## **Regiospecific Synthesis of 3,4-Dihydrocoumarins via Substrate-Controlled** [1,3]- or [3,3]-Sigmatropic Rearrangement

Xiangsheng Xu,\* Xiaoqing Li, Xinhuan Yan, Hanshen Wang, Yun Deng, Jiangbin Shao

College of Chemical Engineering and Materials Science, Zhejiang University of Technology, Hangzhou 310014, P. R. of China Fax +86(571)88320799; E-mail: future@zjut.edu.cn

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**Abstract:** A regiospecific synthesis of 3,4-dihydrocoumarin derivatives has been achieved involving tandem rearrangement–cyclization of (E)-2-(aryloxymethyl)alk-2-enoates catalyzed by a Pd/Cu bimetallic system. Unexpected substrate-controlled [1,3]- or [3,3]sigmatropic rearrangement was observed in the transformations.

**Key words:** [1,3]-sigmatropic rearrangement, [3,3]-sigmatropic rearrangement, palladium/copper bimetallic catalyst, substrate-controlled selectivity, 3,4-dihydrocoumarin

The 3,4-dihydrocoumarin (DHC) moieties represent an important class of structural unit frequently found in many natural and synthetic compounds that exhibit a variety of pharmacological properties, such as antiherpetic activity, <sup>1a</sup> inhibition of protein kinases<sup>1b</sup> and aldose reductase, <sup>1c</sup> activity against several cancer lines, <sup>1d-f</sup> and selective inhibition of HIV-1 reverse transcriptase.<sup>1g</sup> Thus, considerable efforts have been devoted to the efficient and selective synthesis of this type of heterocycles.<sup>2</sup>

The Baylis-Hillman adducts have been increasingly attractive to synthetic organic chemists, as they are versatile molecules with a minimum of three functional groups.<sup>3</sup> Various cyclic and acyclic compounds could be prepared from Baylis-Hillman adducts by various chemical transformations.<sup>4</sup> Recently, it was found that aryl allyl ethers **1** derived from Baylis-Hillman adducts underwent temperature-controlled [1,3]- or [3,3]-sigmatropic rearrangement to form DHC derivatives with diverse substituted patterns in moderate to good yields (Scheme 1).<sup>5</sup> However, such method requires an expensive Au/Ag catalyst and suffers from high reaction temperature in some cases. Therefore, an alternative cheap catalytic system would be needed for this transformation. Herein, we report a regiospecific synthesis of DHC via the [1,3]- or [3,3]-sigmatropic rearrangement of aryl allyl ethers 1 and 3 in the presence of relatively cheaper Pd(OAc)<sub>2</sub>/Cu(OTf)<sub>2</sub> bimetallic catalyst. It is worth to mention that an unexpected substrate-controlled [1,3]- or [3,3]-sigmatropic rearrangement was observed in the transformations.

A model study was initiated with (*E*)-methyl 2-(phenoxymethyl)-3-phenylacrylate (**1a**) as substrate. We expected the formation of DHC in the presence of some common Lewis acid catalysts.<sup>6</sup>

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First, with several monometal catalytic systems tested, only  $Cu(OTf)_2$  showed some catalytic activity to give **2a** in 10% yield via a [1,3]-sigmatropic rearrangement– cyclization process (Table 1, entry 5). A Brønsted acid,

 Table 1
 Optimization of Reaction Conditions for Access to 2a<sup>a</sup>



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Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%) <sup>b</sup>
1	Pd(OAc) <sub>2</sub> <sup>c</sup>	DCE	80	15	0
2	$PdCl_2^{\ c}$	DCE	80	15	0
3	$ZnCl_2^c$	DCE	80	20	0
4	AlCl <sub>3</sub> <sup>c</sup>	DCE	80	20	0
5	Cu(OTf) <sub>2</sub> <sup>c</sup>	DCE	80	15	10
6	FeCl <sub>3</sub> <sup>c</sup>	DCE	80	20	0
7	HOTf	DCE	80	20	21
8	$Pd(OAc)_2/Cu(OTf)_2^d$	DCE	80	15	65
9	Pd(OAc) <sub>2</sub> /CuCl <sup>e</sup>	DCE	80	20	0
10	Pd(OAc) <sub>2</sub> /CuI <sup>e</sup>	DCE	80	20	0
11	Pd(OAc) <sub>2</sub> /CuCl <sub>2</sub> <sup>e</sup>	DCE	80	20	0
12	Pd(OAc) <sub>2</sub> /HOTf	DCE	80	15	25
13	$Pd(OAc)_2/Cu(OTf)_2^d$	dioxane	100	15	23
14	$Pd(OAc)_2/Cu(OTf)_2^d$	$CH_2Cl_2$	45	15	0
15	$Pd(OAc)_2/Cu(OTf)_2^d$	MeCN	80	15	11
16	Pd(OAc) <sub>2</sub> /Cu(OTf) <sub>2</sub> <sup>d</sup>	toluene	110	15	53
17	$Pd(OAc)_2/Cu(OTf)_2^d$	DCE	120	15	55

<sup>a</sup> The reaction was carried out under Ar, using **1a** (1.0 mmol) and catalyst in the indicated solvent (2 mL).

<sup>b</sup> Isolated yield.

<sup>e</sup> Conditions: 5 mol% Pd(OAc)<sub>2</sub>, 10 mol% Cu catalyst.

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<sup>&</sup>lt;sup>c</sup> Conditions: 5 mol% catalyst.

<sup>&</sup>lt;sup>d</sup> Conditions: 5 mol% Pd(OAc)<sub>2</sub>, 5 mol% Cu(OTf)<sub>2</sub>.



Scheme 1 Temperature-controlled tandem rearrangement-cyclization of (E)-2-(aryloxymethyl)alk-2-enoates catalyzed by AuCl<sub>3</sub>/3AgOTf

such as HOTf, also gave poor yield of **2a** in 21% (Table 1, entry 7). Fortunately, when  $Pd(OAc)_2/Cu(OTf)_2$  was used as catalyst, the yield of **2a** was dramatically improved to 65% with 31% of starting material recovered, and isomeric product arising from [3,3]-sigmatropic rearrangement–cyclization process was not observed according to the NMR and GC-MS analysis. Next, other Pd/Cu bimetallic catalysts such as  $Pd(OAc)_2/CuCl$ ,  $Pd(OAc)_2/CuI$ , and  $Pd(OAc)_2/CuCl_2$  were investigated; none of them showed catalytic activity (Table 1, entry 8–11). The product yield was also not improved by using the combination of  $Pd(OAc)_2/HOTf$  (Table 1, entry 12). Other solvents such

as dioxane,  $CH_2Cl_2$ , MeCN, and toluene were proved to be less effective for the reaction (Table 1, entry 13–16).

In order to determine whether the rearrangement of (E)-2-(phenyloxymethyl)alk-2-enoates was also temperaturedepended in the presence of Pd(OAc)<sub>2</sub>/Cu(OTf)<sub>2</sub>, compound **1a** was subjected to react under 120 °C (Table 1, entry 17). Compound **2a** was isolated in 55% yield and no [3,3]-sigmatropic-rearrangement isomer was detected. This result is in marked contrast to that of the AuCl<sub>3</sub>/ 3AgOTf-catalyzed reaction, in which case 4-aryl-3-methylene-3,4-DHC was produced via the [3,3]-sigmatropic rearrangement–cyclization of **1a** at 120 °C.<sup>5</sup>

 Table 2
 Rearrangement–Cyclization Reactions of (E)-2-(Phenyloxymethyl)alk-2-enoates 1<sup>a</sup>



<sup>a</sup> General reaction conditions: substrate 1 (1 mmol),  $Pd(OAc)_2$  (5 mol%),  $Cu(OTf)_2$  (5 mol%), DCE (2 mL), 80 °C, Ar, 15 h. <sup>b</sup> Isolated yield.



Scheme 2 Proposed mechanism for the tandem rearrangement and cyclization of (*E*)-2-(aryloxymethyl)alk-2-enoates catalyzed by Pd/Cu bimetallic system

A selection of various (E)-2-(phenyloxymethyl)alk-2enoates **1** was investigated using Pd(OAc)<sub>2</sub>/Cu(OTf)<sub>2</sub> as a catalyst in DCE. Table 2 summarizes the results. The methyl substituent in the *para* position of the enoates **1b** (Table 2, entry 2) did not much influence the yield as compared to **1a** (Table 2, entry 1), whereas **1c**, bearing an electron-withdrawing chloride group in the same position, only lowered the yield slightly (Table 2, entry 3).<sup>7</sup> The methyl substituent in the *para* position of phenol side also had no significant influence on the reaction (Table 2, entry 4).

Next, rearrangement-cyclization reactions of (E)-2-(naphthyloxymethyl)alk-2-enoates **3** were investigated. Surprisingly, under the optimal conditions for **1a** (Table 1, entry 8), 4-aryl-3-methylene-3,4-DHC **4**, arising from normal Claisen rearrangement-cyclization process was exclusively obtained. (E)-2-(Naphthyloxymethyl)alk-2-enoates **3** substituted with both electron-withdrawing and electron-donating groups on the phenyl ring afforded 4-aryl-3-methylene-3,4-DHC **4** in moderate to good yield (Table 3). This is in sharp contrast with the AuCl<sub>3</sub>/AgOTf system where [3,3]-sigmatropic rearrangement of (E)-2-(naphthyloxymethyl)alk-2-enoates could only take place at 120 °C.

Although the precise mechanism of this reaction remains unclear at this moment, we assume that the first step for the transformation of **1** to **2** is the oxidative addition of Pd(0) to aryl allyl ethers to form a  $\eta^3 - \pi$ -allyl complex **I**,<sup>8</sup> which undergoes reductive elimination to afford intermediate **II** and regenerates the catalyst. The coordination of Cu to the oxygen of the ether and ester groups makes the oxidative addition easier. The easy attack of the  $\alpha$ -carbon of the Pd(II) phenolate onto the less substituted carbon of the allylic cation led to selective [1,3]-sigmatropic rearrangement. In the  $\pi$ -allyl–palladium complex, the aryl R<sup>1</sup> and the ester group prefer the *anti* configuration due to the steric repulsion between them which may lead to the *E* stereoselectivity. Moreover, the stereochemistry may also be ascribed to the thermodynamic outcome of metal-catalyzed double-bond isomerization. At the second step, DHC **2** could be eventually formed via the cyclization of intermediate **II** (Scheme 2, path A).

On the other hand, naphthoxyallyl is difficult to form a  $\pi$ -allyl–palladium complex. Therefore, the Pd/Cu-catalyzed [3,3]-sigmatropic rearrangement of **3** occurs to generate 3,4-dihydrocourmarins **4** after cyclization of intermediate **III** (Scheme 2, path B).

In summary, we have reported a regiospecific synthesis of 3,4-dihydrocoumarin derivatives via substrate-controlled [1,3]- or [3,3]-sigmatropic rearrangement of (E)-2-(aryl-oxymethyl)alk-2-enoates catalyzed by a Pd/Cu bimetallic system. Further investigations on the mechanistic details with respect to the stereoselectivity and the role of the Pd and Cu catalyst are under way in our laboratory.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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Entry	Substrates	Products	Yield (%) <sup>b</sup>
1	CO <sub>2</sub> Me		81
2	Me CO <sub>2</sub> Me	4a Me C C C C C C C C C C C C C C C C C C	80
3	CI CI CI CI CI CO <sub>2</sub> Me	4b Cl Cl Cl O	75
4	3c Br $CO_2Me$	4c $Br$ $0$	79
5	3d Cl CO <sub>2</sub> Me	4d Cl Cl C	82
6	F <sub>3</sub> C CO <sub>2</sub> Me	4e F <sub>3</sub> C C C C C C C C C C C C C C C C C C C	83

 Table 3
 Rearrangement–Cyclization Reactions of (E)-2-(Phenyloxymethyl)alk-2-enoates 3<sup>a</sup>

<sup>a</sup> General reaction conditions: substrate **3** (1 mmol),  $Pd(OAc)_2$  (5 mol%),  $Cu(OTf)_2$  (5 mol%), DCE (2 mL), 80 °C, Ar atmosphere, 15 h. <sup>b</sup> Isolated yield.

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## (7) General Experimental Procedure and Spectroscopic Data

Compound **1a** (268.3 mg, 1.0 mmol), Pd(OAc)<sub>2</sub> (11.2 mg, 0.05 mmol), Cu(OTf)<sub>2</sub> (18.1 mg, 0.05 mmol), and DCE (2 mL) were added to a 10 mL sealed vessel protected under Ar. Then the reaction mixture was stirred under reflux conditions for 15 h. Upon completion of the reaction, the resulting mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and filtered through Celite. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on silica gel (200–300 mesh) using cyclohexane–EtOAc (12:1) as eluent to give pure **2a** (153.7 mg, 65%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz):  $\delta = 4.09$  (d, J = 2.0 Hz, 2 H), 7.01–7.18 (m, 3 H), 7.35–7.57 (m, 6 H), 7.99 (t, J = 2.0 Hz, 1 H).

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