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Rearrangement of Propargylic Esters: Metal-Based Stereospecific Synthesis of (*E*)- and (*Z*)-Knoevenagel Derivatives

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On the basis of the seminal work by Rautenstrauch in 1984,[1] the metal-catalyzed isomerization of propargyl esters has become in recent years a powerful key process which has led to the development of a number of atom-economy cycloisomerization and cascade reactions.[2] Although the reaction course has not been well-established yet, it is assumed that the process is initiated by activation of the C−C triple bond via complexation with the electrophilic catalyst (Scheme 1, complex **A**). Then, two slightly different mechanistic scenarios are recognized to operate: (i) [1,2]-OAc shift (via 5-*exo*-dig cyclization/ring opening) to generate species **B** (path I), and (ii) participation of metal allene complex **C** formed by [1,3]-OAc shift (via 6-*endo*-dig cyclization/ring opening) (path II).

While path I seems to be the preferred course for reactions catalyzed by $PtCl_2$,[3] products arising from either intermediate **B**[4] or **C**[5] have been observed in the case of Au(I) and Au(III) catalysts. In this context, it is relevant that Wang and Zhang[6] have just reported the stereoselective Au(III)-catalyzed isomerization of propargylic esters into α-ylidene-*β*-diketones which takes place via path II.

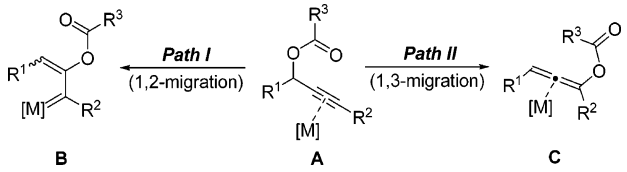
We were intrigued whether the alkyne substituent might control the rearrangement of species **A**. Apart from an isolated example by Sarpong,[7] who employed 4-acetoxy-2-alkynoates ($R^2 = CO_2$-Et), the processes reported all involve neutral substituents (R^2 = H, alkyl, alkenyl, aryl). We hypothesized that starting from alkoxy alkynes (R^2 = OEt) could inhibit path I and thus warrant the reaction to proceed via species **C**.[8] To this end, we have undertaken this study and found that Pt(II) and Cu(I) catalyze the isomerization of 3-alkoxypropynyl carboxylates to α-ylidene-*β*-ketoesters in a stereospecific manner.

On the outset, the isomerization of propargyl acetate **1a** (Scheme 2) was checked at room temperature using a series of transition metal catalysts (Ag(I), Ni(0), Rh(I), Pd(0), Au(I), Au(III), Pt(II), Cu(I); 5 mol %) and common solvents (CH_2Cl_2, THF, toluene) (see Scheme 2 and Supporting Information). Thus, we found that $PtCl_2$ in CH_2Cl_2 produced (*Z*)-**2a** in 81% isolated yield with complete stereoselectivity. Importantly, the isomer (*E*)-**2a** could be obtained by using the copper complex $[Cu(CH_3CN)_4][BF_4]$ in high yield and diastereoselectivity (84% yield, *E*/*Z* = 9:1). Thus, both $PtCl_2$ and $[Cu(MeCN)_4][BF_4]$ catalysts work efficiently and, more importantly, *they perform the isomerization with complementary Z/E selectivity*.

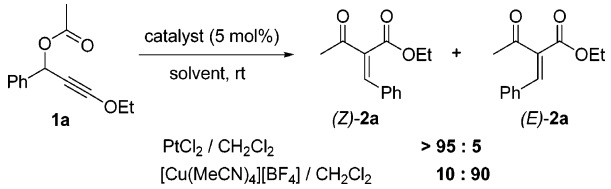
A study of the scope of this selective transformation of propargylic esters into synthetically valuable α-benzylidene-*β*-ketoesters[9] was then undertaken (Table 1).

In relation with the substituent R^1, it was found that substrates containing various aryl, such as phenyl (entry 1), as well as electron-rich (entry 2), electron-poor (entry 3), and condensed aryl (entry 4) and heteroaryl groups (entry 5) afford the corresponding alkylidene adducts in good yield and excellent stereoselectivity.[10] Alkenyl- and alkyl-substituted substrates undergo isomerization

Scheme 1. Proposed Pathways for the Metal-Catalyzed Isomerization of Propargyl Carboxylates



Scheme 2. Isomerization Reaction of Propargyl Acetate **1a**



though the selectivity drops notably in the $PtCl_2$-catalyzed process (entries 6−8). The scope of this reaction can be further expanded to propargylic benzoates, acrylates, and carbonates (entries 9−12) which allow access to an array of acylacetate esters and symmetrical and nonsymmetrical malonates.

Finally, the competitive isomerization between alkyne functionalities of different electronic nature was tested. When the diyne acetate **3** was subjected to metal-catalyzed isomerization (CH_2Cl_2, 5 mol % catalyst, rt), the process was found to occur through the electron-rich alkyne with complete chemoselectivity (Scheme 3). Thus, the treatment of **3** with $PtCl_2$ led to the expected enyne Knoevenagel adduct (*Z*)-**4** with complete stereoselectivity and moderate yield (59%). On the other hand, stirring **3** in the presence of $[Cu(CH_3CN)_4][BF_4]$ resulted in the formation of dimer **5** (74%; ca. 3:1 *E*/*Z* mixture). This latter finding features some points: (i) the copper catalyst plays a two-fold role since the presumed initial adduct (*E*)-**4** undergoes metal-catalyzed 5-*exo*-dig cyclization to provide intermediate **I**;[11] (ii) the copper(I) carbene species **I** not only can be regarded as the precursor of the final dimer **5**[12] but also would eventually allow design of higher order cascade reactions.

A speculative proposal to rationalize the stereoselectivity is given in Scheme 4. First, the mechanism disclosed by Zhang[6] accounts well for the Cu(I)-catalyzed formation of (*E*)-**2** (via intermediates **II** and **IV**). On the other hand, the reversed selectivity for Pt(II) might be understood via intermediate **III**, wherein the platinum is coordinated to oxygen and thus acts as a Lewis acid.[13] Then, the cyclization via attack of the enol ether would form species **V**, in preference over species **VI**, which would suffer ring opening to afford the corresponding *Z* isomer.

In conclusion, we have developed a selective access to (*Z*)- and (*E*)-α-ylidene-*β*-keto and -malonate esters by room temperature Pt-(II)- and Cu(I)-catalyzed rearrangement of propargylic esters. The complementary *E*/*Z* stereoselectivity induced by both catalysts and

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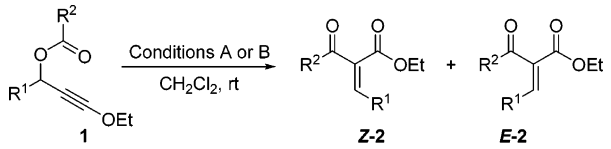
Table 1. Pt(II) and Cu(I)-Catalyzed Rearrangements of Propargyl Derivatives **1**

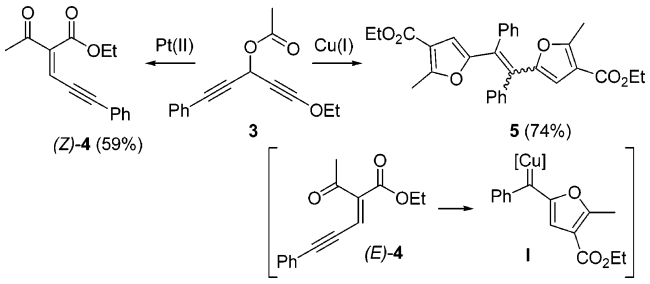


Conditions A: $PtCl_2$ (5 mol%), CH_2Cl_2, rt
Conditions B: $[Cu(CH_3CN)_4][BF_4]$ (5 mol%), CH_2Cl_2, rt

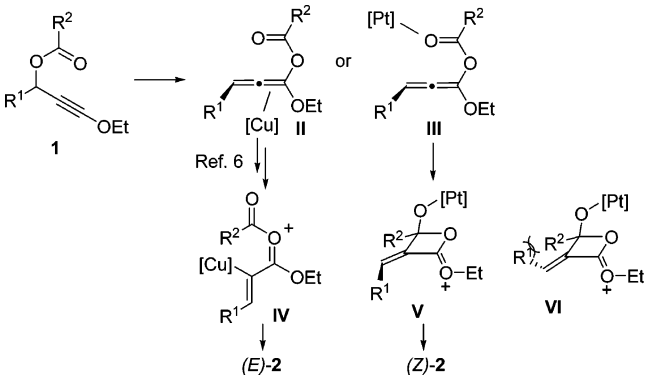
entry	R^1	R^2	**2**	yield (%)[a] (conditions)	*Z*:*E*[b]
1	Ph	Me	**2a**	81 (A)	only *Z*
				84 (B)	10:90
2[c]	*p*-$MeOC_6H_4$	Me	**2b**	71 (A)	50:50
				58 (B)	50:50
3	*p*-$NO_2C_6H_4$	Me	**2c**	75 (A)	only *Z*
				50 (B)	only *E*
4	1-naphthyl	Me	**2d**	70 (A)	only *Z*
				82 (B)	only *E*
5	2-furyl	Me	**2e**	79 (A)	only *Z*
6	^{i}Pr	Me	**2f**	88 (B)[d]	only *E*
7	(*E*)-Ph−CH=CH	Me	**2g**	60 (B)	20:80
8	CH_2=$CH(CH_2)_3$	Me	**2h**	30 (A)	75:25
9	Ph	Ph	**2i**	51 (A)	70:30
10	Ph	CH=CH_2	**2j**	60 (A)	75:25
				70 (B)	only *E*
11	Ph	OEt	**2k**	68 (A)	−
12	Ph	OMe	**2l**	69 (A)	only *Z*

[a] Yield of isolated product after column chromatography. [b] Estimated by ^{1}H NMR (400 MHz) of the reaction crude. The individual isomers were separated in most cases by column chromatography (see Supporting Information). [c] See ref 10. [d] Yield referred to unpurified product as chromatographic purification leads mostly to decomposition.

Scheme 3. Pt(II)- and Cu(I)-Catalyzed Transformations of Diyne **3**



Scheme 4. Proposed Mechanism for the Formation of (*E*)- and (*Z*)-**2**



the effectiveness of Cu(I), which are rarely used in metal-catalyzed cycloisomerization reactions, are noteworthy.[14] In terms of mechanistic and synthetic implications, it is demonstrated that the rearrangement of alkoxy-substituted substrates is totally regioselective (1,3- in preference to 1,2-acyloxy migration) and chemoselective (the ethoxyalkyne unit reacts in preference over the phenylalkyne unit; see diyne **3**). Studies to accomplish new cycloisomerization processes and to get insight into the mechanism are ongoing.

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Supporting Information Available: Experimental procedures and spectral and analytical data for compounds **2**, **4**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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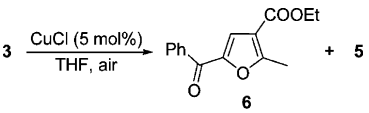
(11) Benzoylfuran **6** resulting from oxidation of carbene **I** is formed in 42% yield when a solution of **3** in THF was stirred in air in the presence of CuCl (5 mol %). For metal-catalyzed cyclization of conjugated ynenones



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