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Palladium-catalyzed hydroacyloxylation of ynamides†‡

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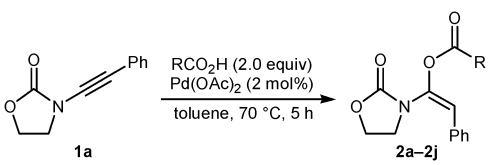
In the presence of substoichiometric $Pd(OAc)_2$, carboxylic acids undergo highly regio- and stereoselective additions to ynamides to provide α-acyloxyenamides.

The transition metal-catalyzed addition of carboxylic acids to alkynes provides synthetically valuable enol esters.[1–3] Although mercury salts have long been known to be effective in this reaction,[4] the use of less toxic alternatives that exhibit increased efficiency is desirable. Since Shvo and co-workers identified $Ru_3(CO)_{12}$ as an effective precatalyst for this transformation,[5] a significant majority of work in this field has targeted the development of improved protocols using ruthenium-based catalysts.[6] Catalysts based upon other metals such as rhodium,[7] iridium,[2c,8] palladium,[9] rhenium,[10] silver,[11] and gold[12] have also been described. However, with only a few exceptions,[4d,5,6k,9,12,13] these studies have employed terminal alkynes as reaction partners. Internal alkynes are more challenging substrates from a reactivity standpoint, due to increased steric hindrance and the unavailability of reaction pathways involving metal vinylidene intermediates that have been implicated in anti-Markovnikov additions to terminal alkynes.[1b,f,14] Furthermore, for internal alkynes flanked by substituents of similar steric and/or electronic properties, controlling the regioselectivity of carboxylate addition can be difficult. The development of solutions to these problems would be highly desirable to increase the range of enol esters that may be accessed.

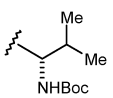
As part of a program[15] aimed at the development of new applications of ynamides[16] in organic synthesis, we became interested in the catalytic hydroacyloxylation of ynamides[17] for the following reasons. First, high regioselectivities have been observed in the addition of heteroatom nucleophiles to the triple bond of ynamides, where the addition usually occurs α to the nitrogen atom.[16–19] Second, these reactions would provide an opportunity to investigate the chemistry of the resulting α-acyloxyenamides, which have rarely been explored in organic synthesis. Herein we report highly regio- and stereoselective palladium-catalyzed hydroacyloxylations of ynamides.

Initially, the addition of propionic acid[20] to oxazolidinone-containing ynamide **1a** was investigated and, although no reaction was observed in the absence of a catalyst even at elevated temperatures, a survey of metal salts[21,22] identified $Pd(OAc)_2$ as an effective promoter. Heating a mixture of **1a** and propionic acid (2.0 equiv.) in toluene at 70 °C in the presence of $Pd(OAc)_2$ (2 mol%) for 5 h delivered α-acyloxyenamide **2a** in 76% yield as a single regio- and stereoisomer (Table 1, entry 1).[23] Under these conditions, a range of other carboxylic acids were also competent reaction partners, undergoing additions to **1a** with similarly high regio- and stereoselectivities. In addition to butyric acid (entry 2), branched aliphatic carboxylic acids were tolerated (entries 3 and 4),

Table 1 Hydroacyloxylation of **1a** with various carboxylic acids[a]



1a **2a–2j**

Entry	R	Product	Yield (%)[b]
1	Et	**2a**	76 (79)[c]
2	*n*-Pr	**2b**	87
3	*i*-Pr	**2c**	86 (84)[d]
4		**2d**	>95
5	Ph	**2e**	>95
6	3,5-$(MeO)_2C_6H_3$	**2f**	83 (89)[d]
7	4-$NO_2C_6H_4$	**2g**	70
8	2-HOC_6H_4	**2h**	75
9	(*E*)-CH=CHPh	**2i**	80
10[e]	C≡CPh	**2j**	73

[a] Reactions were conducted using 0.40 mmol of **1a** in toluene (4 mL). [b] Isolated yield. [c] Yield in parentheses refers to a reaction conducted using 3.0 mmol of **1a**, 3.3 mmol of propionic acid, and 1 mol% of $Pd(OAc)_2$ in toluene (30 mL) for 18 h. [d] Numbers in parentheses refer to reactions conducted using 1.1 equiv. of carboxylic acid. [e] Using 4.0 equiv. of 3-phenylpropiolic acid.

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including an *N*-protected α-amino acid (entry 4). Aromatic carboxylic acids were also effective, as demonstrated by the successful addition of a variety of benzoic acids to **1a** (entries 5–7). The reaction was not affected by the free phenol of salicylic acid (entry 8). While the addition of cinnamic acid also occurred smoothly (entry 9), 4.0 equivalents of 3-phenylpropiolic acid were required to achieve acceptable results (entry 10), as incomplete conversion was observed under the standard conditions. However, employing only 1.1 equivalents of the carboxylic acid was tolerated in several cases (entries 1, 3, and 6, yields in parentheses), and a larger scale reaction conducted using 1 mol% of $Pd(OAc)_2$ provided comparable results to the standard conditions (entry 1, footnote *c*).

Having demonstrated that the process is compatible with a wide range of carboxylic acids, investigation of the scope with respect to the ynamide was undertaken (Table 2). Oxazolidinone-substituted ynamides **1b–1d** containing 2-naphthyl, 4-fluorophenyl, or 3-nitrophenyl groups, respectively, were effective substrates, providing products **3a–3e** in 67–81% yield. However, ynamide **1e** containing an electron-rich 4-methoxyphenyl group was less reactive, and the addition of propionic acid to **1e** provided **3f** in only 43% yield, even with an increased loading of $Pd(OAc)_2$ (4 mol%). Imidazolinone-substituted ynamide **1f** reacted efficiently with isobutyric acid to give **3g**. Acyclic ynamides **1g** and **1h** were also competent substrates, as demonstrated by the formation of **3h** and **3i** in modest to good yields. Again, the use of only 1.1 equivalents of the carboxylic acid provided good results in several cases (products **3c**, **3g**, and **3i**, yields in parentheses). At present, the reactions work best with aryl-substituted ynamides; substrates containing an aliphatic substituent on the alkyne provide low yields of the desired α-acyloxyenamides, accompanied by reduction of the ynamide and other unidentified products.

With an efficient synthesis of α-acyloxyenamides in hand, a preliminary investigation of their reactivity was undertaken (Scheme 1). First, heating **2a** with a substoichiometric quantity of DMAP initiated an *O* → *C*-acyl transfer to provide β-ketoimide **4** in 91% yield. Second, treatment of **2a** with *m*-CPBA led to α-propionoxyimide **6** in 79% yield, presumably *via* ring-opening and intramolecular acyl transfer of the intermediate epoxide **5**.[24]

In conclusion, we have developed the first palladium-catalyzed hydroacyloxylation of ynamides. The process tolerates a diverse range of carboxylic acids and various aryl-substituted ynamides to result in the highly regio- and stereoselective synthesis of α-acyloxyenamides in generally good yields. Future work will target further developments of this methodology, along with efforts to shed light upon the mechanism of hydroacyloxylation.[25]

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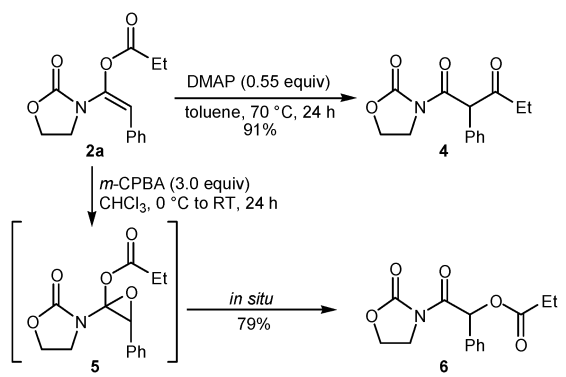
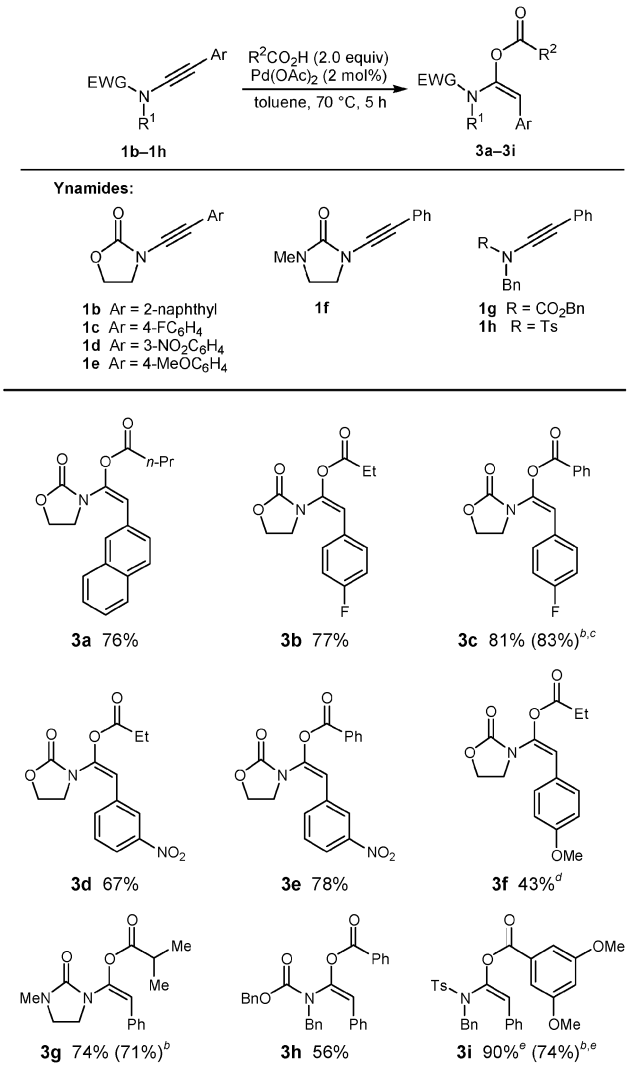


Scheme 1 Transformations of α-acyloxyenamide **2a**.

Table 2 Scope of the Pd-catalyzed ynamide hydroacyloxylation[a]



[a] Reactions were conducted using 0.40 mmol of **1a** in toluene (4 mL). [b] Numbers in parentheses refer to reactions conducted using 1.1 equiv. of carboxylic acid. [c] Reaction time of 6 h. [d] Reaction conducted using 4 mol% of $Pd(OAc)_2$. [e] Reaction time of 24 h.

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20 The product resulting from the addition of acetic acid to **1a** was relatively unstable, and underwent decomposition into *N*-phenylacetyloxazolidin-2-one during attempted purification on silica.

21 Several ruthenium salts surveyed were unsatisfactory. For example, heating **1a** with propionic acid in toluene at 70 °C for 24 h in the presence of $RuCl_3$ hydrate (7 mol%) provided only 23% conversion into **2a**. The use of $[RuCp^*(MeCN)_3]PF_6$ (2 mol%) led to complete consumption of **1a** after heating in toluene at 70 °C for 3 d, but a mixture of **2a** and *N*-phenylacetyloxazolidin-2-one (3 : 2 ratio) was produced. The use of $[RuCl_2(p\text{-cymene})]_2$ (1 mol%), P(2-Fur)$_3$ (2 mol%), and Na_2CO_3 (4 mol%) in toluene/THF at 70 °C for 24 h, which are conditions similar to those described by Goossen and co-workers for the addition of carboxylic acids to terminal alkynes, provided *ca*. 14% of **2a** accompanied by significant quantities of side products; see: L. J. Goossen, J. Paetzold and D. Koley, *Chem. Commun*., 2003, 706–707.

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23 The regio- and stereoselectivities of the hydroacyloxylation reactions herein were assigned by analogy to the reaction producing **3e**, the structure of which was determined by X-ray crystallography. See ESI for details. In addition, the formation of products **4** and **6** from **2a** (Scheme 1) lends further support for the regioselectivity of the reaction producing **2a** (Table 1, entry 1).

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