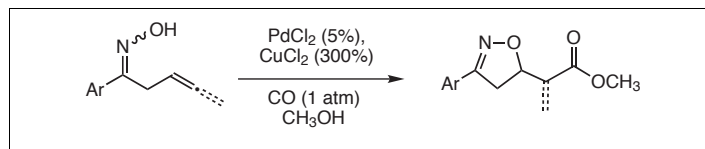


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3,5-Disubstituted Δ^2 -isoxazolines can be prepared using the palladium-mediated nucleometalation / methoxycarbonylation of β,γ -unsaturated oximes. This novel route to this class of compounds is tolerant of a wide variety of functionality in the starting material, and provides a rapid route to highly functionalized isoxazolines.

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During our investigation of the palladium-mediated 5-*exo-trig* cyclization of β,γ -unsaturated carbonyls, we noted the recent report of an antagonist of macrophage migration inhibitory factor (MIF)[1]. MIF, a homotrimer structurally related to the bacterial enzymes 4-oxalocrotonate tautomerase and 5-carboxymethyl-2-hydroxymuconate isomerase, has been discovered to be an important regulatory protein in the immune system that promotes an inflammatory response. Moreover, MIF has been implicated in the development of Type 1 diabetes. Antagonists of MIF have been shown to limit and even prevent the development of diabetes [2].

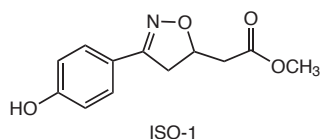


Figure 1. ISO-1 (methyl 3-(*p*-hydroxyphenyl)-5- Δ^2 -isoxazolyl acetate).

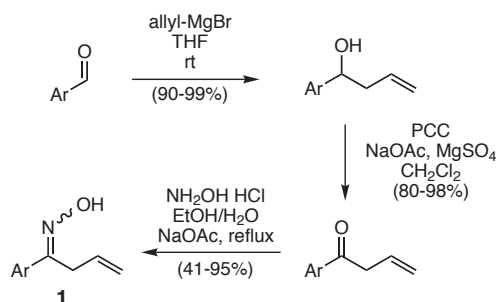
For example, ISO-1, shown in Figure 1, a racemic 3,5-disubstituted Δ^2 -isoxazoline shows remarkable anti-diabetogenic activity as a MIF antagonist. Specifically, researchers have determined that racemic methyl 3-(*p*-hydroxyphenyl)-5- Δ^2 -isoxazolyl acetate (ISO-1) reduces the production of MIF protein in pancreatic islets and suppresses the development of hyperglycemia. Further studies using X-ray crystallography of an MIF-ISO-1 complex, indicate that only the R-isomer binds to MIF [1]. This discovery indicates a potential therapy and / or a pharmacological curative for persons affected by Type 1 diabetes.

Syntheses of ISO-1 and other Δ^2 -isoxazolines have been previously accomplished *via* the intermolecular nitrile oxide cycloaddition of an appropriately substituted aldehyde oxime with a β,γ -unsaturated ester [3]. The regiochemistry of the product, while well-defined in the

reaction of monosubstituted α,β -unsaturated esters, can be more difficult to control in more substituted and functionalized derivatives [2]. Moreover, there are limits to the functionality present in both starting materials for the final cyclization step.

Herein, we wish to report an alternative synthesis of this class of compounds, including a viable route to ISO-1, *via* the palladium(II)-mediated nucleometalation / methoxycarbonylation of substituted β,γ -unsaturated oximes. Since their initial discovery [4], palladium-mediated reactions have become prominent in synthetic organic chemistry [5]. These reactions have been instrumental in the facile preparation of five- and six-membered carbo- and heterocyclic rings [6]. In fact, synthetic application of this method has generated rapid routes to a wide variety of natural products [7]. Many of these reactions involve the close proximity of a nucleophile to an *in-situ* generated electron deficient alkyne, arene, or allene.

Scheme 1

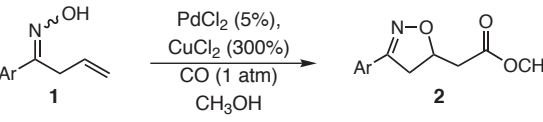


Synthetic Route to **1**

The β,γ -alkenyl oximes (**1**) used in this investigation were prepared using standard organic chemistry reactions from commercially available starting materials as shown in Scheme 1. Specific substituents on the aromatic ring were

chosen so that the electronic effects of the final step (**1**→**2**) could be explored. Specifically, starting with an appropriately substituted benzaldehyde, a solution of allyl magnesium bromide in tetrahydrofuran was added at room temperature to give excellent yield of the corresponding β,γ -unsaturated carbinols [9]. The alcohol functional group was then oxidized to the corresponding ketone using pyridinium chlorochromate (PCC) in dichloromethane. Magnesium sulfate was added to the reaction mixture to serve as a support for the reduced chromium salts [10]. Simple filtration through a pad of Florisil provided the desired ketone. The oximes (**1**), as a mixture of *syn* and *anti* isomers (>5:1, *syn* to the allyl group), were prepared by briefly refluxing the ketone in a mixture of hydroxylamine hydrochloride with sodium acetate in 50% ethanol [11]. Each of the products in this sequence was isolated by extractive workup, purified by column chromatography on silica gel, and their identity confirmed by spectroscopic methods. Interestingly, under the conditions employed in this synthetic scheme to prepare **1**, no rearrangement of the alkene to afford the conjugated system was observed.

Table 1
Palladium-mediated cyclization of **1**.

		
Compound	Ar	Yield (%)
2a	Ph	78
2b	<i>p</i> -CH ₃ Ph	62
2c	<i>p</i> -CH ₃ OPh	99
2d	<i>p</i> -BrPh	nd
2e	<i>p</i> -FPh	60
2f	<i>m</i> -FPh	15
2g	2,5-(CH ₃ O)Ph	10 ^a
2h	<i>p</i> -tBDPSiOPh	83
2i	<i>p</i> -HOPh	21

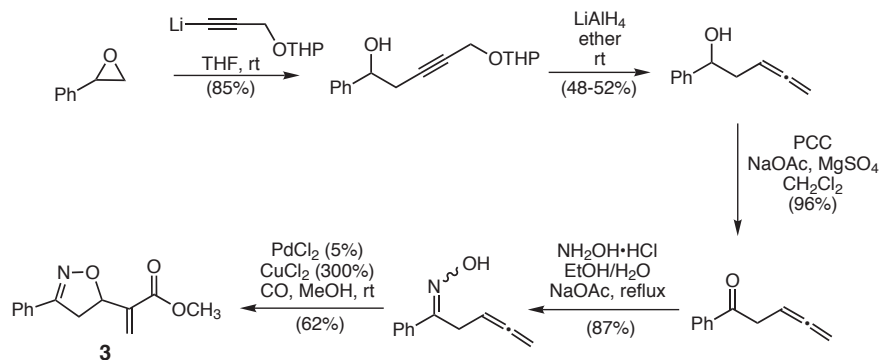
a. yield not optimized nd = not detected

Cyclization of **1** using catalytic palladium(II) chloride under a carbon monoxide atmosphere (5 mol% PdCl₂, 300 mol% CuCl₂, carbon monoxide, methanol) gave a racemic mixture of the desired acetate substituted isoxazolines (**2**) in variable yields as shown in Table 1. Copper(II) chloride was added to the reaction to reoxidize the palladium(0) generated in the preparation of the isoxazoline ring system. The product isoxazolines were readily identifiable by both proton and carbon nmr spectroscopy. Specifically, the hydrogen atoms at C-4 of the Δ^2 -isoxazoline ring exist as a doublet of doublets coupled to the hydrogen atom at C-5. The alpha hydrogen atoms on the acetyl substituent are also clearly observable as doublets of doublets coupled to the hydrogen at C-5. Modeling of the spin system using Bruker's NMRSIM software package confirmed the assigned coupling constants.

A vinylogue of **2** was prepared by the method outlined in Scheme 2. The lithium salt of THP-protected propargyl alcohol was added to a solution of styrene oxide to give the alkynyl alcohol. Treatment of this compound with lithium aluminum hydride in warm ether produced the allene in approximately 50% yield [12]. The oxime was then prepared using the same method outlined in Scheme 1. The palladium(II) catalyzed nucleometalation / methoxycarbonylation of the mixture of *syn* and *anti* oximes produced in the oximation reaction provided racemic **3** in moderate yield.

Some obvious limitations are to be noted in the palladium-mediated cyclization of β,γ -unsaturated oximes. For example, compound **1d** did not produce the desired product **2d** to any measurable extent as evidenced by proton nmr of the reaction mixture, most likely due to the presence of the aryl halide. Such functionality has been shown to undergo oxidative addition to palladium metal, an intermediate in the proposed mechanism of the reaction [13]. In contrast, compounds **1e** and **1f** did not suffer from this oxidative addition to palladium, since the

Scheme 2



Synthetic Route to Vinylogue of **2**.

carbon-fluorine bond is considerably stronger than other carbon-halogen bonds. Further observations of the yield of the reaction with respect to the electronic character of the phenyl substituent indicate a strong correlation. Oximes containing electron donating substituents, **1c** and **1h**, provided very high yields of the corresponding isoxazolines **2c** and **2h**.

The known compound, ISO-1 (**2i**) was also prepared using this method. Initially, the commercially available starting material, *p*-hydroxybenzaldehyde, was protected as the *tert*-butyldiphenylsilyl ether [14] then converted to the oxime by the procedure described in Scheme 1. Cyclization of the resulting compound **1h** gave the desired isoxazoline **2h** in good yield. The protecting group was then easily removed with potassium fluoride and 18-crown-6 in a mixture of water and dichloromethane [15] to give **2i** (>98% yield after column chromatography). Alternatively, deprotection of **1h** using the potassium fluoride / 18-crown-6 method, followed by the palladium(II) catalyzed cyclization provided the expected isoxazoline, **2i**, albeit in significantly lower yield. The acidic nature of the *p*-hydroxyphenyl derivative **1h** could explain the repeated low yields for this reaction.

The results of this work stand in contrast to the work of Murahashi [16], who prepared pyridines and isoxazoles *via* the palladium(II) mediated cyclization of β,γ -unsaturated oximes in the presence of a base. The differences in the outcome of the Murahashi method and our method are based solely on the conditions of the palladium(II) cyclization. While the mechanism of the Murahashi cyclization is essentially identical to that in our preparation of Δ^2 -isoxazolines, the Murahashi method utilizes stoichiometric quantities of palladium(II), an inert atmosphere, and a base. The lack of carbon monoxide in a protic solvent gives rise to the reductive elimination of the intermediate sigma-palladium complex and produces an aromatic heterocycle.

Conclusion.

We have shown that β,γ -unsaturated oximes undergo palladium-mediated cyclization to Δ^2 -isoxazolines. This method provides an alternate route to derivatives of ISO-1. β -Allenyl oximes have been shown to give vinylogous compounds. We have also demonstrated that the cyclization of β,γ -unsaturated oximes provides a convenient and synthetically useful route to 3,5-disubstituted Δ^2 -isoxazolines.

Acknowledgements.

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EXPERIMENTAL

Exact masses were determined by high-resolution fast atom bombardment mass spectrometry at the Nebraska Center for Mass Spectrometry, in Lincoln, Nebraska. The oximes **1** were prepared using standard methods indicated in the text. Nmr spectra (^1H and ^{13}C) were obtained on a Bruker Avance 300 multinuclear FT-NMR (300 MHz for ^1H). Combustion analyses were performed by Desert Analytics Laboratory, PO Box 41838, Tucson, AZ 85717. All reactions were performed under an inert atmosphere of nitrogen or argon, unless otherwise noted. Anhydrous methanol was prepared by distillation under an inert atmosphere from a slurry of magnesium methoxide in methanol. Flash chromatography was performed on silica gel (70-230 mesh) with freshly distilled solvents by the method of Still [17]. Palladium and copper chlorides were purchased from Aldrich Chemical Company and maintained under an inert atmosphere before use.

Compound **1a** has been prepared previously [1,18]. Compounds **1b-1i** were prepared using the method outlined in Scheme 1 and used after purification by flash chromatography (hexane:ethyl acetate 9:1).

General Procedure for the Palladium-mediated Cyclization.

To a dry roundbottom flask containing 5.0 mL anhydrous methanol was added palladium(II) chloride (0.050 mol equiv), anhydrous copper(II) chloride (3.0 mol equiv), and a 500 mL balloon of carbon monoxide. The appropriate oxime **1** (1.00 mol equiv) in 1.0 mL anhydrous methanol was added to the vigorously stirred solution. After 12-18 h, the solution had darkened and a palladium mirror had formed on the inside of the flask. The solvents were removed by rotary evaporation and the residue extracted with ethyl acetate (3 x 15 mL). The ethyl acetate was then washed with water (3 x 20 mL), brine (1 x 20 mL), dried over anhydrous magnesium sulfate, filtered, and evaporated to give the desired product as a crude yellow oil.

Methyl 3-phenyl-5-isoxazolinylacetate (**2a**).

Flash chromatography (hexane:ethyl acetate 9:1) gave 78% yield of the desired product as an off-white solid that agreed with the literature data [1,18] for this compound. ^1H nmr (deuteriochloroform): δ 7.85 (m, 2H), 7.53 (m, 3H), 5.05 (dddd, J = 10.2, 7.2, 6.0Hz, 1H), 3.73 (s, 3H), 3.56 (dd, J = 16.8, 6.0Hz, 1H), 3.13 (dd, J = 16.8, 7.2Hz, 1H); 2.89 (dd, J = 15.9, 6.0Hz, 1H), 2.66 (dd, J = 15.9, 7.2Hz, 1H). ^{13}C nmr (deuteriochloroform): δ 170.6, 156.6, 130.2, 129.3, 128.7, 126.7, 77.3, 52.8, 40.2, 39.8.

Methyl 3-(*p*-toluyl)-5-isoxazolinylacetate (**2b**).

Flash chromatography (hexane:ethyl acetate 9:1) gave 62% yield of the desired product as an off-white solid. mp 58-61°C. ^1H nmr (deuteriochloroform): δ 7.57 (m, 2H), 7.22 (m, 2H), 5.11 (dddd, J = 10.2, 7.5, 7.2, 6.0Hz, 1H), 3.75 (s, 3H), 3.55 (dd, J = 16.8, 10.2Hz, 1H), 3.13 (dd, J = 16.8, 7.2Hz, 1H), 2.89 (dd, J = 15.9, 6.0Hz, 1H), 2.63 (dd, J = 15.9, 7.5Hz, 1H), 2.39 (s, 3H). ^{13}C nmr (deuteriochloroform): δ 170.6, 156.5, 140.4, 129.4, 126.7, 126.6, 76.8, 51.9, 40.4, 39.6, 21.4. hrms (FAB) Calcd. for $\text{C}_{13}\text{H}_{16}\text{NO}_3$: 234.11302; Found: 234.11399

Anal. Calcd. for $\text{C}_{13}\text{H}_{15}\text{NO}_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.15; H, 6.71; N, 6.06.

Methyl 3-(*p*-methoxyphenyl)-5-isoxazolinylnacetate (**2c**).

Flash chromatography (hexane:ethyl acetate 9:1) gave 99% yield of the desired product as an off-white solid that agreed with the literature data [1] for this compound. ^1H nmr (deuteriochloroform): δ 7.65 (m, 2H), 6.93 (m, 2H), 5.10 (dddd, $J=10.2, 7.8, 7.2, 6.0$, 1H), 3.86 (s, 3H), 3.74 (s, 3H), 3.54 (dd, $J=16.8, 10.2\text{Hz}$, 1H), 3.11 (dd, $J=16.8, 7.2\text{Hz}$, 1H), 2.89 (dd, $J=16.0, 6.0\text{Hz}$, 1H), 2.66 (dd, $J=16.0, 7.8\text{Hz}$, 1H). ^{13}C nmr (deuteriochloroform): δ 170.8, 156.8, 144.5, 139.8, 129.5, 126.7, 77.1, 60.4, 52.5, 40.4, 39.1.

Anal. Calcd. for $\text{C}_{13}\text{H}_{15}\text{NO}_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.90; H, 6.41; N, 5.73.

Methyl 3-(*p*-fluorophenyl)-5-isoxazolinylnacetate (**2e**).

Flash chromatography (hexane:ethyl acetate 9:1) gave 60% yield of the desired product as an off-white solid. mp 67–69°C. ^1H nmr (deuteriochloroform): δ 7.53 (m, 2H), 6.95 (m, 2H), 4.98 (dddd, $J=10.5, 7.5, 7.2, 6.3\text{Hz}$, 1H), 3.59 (s, 3H), 3.40 (dd, $J=16.8, 10.5\text{Hz}$, 1H), 2.99 (dd, $J=16.8, 7.5\text{Hz}$, 1H), 2.74 (dd, $J=15.9, 6.3\text{Hz}$, 1H), 2.55 (dd, $J=15.9, 7.2\text{Hz}$, 1H). ^{13}C nmr (deuteriochloroform): δ 170.5, 163.5 (d, $J_{13\text{C}-19\text{F}}=250\text{Hz}$), 155.5, 128.6 (d, $J_{13\text{C}-19\text{F}}=8\text{Hz}$), 125.7 (d, $J_{13\text{C}-19\text{F}}=4\text{Hz}$), 115.7 (d, $J_{13\text{C}-19\text{F}}=22\text{Hz}$), 77.1, 51.7, 40.1, 39.4. hrms (FAB) Calcd. for $\text{C}_{12}\text{H}_{13}\text{NO}_3\text{F}$: 238.08795; Found: 238.08746.

Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{FNO}_3$: C, 60.76; H, 5.10; N, 5.90. Found: C, 61.08; H, 4.69; N, 5.51.

Methyl 3-(*m*-fluorophenyl)-5-isoxazolinylnacetate (**2f**).

Flash chromatography (hexane:ethyl acetate 9:1) gave 15% yield of the desired product as an off-white waxy solid. mp 44–46°C. ^1H nmr (deuteriochloroform): δ 7.30 (m, 3H), 7.01 (m, 1H), 5.04 (dddd, $J=10.2, 7.5, 7.4, 6.0\text{Hz}$, 1H), 3.64 (s, 3H), 3.44 (dd, $J=16.5, 10.2\text{Hz}$, 1H), 3.02 (dd, $J=16.5, 7.5\text{Hz}$, 1H), 2.79 (dd, $J=15.9, 6.0\text{Hz}$, 1H), 2.58 (dd, $J=15.9, 7.4\text{Hz}$, 1H). ^{13}C nmr (deuteriochloroform): δ 170.1, 169.5, 161.8 (d, $J_{13\text{C}-19\text{F}}=247\text{Hz}$), 154.7 (d, $J_{13\text{C}-19\text{F}}=3\text{Hz}$), 129.3 (d, $J_{13\text{C}-19\text{F}}=8\text{Hz}$), 121.5 (d, $J_{13\text{C}-19\text{F}}=3\text{Hz}$), 116.1 (d, $J_{13\text{C}-19\text{F}}=21\text{Hz}$), 112.5 (d, $J_{13\text{C}-19\text{F}}=23\text{Hz}$), 77.3, 50.8, 39.0, 38.5. hrms (FAB) Calcd. for $\text{C}_{12}\text{H}_{13}\text{NO}_3\text{F}$: 238.08795; Found: 238.08905.

Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{FNO}_3$: C, 60.76; H, 5.10; N, 5.90. Found: C, 61.04; H, 5.10; N, 5.90.

Methyl 3-(2',5'-dimethoxyphenyl)-5-isoxazolinylnacetate (**2g**).

Flash chromatography (hexane:ethyl acetate 9:1) gave 10% yield of the desired product as an off-white solid. ^1H nmr (deuteriochloroform): δ 7.30 (m, 1H), 6.92 (m, 2H), 5.09 (dddd, $J=10.2, 7.5, 7.2, 6.5\text{Hz}$, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.74 (s, 3H), 3.66 (dd, $J=17.4, 10.2\text{Hz}$, 1H), 3.22 (dd, $J=17.4, 7.2\text{Hz}$, 1H), 2.86 (dd, $J=15.9, 6.3\text{Hz}$, 1H), 2.64 (dd, $J=15.9, 7.5\text{Hz}$, 1H). ^{13}C nmr (deuteriochloroform): δ 170.8, 156.1, 153.5, 151.9, 119.0, 117.7, 113.3, 112.9, 77.1, 56.1, 55.8, 51.8, 42.7, 39.6. hrms (FAB). Calcd. for $\text{C}_{14}\text{H}_{18}\text{NO}_5$: 280.11850; Found: 280.11920.

Anal. Calcd. for $\text{C}_{14}\text{H}_{17}\text{NO}_5$: C, 60.21; H, 6.14; N, 5.01. Found: C, 60.42; H, 6.38; N, 5.27.

Methyl 3-(*p*-*t*-butyldiphenylsilyloxyphenyl)-5-isoxazolinylnacetate (**2h**).

Flash chromatography (hexane:ethyl acetate 9:1) gave 83% yield of the desired product as an off-white solid. mp 52–60°C.

^1H nmr (deuteriochloroform): δ 7.73 (m, 4H), 7.4 (m, 8H), 6.70 (m, 2H), 5.05 (dddd, $J=10.2, 7.8, 7.2, 6.0\text{Hz}$, 1H), 3.73 (s, 3H), 3.46 (dd, $J=16.8, 10.2\text{Hz}$, 1H), 3.04 (dd, $J=16.8, 7.2\text{Hz}$, 1H), 2.85 (dd, $J=15.9, 6.0\text{Hz}$, 1H), 2.62 (dd, $J=15.9, 7.8\text{Hz}$, 1H), 1.13 (s, 9H). ^{13}C nmr (deuteriochloroform): δ 170.6, 157.4, 156.1, 135.4, 132.4, 130.1, 128.0, 127.9, 122.3, 120.0, 76.7, 51.9, 40.4, 39.6, 26.5, 19.5.

Anal. Calcd. for $\text{C}_{28}\text{H}_{31}\text{NO}_4\text{Si}$: C, 71.00; H, 6.60; N, 2.96. Found: C, 71.12; H, 6.48; N, 2.70.

Methyl 2-(3'-phenyl-5'-isoxazolinyln)acrylate (**3**).

Flash chromatography (hexane:ethyl acetate 9:1) gave 62% yield of the desired product as a slightly yellow solid. ^1H nmr (deuteriochloroform): δ 7.69 (m, 2H), 7.42 (m, 3H), 6.37 (m, 1H), 6.09 (m, 1H), 5.54 (dddd, $J=11.0, 7.2, 0.9, 0.6\text{Hz}$, 1H), 3.83 (s, 3H), 3.74 (dd, $J=17, 11\text{Hz}$, 1H), 3.20 (dd, $J=17, 7.2\text{Hz}$). ^{13}C nmr (deuteriochloroform): δ 165.8, 156.3, 138.8, 130.3, 129.3, 128.7, 126.7, 125.7, 78.6, 52.1, 41.9.

Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{NO}_3$: C, 67.52; H, 5.66; N, 6.05. Found: C, 67.68; H, 5.91; N, 6.17.

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