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$PtCl_2$-Catalyzed Tandem Enyne Cyclization/1,2 Ester Migration Reaction Controlled by Substituent Effects of All-Carbon 1,6-Enynyl Esters

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Cyclopentenes are important structural motifs in many natural products of significant bioactivity such as Roseophilin,[1] Scabronine G[2], and Przewalskin B (Figure 1).[3] In the past two decades, numerous methods to prepare cyclopentenes based on simple acyclic building blocks have been developed.[4] Among them, transition metal-catalyzed (especially Pt, Au, and Ru) 1,6-enyne cycloisomerization reactions play an extremely important role considering their atom-economy and synthetic efficiency.[5–10]

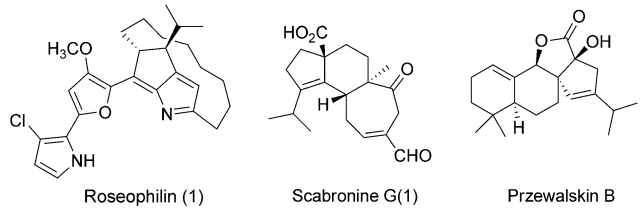
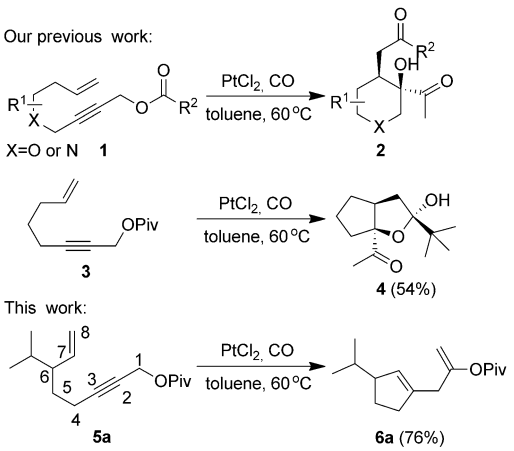


Figure 1. Natural products with cyclopentene motifs.

Propargylic esters, which are well known for their transition metal-catalyzed 1,2- and 1,3-acyloxy migrations reactions, are a specific class of alkynes that have been studied by many groups.[11] Among them, the 1,*n*-enyne esters are most widely used. However, in most studies, an acetate group was required to be located between the alkyne and the alkene group. Recently, several groups reported examples of 1,*n*-enyne esters in which an acyloxy group was located on the far side of the triple bond away from the alkene. In all cases, however, no enyne cycloisomerization products were obtained.[11c,12]

Recently, our group reported a $PtCl_2$-catalyzed cascade 1,2-acyloxy migration/intramolecular [3+2]-1,3-dipolar cycloaddition reaction of oxygen-tethered 1,7-enynyl esters **1**. A series of useful substituted hexahydropyrans were obtained based on this transformation (Scheme 1).[13] This reaction was subsequently expanded successfully to its nitrogen series using $[AuCl(PPh_3)]$ as catalyst.[12b] When the reaction conditions were applied to the simple all-carbon 1,6-enynyl ester **3**, the expected cyclopentane **4** was obtained in 54% yield as a major product. However, when all-carbon 1,6-enynyl ester **5a** with a isopropyl substituent at C6 was tested under the standard conditions, to our surprise, the enol ester **6a** was obtained in 76% yield. Obviously, the formation of **6a** was attributed to the effect of the isopropyl substituent, and it could be rationalized as the result of a tandem enyne cyclization/1,2-ester migration reaction of precursor **5a**. To our knowledge, a substituent-controlled enyne cyclization reaction has not been reported previously. This inspired us to investigate the effects of substituents on the reaction in detail. Herein, we report a new $PtCl_2$-catalyzed tandem 1,6-enyne cyclization/1,2-acyloxy migration reaction controlled by substituent effects.



Scheme 1. $PtCl_2$-catalyzed tandem reaction of 1,*n*-enyne ester.

To determine the factors that control the chemoselectivity and to examine the scope of the tandem enyne cyclization

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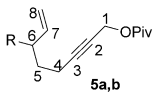
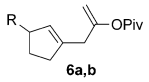
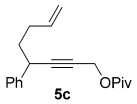
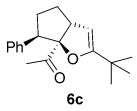
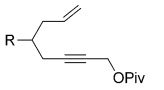
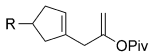
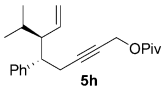
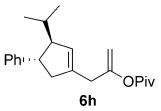
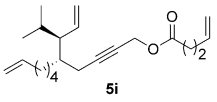
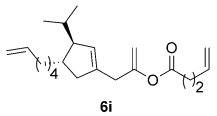
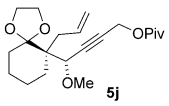
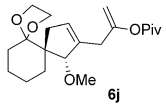
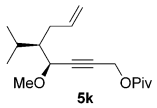
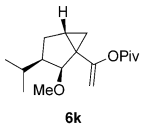
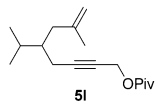
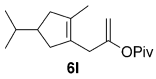
Table 1. Platinum-catalyzed tandem enyne cyclization/1,2-ester migration reaction.[a]

Entry	Substrate	R	Products	Yield [%][b]
1	 5a,b	*i*Pr = **5a**	 6a,b	76
2		Ph = **5b**		48
3	 5c	–	 6c	50
4	 5d-g	*i*Pr = **5d**	 6d-g	94
5		Ph = **5e**		92
6		Cy = **5f**		79
7				90
8[c]	 5h	–	 6h	90
9[c]	 5i	–	 6i	68
10[d]	 5j	–	 6j	32
11	 5k	–	 6k	66
12	 5l	–	 6l	66

[a] Reaction conditions: enynyl ester (0.1 M in toluene), 10 mol% $PtCl_2$, CO (1 atm), 60 °C, 1 h. Piv = pivaloyl, Cy = cyclohexyl. [b] Isolated yields. [c] Relative configuration. [d] Reaction time of 8 h; the starting material was recovered in 40% yield.

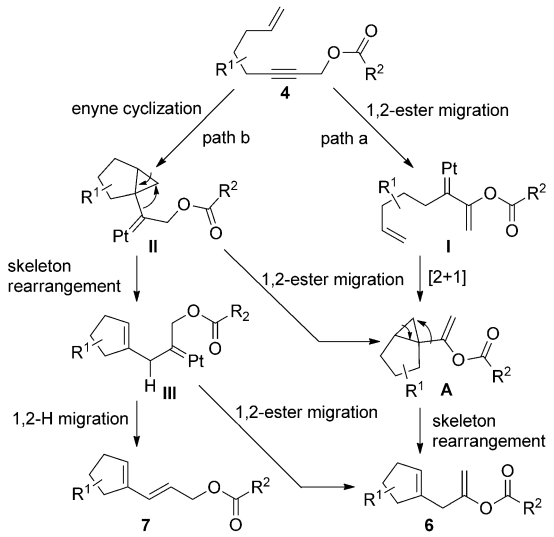
reaction, a series of 1,6-enynyl esters with different substituents were prepared and tested under the standard conditions (Table 1). First, substrates with a single alkyl or phenyl substituent were tested (Table 1, entries 1–7). When the substituent was located at C6 of 1,6-enynyl esters (Table 1, entries 1 and 2), it could be seen that the tandem enyne cyclization was favored in case of a more bulky substituent. For enynyl ester **5c**, which has a substituent at C4 (Table 1, entry 3), only the [3+2] cycloaddition product **6c** was obtained, thus indicating that the substituent at this position inhibited completely the enyne cycloisomerization reaction. For enynyl esters with C5 substituents (Table 1, entries 4–7), the substituents had no effect on the conversion and the corresponding cyclopentene enol esters were obtained in high yields.

Enynyl esters with two substituents attached were also tested (Table 1, entries 8–11). Those with C5,C6 disubstitution in *trans* (**5h**, **5i**) could generate cyclopentene enol esters **6h** and **6h** in yields of 90% and 68%, respectively (Table 1, entries 8 and 9), of which the latter contains the core of Roseophilin. It is worth mentioning here that the 5,6-spiro bicyclic skeleton that is present in many natural products could also be prepared by this method from enynyl ester **5j** (Table 1, entry 10).[3,14] Surprisingly, the C4,C5-disubstituted ester **5k** gave the [3-1-0]-fused ring product **6k** (Table 1, entry 11), which indicated that a cyclopropyl intermediate exists in this tandem process. The substrate with a substituent at C7 was also tolerated (Table 1, entry 12).

On the basis of the above observations, this Pt-catalyzed cascade transformation should involve one of two possible pathways (Scheme 2, path a or b). In path a, Pt-promoted 1,2-ester migration of the propargylic ester **4** occurs first and leads to the formation of the Pt carbene intermediate **I**, followed by cyclopropanation with the terminal alkene to give the bicyclic [3-1-0] intermediate **A**. Skeleton rearrangement of this fused bicyclic intermediate **A** produces the product **6**.[15] Alternatively, in path b, in which enyne cyclization occurs first, the cyclopropyl metal carbenoid **II** is formed. If 1,2-ester migration reaction of **II** occurs subsequently, the same bicyclic [3-1-0] intermediate **A** will be generated. On the other hand, skeleton rearrangement of carbenoid **II** will deliver a new carbenoid **III**. For cabenoid **III**, 1,2-ester migration reaction will generate the final product **6**,[16] and 1,2-H migration will produce the conjugated cyclopentene ester **7**.

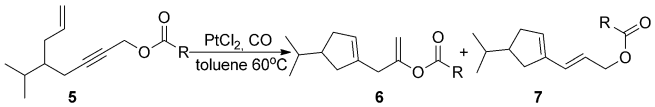
Both of the two mechanisms seem plausible based on the formation of the bicyclic [3-1-0] product **6k** (Table 1, entry 11) mentioned above. To obtain more conclusive evidence concerning the mechanism in this tandem reaction, additional enynyl esters **5m–o** with different esters were used under our standard conditions. The corresponding cyclopentene enol esters **6m–o** were obtained in 69, 56 and 22% yield, respectively, along with the corresponding conjugated dienes **7m–o** (Table 2, entries 1–3). The formation of conjugated dienes **7** indicates that cabinoid **III** exists as an intermediate in this tandem process, thus supporting the existence of the proposed path b. Furthermore, the ratio of products **6** and **7** in these three examples also indicated that the electronegativity at the ester carbonyl has a great influence on the reaction rate of the 1,2-H migration step.

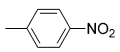
In conclusion, a new $PtCl_2$-catalyzed tandem enyne cyclization/1,2-ester migration reaction of all-carbon 1,6-enynyl esters, which was controlled by substitution, was developed. By using this reaction, cyclopentene enol esters with various alkyl substituents can be efficiently synthesized starting from the corresponding 1,6-enyne ester. Further modifica-



Scheme 2. Proposed mechanism.

Table 2. Reactions performed for further investigation on the mechanism of the tandem reaction.



Entry	Substrate	**6**, yield [%]	**7**, yield [%]
1	**5m**, R = Ph	**6m**, 69	**7m**, 25
2	**5n**, R = Me	**6n**, 56	**7n**, 40
3	**5o**, R = 	**6o**, 22	**7o**, 64

tion of this reaction and its application to synthesize Roseophilin is currently in progress and will be reported in due course.

Experimental Section

General experimental procedure: A suspension of the propargylic ester **5** (0.15 mmol) and $PtCl_2$ (0.015 mmol) in toluene (1.5 mL) under CO (1 atm) was stirred for 1 h at 60 °C. After cooling to room temperature, the mixture was directly loaded onto a silica gel column. Elution with PE/EtOAc 100:1 afforded the desired products (see the Supporting Information for characterization data).

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Keywords: catalysis · enyne cyclization · ester migration · platinum · synthesis

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