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Pt-Catalyzed Tandem 1,2-Acyloxy Migration/Intramolecular [3 + 2] Cycloaddition of Enynyl Esters

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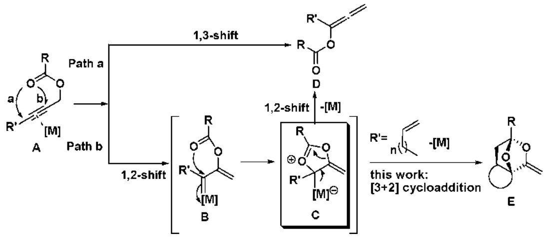
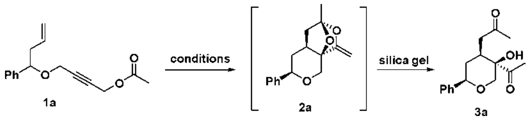
In recent years, utilization of Pt and Au catalysts to promote reactions of enyne derivatives has attracted considerable attention in modern catalysis.[1,2] Among these reports, the propargylic carboxylate is a unique class of substrates because of its significant reactivity pattern involving C≡C triple-bond activation and *O*-ester rearrangement.[3] As shown in Scheme 1, the *O*-ester group undergoes an internal 1,3-shift catalyzed by the transition metal, giving the rearranged allenic intermediate **D**,[4] wherein the computational calculation suggests that 1,3-acyloxy migration might also account for the double 1,2-acyloxy migrations involving the in situ generation of synthetically valuable 1,3-dipole intermediate **C**.[4a,5] To explore the diversity of reactivity of enyne chemistry, we envisioned that the intermediate **C**, a metal-involved 1,3-dipolar synthon, might experience cycloaddition with an appropriate olefin to generate cycloaddition product **E**. To our knowledge, this tandem transformation involving 1,2-acyloxy migration of propargylic carboxylates followed by 1,3-dipolar cycloaddition has not been reported previously. Herein, we present a cascade process involving $PtCl_2$-catalyzed 1,2-acyloxy migration of propargylic esters and subsequent intramolecular [3 + 2] cycloaddition, giving access to various functionalized cyclic compounds that are synthetically interesting building blocks in the total synthesis of structurally relevant natural products.

Scheme 1. Transition-Metal-Catalyzed Reactivity of Propargylic Carboxylates



Initially, enynyl ester **1a** was selected as a model substrate to investigate this proposed tandem transformation. Pleasingly, the reaction proceeded in the presence of $PtCl_2$ (10 mol %) in toluene at 80 °C for 4 h, leading to the formation of **3a** in 35% yield (Table 1, entry 1), in which the instability of the resulting enol ether **2a** enabled rapid hydrolysis on silica gel. The yield was readily increased to 74% within 6 h by lowering the temperature to 60 °C (entry 2). When the reaction was carried out in toluene at 80 °C under an atmosphere of CO (1 atm), **3a** was obtained in 60% yield with a reduced reaction time of 1 h (entry 3). The optimal result was further obtained in 78% yield in toluene at 60 °C under an atmosphere of CO (entry 4). The reaction also proceeded in 1,2-dichloroethane (DCE) or tetrahydrofuran (THF) solvent (entries 6 and 7). When the reaction was carried out in CH_3CN at 60 °C or in toluene at room temperature under an atmosphere of CO, no reaction was observed (entries 5 and 8). In addition to $PtCl_2$, several Au catalysts were also examined (entries 9−12). Simple Au catalysts such as $AuCl_3$ and AuCl were ineffective for this transformation, but interestingly, the cationic Au catalyst modified with phosphines or N-heterocyclic carbene (NHC)-containing ligands[6] promoted the formation of **3a**, despite the low to moderate yield.

Table 1. Optimization of Reaction Conditions



entry	catalyst	solvent	*T* (°C)	time (h)	yield (%)[a]
1	$PtCl_2$ (10% mol)	toluene	80	4	35
2	$PtCl_2$ (10% mol)	toluene	60	6	74
3	$PtCl_2$/CO (10% mol/1 atm)	toluene	80	1	60
4	$PtCl_2$/CO (10% mol/1 atm)	toluene	60	1	78
5	$PtCl_2$/CO (10% mol/1 atm)	toluene	rt	24	NR
6	$PtCl_2$/CO (10% mol/1 atm)	DCE[b]	60	8	71
7	$PtCl_2$/CO (10% mol/1 atm)	THF	60	4	61
8	$PtCl_2$/CO (10% mol/1 atm)	MeCN	60	8	NR
9	$AuCl_3$ (5% mol)	toluene	60	12	trace[c]
10	AuCl (5% mol)	toluene	60	12	trace[c]
11	$PPh_3AuCl/AgSbF_6$ (5% mol/5% mol)	DCM	rt	1	17
12	Au(IMes)Cl/$AgSbF_6$ (10% mol/10% mol)	DCE[b]	rt	2	58

[a] Isolated yields. [b] DCE = 1,2-dichloroethane. [c] The remaining **1a** was recovered.

With optimized reaction conditions in hand, we then investigated a series of enynyl esters under our $PtCl_2$-catalyzed tandem protocol, and various synthetically valuable multisubstituted pyrans were accessed in good to excellent yields (Table 2). The ester group could be varied from propargylic acetate to benzoate and pivaloate with satisfactory yields (entry 1). Investigations of the substituent effects at the C6−C9 positions indicated that this tandem reaction has a wide range of substrate scope. Substrates bearing various aryls at C6 afforded the corresponding pyran adducts in good to excellent yields (entries 1−3). The C6 alkenyl- and alkyl-substituted substrates were also suitable for this reaction (entries 4−7). Substituents at C7 or C8 of the substrate were also tolerated but gave the partially hydrolyzed dihydrofurans **3j** and **3k** (entries 8 and 9), in which the related completely hydroxyl diketones were not isolated. Contrarily, the C9 dimethyl-substituted substrate **1l** failed to undergo this transformation, and the fragmented alcohol **4** was produced in 45% yield with the recovery of **1l** in 52% yield (entry 10). Surprisingly, substituents at the C1 position offered severe disadvantages to the expected reaction because of the steric bulk of the two methyl groups (entry 11).[7] In the case of substrate **1m**, the undesired conjugated diene **5** was obtained in 67% yield. Furthermore, the scope of this reaction was expanded to enynyl esters **1n**−**r** containing the homopropargylic moiety, and a series of structurally differantial pyrans were smoothly produced in good yields (entries 12−16).

In order to demonstrate the synthetic utility of this tandem reaction in the synthesis of non-pyran cyclic componds, three

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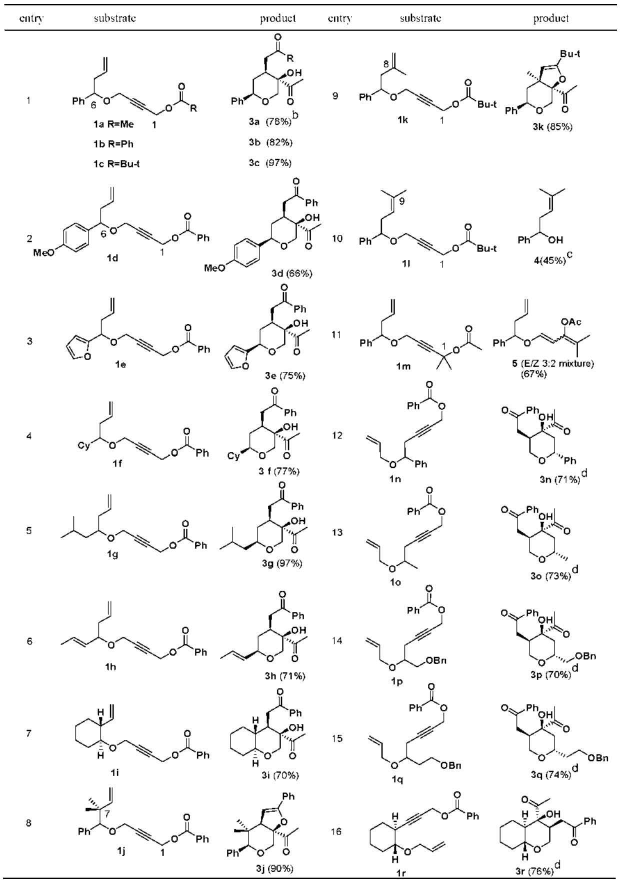
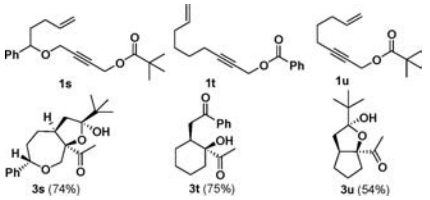
Table 2. Pt-Catalyzed Tandem 1,2-Acyloxy Migration/ Intramolecular [3 + 2] Cycloaddition Reaction of Enynyl Esters[a]



entry	substrate	product
1	1a R=Me 1b R=Ph 1c R=Bu-t	3a (78%)[b] 3b (82%) 3c (97%)
2	1d	3d (66%)
3	1e	3e (75%)
4	1f	3 f (77%)
5	1g	3g (97%)
6	1h	3h (71%)
7	1i	3i (70%)
8	1j	3j (90%)
9	1k	3k (85%)
10	1l	4(45%)[c]
11	1m	5 (E/Z 3:2 mixture) (67%)
12	1n	3n (71%)[d]
13	1o	3o (73%)[d]
14	1p	3p (70%)[d]
15	1q	3q (74%)[d]
16	1r	3r (76%)[d]

[a] Reaction conditions: enynyl ester (0.1 M in toluene), 10 mol % $PtCl_2$, CO (1 atm), 60 °C, 1 h. [b] Isolated yields. [c] Starting material was recovered in 52% yield. [d] Reaction time of 4 h.

Scheme 2. Modified Pt-Catalyzed Reaction of Enynyl Esters



1s 1t 1u

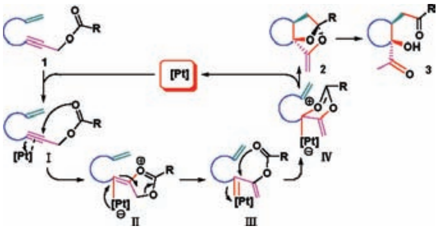
3s (74%) 3t (75%) 3u (54%)

additional acyclic enynyl esters **1s**−**u** were employed (Scheme 2). It is worth mentioning that seven-membered-ring compound **3s** can also be generated under these conditions. For the full-carbon-chain substrates 1,7-enynyl ester **1t** and 1,6-enynyl ester **1u**, the cyclohexane derivative **3t** and the fused cyclopentane derivative **3u** were obtained in 75 and 54% yield, respectively.

For products **3c**, **3r** and **3u**, the corresponding structures and relative configurations were further confirmed by X-ray crystallography (for details, see the Supporting Information).

A rational mechanism for this Pt-catalyzed cascade transformation is proposed in Scheme 3. Pt-promoted 1,2-acyloxy migration of the propargylic ester leads to the formation of the Pt carbene intermediate **III** via **II**. The Pt carbenoid then undergoes an intramolecular nucleophilic addition of the carbonyl to give the 1,3-dipolar intermediate **IV**, which forms enol ketal **2** through [3 + 2] cycloaddition with the release of the Pt catalyst for the next catalytic cycle. After hydrolysis on silica gel, enol ketal **2** provides the desired product **3**.

Scheme 3. $PtCl_2$-Catalyzed [3 + 2] Cycloaddition of Enynes and the Proposed Mechanism



In conclusion, we have completed a platinum-catalyzed tandem reaction involving enynyl ester isomerization and subsequent intramolecular [3 + 2] cyclization. This strategy provides an efficient approach to five-, six-, or seven-membered cyclic polyfunctional compounds. This study permitted the details of a novel cycloisomerization mode to be uncovered and, more generally, provided insight into mechanistic aspects of the intricate cyclization mode of enynes bearing a propargylic ester group. Further studies taking advantage of this tandem protocol to address complex synthetic issues are ongoing.

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Supporting Information Available: Experimental procedures, compound characterization data, and CIF files for **3c**, **3r**, and **3u**. This material is available free of charge via the Internet at http://pubs.acs.org.

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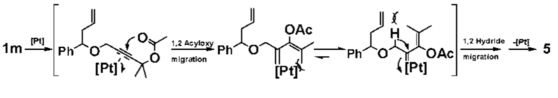
(7) The formation of the conjugated diene **5** may involve 1,2-acyloxy migration and 1,2-hydride migration, for which the proposed mechanism is shown below:



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