J* = 12.4, 3.2 Hz, 1 H), 3.79 (dd, *J* = 12.4, 4.8 Hz, 1 H), 2.86 (m, 2 H), 2.08 (s, 3 H), 2.06 (s, 3 H), 2.06 (s, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.39, 170.16, 169.99, 151.99, 147.29, 138.22, 136.84, 123.87, 72.06, 70.13, 62.44, 23.99, 20.90, 20.84, 20.71, 14.59.

1-(3-Methoxypyridin-2-yl)propane-1,2,3-triyl Triacetate (10b)
^{1}H NMR spectroscopic analysis of the crude reaction mixture after 6 h at 100 °C showed that substrate **10** reacted with $PhI(OAc)_2$ to afford **10b** in 34% yield. To isolate **10b**, substrate **10** (50 mg, 0.34 mmol) was heated for 12 h under the reaction conditions. Product **9b** was purified by chromatography on silica gel using hexanes–EtOAc (60:40) and was isolated as a 1.4:1.0 mixture of diastereomers as a yellow oil; yield: 37 mg (34%). Pure samples of each diastereomer were obtained from individual column fractions.

IR (film, mixture of diastereomers): 1734 cm^{-1}.

HRMS (mixture of diastereomers, ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{19}NO_7$ + Na: 348.1059; found: 348.1051.

Major Diastereomer
R_f = 0.16 (EtOAc–hexanes, 60:40).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (m, 1 H), 7.22 (m, 1 H), 7.17 (m, 1 H), 6.40 (d, *J* = 5.6 Hz, 1 H), 5.74 (ddd, *J* = 6.4, 5.6, 4.0 Hz, 1 H), 4.29 (dd, *J* = 12.0, 4.0 Hz, 1 H), 4.09 (dd, *J* = 12.0, 6.4 Hz, 1 H), 3.88 (s, 3 H), 2.14 (s, 3 H), 2.03 (s, 3 H), 1.99 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.52, 170.05, 170.05, 153.29, 144.06, 141.03, 124.12, 117.83, 70.80, 68.72, 62.47, 55.63, 20.88, 20.72, 20.70.

Minor Diastereomer
R_f = 0.22 (EtOAc–hexanes, 60:40).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (m, 1 H), 7.22 (m, 1 H), 7.18 (m, 1 H), 6.37 (d, *J* = 4.8 Hz, 1 H), 5.62 (m, 1 H), 4.47 (dd, *J* = 12.0, 2.0 Hz, 1 H), 4.36 (dd, *J* = 12.0, 7.2 Hz, 1 H), 3.88 (s, 3 H), 2.15 (s, 3 H), 2.00 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.68, 169.95, 169.87, 153.48, 144.15, 140.99, 124.09, 117.83, 71.14, 69.46, 62.23, 55.65, 20.91, 20.84, 20.74.

3-(3-Methylpyridin-2-yl)allyl Acetate (8c)
Substrate **8** (200 mg, 1.5 mmol, 1.0 equiv), $Pd(OAc)_2$ (33.7 mg, 0.15 mmol, 10 mol%), and $PhI(OAc)_2$ (484 mg, 1.5 mmol, 1.0 equiv) were weighed into a scintillation vial containing a stir bar. CH_2Cl_2 (7.5 mL) was added, and the vial was sealed with a Teflon-lined cap. The reaction mixture was stirred at r.t. for 48 h. The solvent was then removed under vacuum. The product **8c** was obtained as a yellow oil after purification by flash chromatography on silica gel using PE–Et_2O (80:20) [5 mg (*E*)-**8c**, 14 mg (*Z*)-**8c**, 7% total yield].

(*E*)-8c
R_f = 0.35 (EtOAc–hexanes, 70:30).

IR (film, isomer 1): 1736 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (d, *J* = 4.8 Hz, 1 H), 7.43 (d, *J* = 7.6 Hz, 1 H), 7.05 (dd, *J* = 7.6, 4.8 Hz, 1 H), 6.68 (d, *J* = 11.6 Hz, 1 H), 5.97 (ddd, *J* = 11.6, 5.6, 5.6 Hz, 1 H), 5.22 (dd, *J* = 5.6, 1.6 Hz, 2 H), 2.33 (s, 3 H), 2.08 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.98, 154.00, 146.61, 137.57, 131.58, 131.52, 126.98, 121.85, 63.48, 21.07, 18.95.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{14}NO_2$: 192.1019; found: 192.1017.

(*Z*)-8c

R_f = 0.17 (EtOAc–hexanes, 70:30).

IR (film, isomer 1): 1736 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (m, 1 H), 7.43 (m, 1 H), 7.07 (dd, *J* = 7.6, 4.8 Hz, 1 H), 6.90–6.89 (multiple peaks, 2 H), 4.81 (dd, *J* = 2.8, 1.2 Hz, 2 H), 2.36 (s, 3 H), 2.10 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.71, 152.47, 147.06, 138.19, 130.62, 129.04, 128.81, 122.51, 64.60, 20.95, 18.65.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{14}NO_2$: 192.1019; found: 192.1019.

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