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Amide-Assisted Acetoxylation of Vinyl C(sp^2)−H Bonds by Rhodium Catalysis

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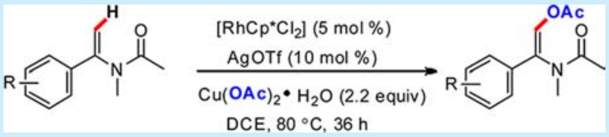
Supporting Information

ABSTRACT: A direct regioselective acetoxylation of enamides has been accomplished using a combination of Cu(OAc)$_2$ and rhodium catalyst. Cu(OAc)$_2$ is served as the oxidant and also provides the source of acetate in the reaction.

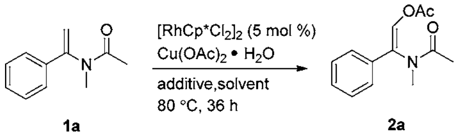


The selective oxidation of unactivated C(sp^2)−H bonds represents a fundamentally important transformation and occupies a prominent position in synthetic organic chemistry.[1] Advances on the development of new methodologies and their applications in both target- and diversity-oriented synthesis have constituted one of the most actively investigated areas of current organic synthesis.[2] Pd-catalyzed direct acetoxylation of the nonselective C(sp^2)−H bond was discovered several centuries ago.[3] In 2004, Sanford and co-workers demonstrated the first example of a highly regio- and chemoselective Pd-catalyzed acetoxylation of an aromatic C−H bond by using the pyridine group as the directing group.[4] Later, oxime,[5] sulfoximine,[6] amides,[7] and organophosphate[8] groups were successfully employed as the directing groups for the selective acetoxylation of arenes. A recent novel approach has been demonstrated by Yu and co-workers exploring dioxygen gas as the terminal oxidant with copper catalysts for the *ortho*-acetoxylation of aryl C−H bonds.[9]

Despite these impressive advances, no method is capable of offering acetoxylated products from vinyl C(sp^2)−H bonds, which represents a broad spectrum of important substrates. In fact, the current direct functionalization of vinyl C(sp^2)−H involving metal catalysts is mainly focused on the olefins activated by an electron-withdrawing group.[10] Transition metal-catalyzed direct functionalizations of unactivated olefins are comparatively underexplored in terms of the olefinic substrate scope and selectivity.[11] Herein we present our results on the rhodium-catalyzed direct acetoxylation of enamides by using amide as directing group. Cu(OAc)$_2$·H$_2$O is employed as both oxidant and acetate source. The reaction is highly regioselective to give the exclusive acetoxylated *Z*-enamides.

We initiated the investigation by using *N*-(1-phenylvinyl)-acetamide as substate in the presence of [RhCp*Cl$_2$]$_2$ (5 mol %), AgSbF$_6$ (10 mol %), and Cu(OAc)$_2$·H$_2$O (2.2 equiv) at 80 °C in 1,2-dichloroethane. Unfortunately, the enamide decomposed to the corresponding ketone under the reaction conditions. We assumed that protecting the nitrogen atom of the enamide would prevent enamides from decomposing and increase the chemical stability of the enamide under the reaction conditions. Therefore, we examined the acetoxylation reaction using *N*-methyl-*N*-(1-phenylvinyl) acetamide. To our delight, the desired product **2a** was isolated in 17% yield (Table 1, entry 1). Encouraged by this promising result, the catalytic reaction conditions were optimized using the *N*-methylated enamide **1a** as the model substrate (see Supporting Information). The efficiency of the reaction was dramatically improved when the silver salt was switched to AgOTf and 78% yield of **2a** was obtained (Table 1,

Table 1. Optimization of the Reaction Conditions[a]



entry	additive	acetate source	solvent	yield[b] (%)
1	AgSbF$_6$	Cu(OAc)$_2$·H$_2$O	DCE	17
2	AgOAc	Cu(OAc)$_2$·H$_2$O	DCE	trace
3	AgOTFA	Cu(OAc)$_2$·H$_2$O	DCE	15
4	AgOTf	Cu(OAc)$_2$·H$_2$O	DCE	78
5		Cu(OAc)$_2$·H$_2$O	DCE	NR
6	AgOTf		DCE	NR
7	AgOTf	KOAc[c]	DCE	NR
8	AgOTf	AgOAc[d]	DCE	trace
9	AgOTf	Cu(OAc)$_2$·H$_2$O	DMF	NR
10	AgOTf	Cu(OAc)$_2$·H$_2$O	PhMe	NR
11	AgOTf	Cu(OAc)$_2$·H$_2$O	PhF	26
12	AgOTf	Cu(OAc)$_2$·H$_2$O	PhCl	43

[a]Reactions were carried out by using **1a** (0.2 mmol), Cu(OAc)$_2$·H$_2$O (0.44 mmol), additive (10 mol %), solvent (2.0 mL), 80 °C, air, 36 h. [b]Isolated yield. [c]Cu(OAc)$_2$·H$_2$O was replaced by KOAc (0.44 mmol) and Cu(NO$_3$)$_2$ (0.44 mmol). [d]Cu(OAc)$_2$·H$_2$O was replaced by AgOAc.

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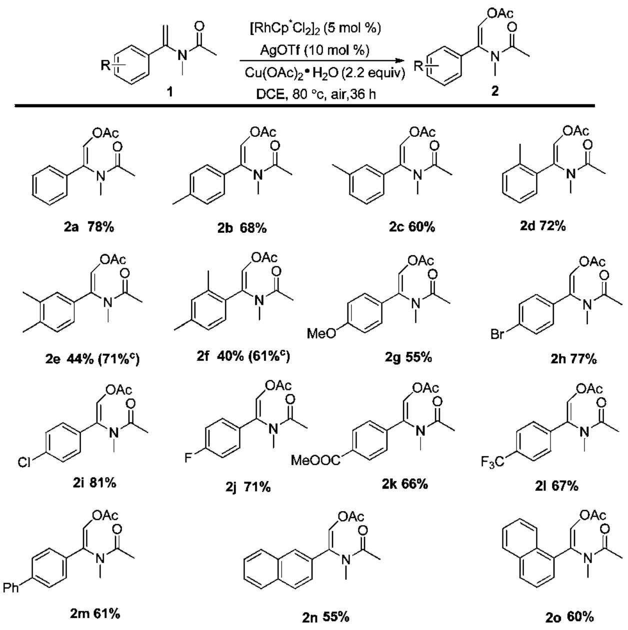
entry 4). Other silver salts such as AgOAc and AgOTFA were found to be less effective (Table 1, entries 2 and 3). The desired product is not observed in the absence of silver salts (Table 1, entry 5). Besides the role of oxidant, $Cu(OAc)_2{\cdot}H_2O$ was proved to be the most efficient acetate source. For instance, only a trace of product **2a** was obtained when 2.2 equiv of AgOAc was employed, and no reaction was observed with a combination of KOAc and $Cu(NO_3)_2$ (Table 1, entries 6−8). The solvent was crucial for this transformation and the 1, 2-dichloroethane (DCE) gave the best yields (Table 1, entry 4 and entries 9−12).

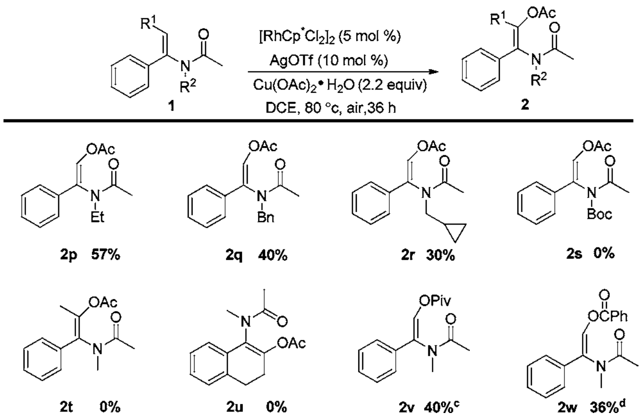
Having established the optimized reaction conditions, we began to survey the scope of various enamides for the acetoxylation using $Cu(OAc)_2{\cdot}H_2O$ as the acetate sources as shown in Scheme 1. The acetoxylation of enamides with various functional groups in the aryl ring proceeded well to provide the expected products in moderate to good yields. The electronic nature of the substituents in aryl ring has little effect on the efficiency of the acetoxylation. For example, the electron-donating groups such as methyl afforded the corresponding product in 68% yield (Scheme, **2a**). Comparable yields with electron-withdrawing groups, including bromide, chloride, fluoride, and ester, were obtained under the reaction conditions (Scheme 1, **2h**−**2k**), showing a typical feature of concerted metalation deprotonation process. Notably, the steric hindrance played a poor role in the reaction, and both *para*- and *ortho*-methyl substituted substrates gave good yields (Scheme 2, **2c**,**2d**). However, a considerable amount of ketones was isolated with the strong electron-rich enamides, such as 3,4-dimethyl and 2, 4-dimethyl substituted enamides (Scheme 2, **2e**,**2f**), which might lead to the decrease of the reaction yields. Considering water may facilitate the hydrolysis of active enamides under the reaction conditions, we purified the solvent DCE by P_2O_5 and performed the reaction by using $Cu(OAc)_2$ instead of $Cu(OAc)_2{\cdot}H_2O$. Indeed, the significantly improved yields were obtained after the modification of reaction conditions (Scheme 1, **2e**,**2f**). Phenyl substituted enamides participated in the reaction smoothly to give the acetoxylated product in 61% yield (Scheme 1, **2m**). Both α- and β-naphthyl enamides were the effective substrate for this transformation to gave the acetoxylated products in good yields (Scheme 1, **2n**,**2o**). It was worth to note that the acetoxylation products were formed with complete regio- and stereoselectivity to afford only *Z*-acetoxylated enamides as the single stereoisomer in all cases. The structure of the acetoxylated product **2a** was further confirmed by X-ray crystallography (Figure 1).[12]

Scheme 1. Rhodium(III) Catalyzed C−H Acetoxylation of Enamides[a,b]



[a]Reactions were carried out by using **1** (0.2 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.44 mmol), $[RhCp^*Cl_2]_2$ (5 mol %), AgOTf (10 mol %), DCE (2.0 mL), 80 °C, air, 36 h. [b]Isolated yield. [c]$Cu(OAc)_2{\cdot}H_2O$ was replaced by $Cu(OAc)_2$.

Scheme 2. Acetoxylation of Enamides with Various *N*-Protecting Groups[a,b]



[a]Reactions were carried out by using **1** (0.2 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.44 mmol), $[RhCp^*Cl_2]_2$ (5 mol %), AgOTf (10 mol %), DCE (2.0 mL), 80 °C, air, 36 h. [b]Isolated yield. [c]$Cu(OAc)_2{\cdot}H_2O$ was replaced by $Cu(OPiv)_2$. [d]$Cu(OAc)_2{\cdot}H_2O$ was replaced by $Cu(PhCOO)_2$.

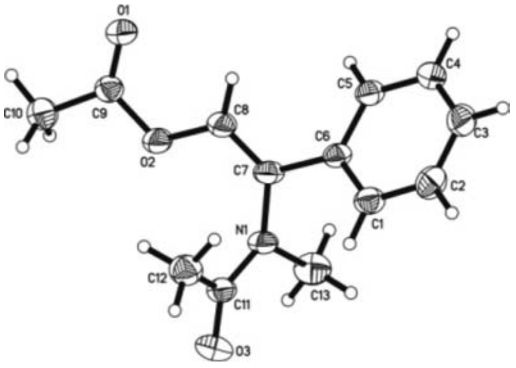
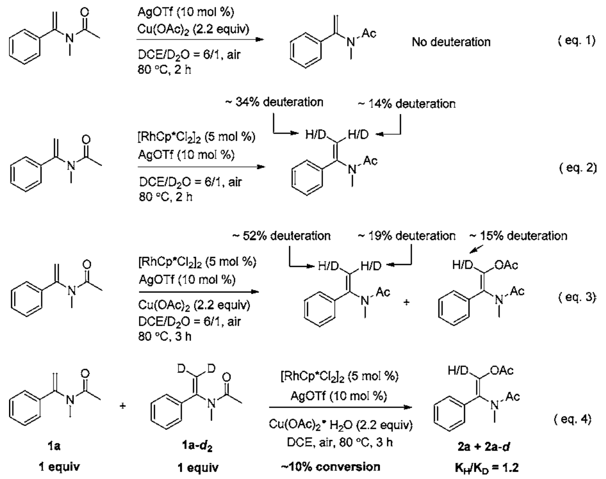


Figure 1. X-ray structure of **2a**.

The nitrogen-protecting groups had a significant influence to the reaction. The reactivity of enamides decreased with the larger nitrogen-protecting groups. For example, *N*-ethyl and *N*-benzyl enamides gave the desired products in relatively lower yields (Scheme 2, **2p**,**2q**). *N*-Cyclopropylmethyl enamides participated in the reaction, but with very low yield (Scheme 2, **2r**). For the largest *N*-Boc protecting group, the corresponding enamide was not obtained under the reaction conditions (Scheme 2, **2s**). The β-substituted enamides and aliphatic α-substituted vinylacetamides, however, failed to give the products (Scheme 2, **2t**,**2u**). It should be noted that this reaction sequence could be induced using other copper(II) carboxylate instead of copper acetate. For instance, when $Cu(OPiv)_2$ or $Cu(PhCOO)_2$ was used, the corresponding pivaloxylated **2u** and benzoxylated product **2v** were furnished (Scheme 2, **2v**,**2w**).

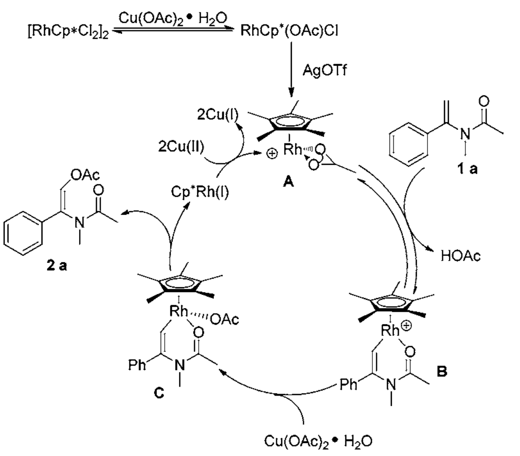
The isotope effect studies were conducted under different reaction conditions (Scheme 1). It was found that the deuteration in the olefin did not occur in the absence of rhodium catalyst (Scheme 3, eq 1). Treatment of the enamide **1a** in the absence of $Cu(OAc)_2$ led to recovery of starting material with a significant incorporation of deuterium in the *Z*-olefinic H in the presence of D_2O (Scheme 3, eq 2). The isotopic exchange study with $Cu(OAc)_2$ under the standard reaction conditions revealed that *Z*-olefinic H/D exchange still proceeded faster than the *E*-olefinic H/D exchange (Scheme 3, eq 3). This result suggests that the step of carbometalation by abstracting the olefinic hydrogen is reversible. An intermolecular competition between **1a** and the dideuterated analogue **1a**-d_2 allowed calculating a kinetic isotope effect k_H/k_D = 1.2 (Scheme 3, eq 4), indicating that the C−H bond cleavage might not be involved in the rate-determining step.[13]

Scheme 3. Deuteration Experiments



On the basis of the above results and the previous rhodium chemistry reported in the literature,[14] a tentative reaction mechanism for this direct acetoxylation reaction is proposed as shown in Scheme 4. Initially, the rhodium cation **A** is formed by the reaction of $[RhCp^*Cl_2]_2$ and AgOTf. The six-membered rhodacycle intermediate **B** is subsequently formed after reversible amide-assisted carbometalation/hydrogen abstraction. The coordination of acetate into rhodacycle intermediate **B** in the presence of $Cu(OAc)_2{\cdot}H_2O$ results in the formation of intermediate **C**, which undergoes the reductive elimination to give the acetoxylated product **2a** and release Rh(I) species. The oxidation of Rh(I) species by $Cu(OAc)_2$ regenerates the active Rh(III) catalyst to fulfill the catalytic cycle.

Scheme 4. Proposed Mechanism



In summary, we have developed the first rhodium-catalyzed acetoxylation of an olefinic C−H bond in enamides with high regio- and stereoselectivity to give absolute *Z*-configuration products. This novel acetoxylation reaction tolerates a wide range of functional groups and is a reliable method for the rapid elaboration of readily available enamides into a variety of substituted vinyl acetate. Further efforts will be devoted to understand the mechanism and develop new efficient transformations.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and full spectroscopic data for all new compounds and X-ray crystallographic data of the compound **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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