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Palladium-catalyzed C–H acetoxylation of 2-methoxyimino-2-aryl-acetates and acetamides†

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Palladium-catalyzed C–H acetoxylation reactions of 2-methoxyimino-2-aryl-acetates and acetamides have been developed. These transformations feature excellent regioselectivity, wide substrate scope, and moderate to good yields. The product can be easily converted into naturally unprecedented α -amino acids in excellent yields.

Methoxyimino-2-aryl acetate and acetamide moieties are an important class of antifungal pharmacophoric substructures, which frequently occur in agricultural chemicals and drug candidates. For instance, Kresoxim-methyl, Dimoxystrobin and Trifloxystrobin possess manifold biological activities, such as fungicidal, insecticidal and herbicidal activities (Fig. 1).^{1,2} It has been found that the variation of the substituents on the benzene ring of these compounds greatly affect their biological activities.³ Not surprisingly, the development of methods for the preparation of methoxyimino-acetate and acetamide derivatives with structural and functional diversity is highly desirable for drug discovery.

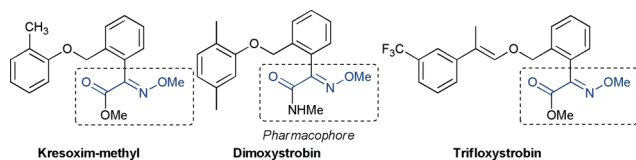


Fig. 1 Examples of agricultural chemicals bearing methoxyimino-acetate and acetamide scaffolds.

Over the past decade, transition-metal-catalyzed direct C–H bond functionalization has been established as one of the most powerful protocols for the construction of complex molecules.^{4,5} Basically, nitrogen- or oxygen-containing directing groups are essential to direct C–H bond functionalization.⁶ For example, Sanford and co-workers have disclosed highly regio- and chemoselective Pd-catalyzed procedures for the conversion of sp^2 and sp^3 C–H bonds into esters, ethers, and aryl-halides with the use of *N*-heterocycle and *O*-acetyl oximes as directing groups, respectively.⁷

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From a chemical perspective, it is important that a directing group is not only efficient to facilitate direct C–H functionalization, but also easy to be removed or converted to useful functional groups. In this regard, Yu and co-workers have developed an oxazoline-directing conversion of *gem*-dimethyl groups into cyclopropanes via Pd-catalyzed C–H activation and a radical cyclization sequence wherein the oxazoline unit can be readily hydrolyzed to carboxylic acids.⁸ In 2007, Daugulis and co-workers successfully employed carboxylic acids as the directing group in Pd-catalyzed *ortho*-arylation of benzoic acids,^{9,10} which could be removed by decarboxylation according to Gooßen's method.¹¹ Despite advances, to our knowledge, methoxyimino-acetate and acetamide units have not yet been utilized in direct C–H functionalization reactions. Given the significance of such biologically interesting scaffolds, we reasoned that their functionalization through palladium-catalyzed C–H acetoxylation process could, in principle, afford structurally complex methoxyimino-acetate and acetamide derivatives. We also recognized that the product can be readily converted into naturally unprecedented α -amino acids.

The proposed transformation was initially examined using 1.0 equiv. of methoxyimino-acetate **1a** and 1.2 equiv. of $\text{PhI}(\text{OAc})_2$ in the presence of palladium catalysts (Table 1). To our delight, we

Table 1 Optimization of reaction conditions for C–H acetoxylation^a

Entry	Catalyst	Solvent	<i>T</i> /°C	Yield (%) ^b
1 ^c	$\text{Pd}(\text{OAc})_2$	HOAc	100	73
2 ^d	$\text{Pd}(\text{OAc})_2$	Ac_2O	100	66
3	$\text{Pd}(\text{OAc})_2$	$\text{HOAc}/\text{Ac}_2\text{O}$	100	83
4	PdCl_2	$\text{HOAc}/\text{Ac}_2\text{O}$	100	71
5	$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$	$\text{HOAc}/\text{Ac}_2\text{O}$	100	68
6	$\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$	$\text{HOAc}/\text{Ac}_2\text{O}$	100	65
7	$\text{Pd}(\text{PPh}_3)_4$	$\text{HOAc}/\text{Ac}_2\text{O}$	100	63
8	$\text{Pd}_2(\text{dba})_3$	$\text{HOAc}/\text{Ac}_2\text{O}$	100	74
9	$\text{Pd}(\text{TFA})_2$	$\text{HOAc}/\text{Ac}_2\text{O}$	100	73
10	$\text{Pd}(\text{PhCN})_2\text{Cl}_2$	$\text{HOAc}/\text{Ac}_2\text{O}$	100	71
11	$\text{Pd}(\text{OAc})_2$	$\text{HOAc}/\text{Ac}_2\text{O}$	80	66
12	$\text{Pd}(\text{OAc})_2$	$\text{HOAc}/\text{Ac}_2\text{O}$	110	80
13	$\text{Pd}(\text{OAc})_2$	$\text{HOAc}/\text{Ac}_2\text{O}$	120	78

^a Reaction conditions: **1a** (0.30 mmol), $\text{PhI}(\text{OAc})_2$ (0.36 mmol), $\text{Pd}(\text{OAc})_2$ (0.015 mmol, 5 mol%), HOAc (1.0 mL), and Ac_2O (1.0 mL). ^b Isolated yields. ^c HOAc (2.0 mL). ^d Ac_2O (2.0 mL).

found that 5 mol% of $\text{Pd}(\text{OAc})_2$ in HOAc could indeed efficiently catalyze the reaction and gave the desired product **2a** in 73% yield at 100 °C. The structure of **2a** was unambiguously confirmed by the X-ray crystallographic analysis (Fig. 2).¹² Encouraged by this result, we continued to optimize reaction conditions to further improve the chemical yield. Notably, the yield was drastically increased to 83% when the reaction was carried out in HOAc– Ac_2O (Table 1, entry 3).¹³

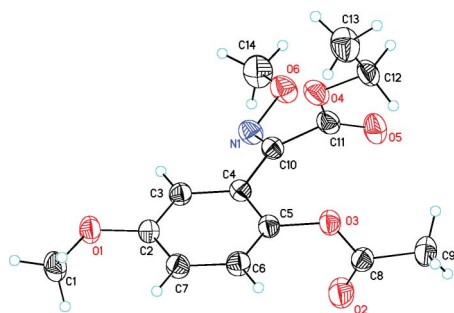


Fig. 2 X-ray crystal structure of **2a**.

Catalyst screening indicated that $\text{Pd}(\text{OAc})_2$ displayed the highest catalytic activity toward the formation of **2a** (Table 1, entries 3–10). The reaction temperature is another critical factor for this transformation with the best result being attained at 100 °C. Variations of the temperature from this value proved detrimental for the reaction (Table 1, entries 11–13). Control experiments showed that no desired product was generated in the absence of either palladium catalyst or $\text{PhI}(\text{OAc})_2$.¹³

Having established the optimal reaction conditions, we next examined the substrate scope of the current reaction. As summarized in Table 2, a series of 2-methoxyimino-2-aryl-acetates are suitable for this palladium-catalyzed process (Table 2, entries 1–10). A number of alkyl and alkoxy substituents can be incorporated on the benzene ring at *ortho*-, *meta*-, and *para*-positions without significant loss in reaction efficiency (Table 2, entries 1–5, R = Me, MeO, or BnO). It is well known that fluorine can affect the biological activity of compounds.¹⁴ As revealed in entry 6, we have successfully utilized a fluoro-substituted substrate in this reaction. Furthermore, unsubstituted and disubstituted methoxyimino-acetates could also be well tolerated to afford the desired oxidative products in good yields (Table 2, entries 7–10). Moreover, the aryl framework can be successfully extended to naphthalene-derived system (Table 2, entry 11). Perhaps more importantly, the heteroaryl-substituted methoxyimino-acetate **1l** could participate in this C–H acetoxylation reaction albeit with a low yield (Table 2, entry 12). Interestingly, changing the solvent to *t*- BuCO_2H resulted in another oxidative coupling product **2s** in 57% yield (Table 2, entry 13).

It has been well documented that the ester or amide moiety of methoxyimino-acetates and acetamides has a significant effect on their biological activities.² Accordingly, we have investigated the structural variation of the ester and amide moieties in the C–H oxidative acetoxylation reaction. For example, when the ethoxy was replaced with the methoxy, butoxy, isopropoxy, and benzyloxy, the corresponding products were obtained in a range of 72–83% yields (Table 3, entries 1–4). Significantly, we were pleased to find that the methoxyimino-acetamide **1q** and **1r** could

Table 2 Palladium-catalyzed direct C–H acetoxylation of methoxyimino-acetates^a

Entry	Substrate	Product	Yield (%) ^b
1			83
2			74
3			80
4			80
5			61
6			47
7			66
8			85
9			82
10			56
11			73
12			17
13 ^c			57

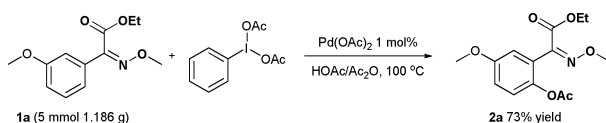
^a Reaction conditions: **1** (0.30 mmol), $\text{PhI}(\text{OAc})_2$ (0.36 mmol), $\text{Pd}(\text{OAc})_2$ (0.015 mmol, 5 mol%), HOAc (1.0 mL), and Ac_2O (1.0 mL). ^b Isolated yields. ^c The reaction was carried out in *t*- BuCO_2H (2.0 mL).

Table 3 Palladium-catalyzed direct C–H acetoxylation of methoxyiminoacetates and acetamides^a

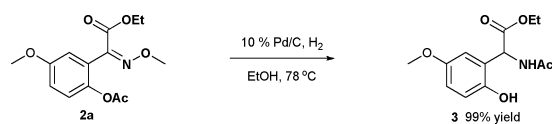
Entry	Substrate	Product	Yield (%) ^b
1			83
2			73
3			75
4			72
5			85
6			76

^a Reaction conditions: **1** (0.30 mmol), PhI(OAc)₂ (0.36 mmol), Pd(OAc)₂ (0.015 mmol, 5 mol%), HOAc (1.0 mL) and Ac₂O (1.0 mL). ^b Isolated yields.

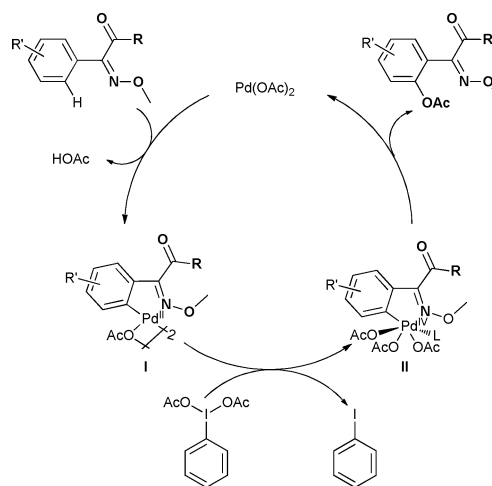
also efficiently participate in this oxidative acetoxylation reaction (Table 3, entries 5–6). To demonstrate the synthetic potential of the current strategy, the acetoxylation of **1a** was carried out on a gram scale (1.186 g, 5.0 mmol) and product **2a** was gained in 73% yield (Scheme 1).

**Scheme 1** A gram-scale experiment for the C–H acetoxylation reaction.

In addition, the resulting α -imino esters could be easily converted into α -amino acid derivatives, which are a class of important structural motifs in a number of natural products and medicinal agents.¹⁵ As shown in Scheme 2, treatment of imino esters **2a** with 10% Pd/C under atmosphere of H₂ afforded the amino acid ester **3** in almost quantitative yield.

**Scheme 2** Synthesis of the α -amino acid derivative **3**.

A possible pathway of this palladium-catalyzed C–H acetoxylation reaction was proposed in Scheme 3. The N of methoxyimino preferentially coordinated with Pd to form a cyclic Pd complex **I**, which might generate the Pd^{IV} intermediate **II** through the oxidation by PhI(OAc)₂.⁷ The subsequent reductive elimination would afford the desired product and regenerate the catalyst for the next catalytic cycle.

**Scheme 3** Proposed mechanism.

In conclusion, we have developed a palladium-catalyzed direct C–H acetoxylation reaction of 2-methoxyimino-2-aryl-acetates and acetamides. The reaction is applicable to a wide range of substrates with various functional groups and the corresponding products were obtained in moderate to good yields. Further application of this methodology to the synthesis of biologically important compounds is currently ongoing in our group.

Acknowledgements

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