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Tandem Ruthenium-Catalyzed Transfer-Hydrogenative Cyclization/Intramolecular Diels–Alder Reaction of Enediynes Affording Dihydrocoumarin-Fused Polycycles

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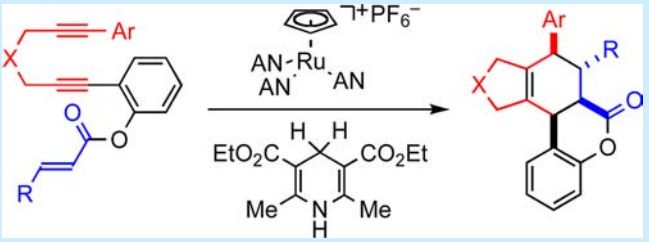
Supporting Information

ABSTRACT: A tandem transfer-hydrogenative cyclization/intramolecular Diels–Alder reaction of enediyne substrates, containing 1,6-diyne, acrylate dienophile, and phenol tether moieties, was successfully accomplished using the combination of a cationic ruthenium complex, $[CpRu(AN)_3]PF_6$ (**1b**, Cp = η^5-C_5H_5, AN = MeCN), as the catalyst and a Hantzsch ester as the H_2 surrogate to afford interesting dihydrocoumarin-fused polycyclic products as single diastereomers.

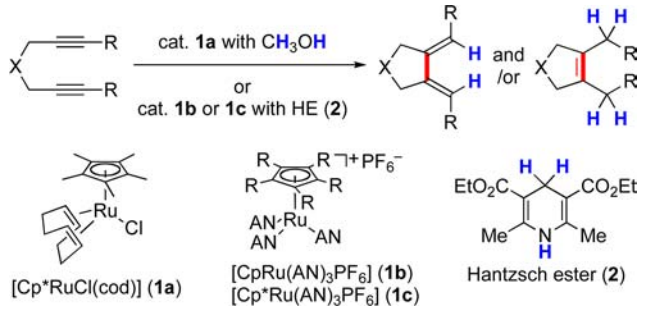


Transition-metal-catalyzed carbocyclizations have been recognized as efficient methods to synthesize valuable cyclic products with increasing complexity from simple acyclic precursors.[1] Among them, the hydrogenative cyclization of α,ω-diynes is a powerful route to exocyclic 1,3-dienes, which are useful synthetic intermediates, via carbon–carbon bond formation with concomitant hydrogenation.[2] This fascinating catalytic process was first pioneered by Trost and Lee, who used a palladium catalyst with acetic acid and hydrosilanes as the proton and hydride sources, respectively.[3] Recently, several research groups have also reported that rhodium, iron, or platinum catalysts enable the direct use of molecular hydrogen for the hydrogenative cyclization of α,ω-diynes, even though the platinum-catalyzed reaction selectively afforded cycloalkenes instead of exocyclic 1,3-dienes.[4]

Our group has independently developed the transfer-hydrogenative cyclization of 1,6-diynes using a ruthenium catalyst, Cp*RuCl(cod) (**1a**, Cp* = η^5-Me_5C_5, cod = 1,5-cyclooctadiene, Scheme 1).[5,6] Notably, we used methanol as an inexpensive and safe H_2 surrogate, selectively affording exocyclic 1,3-dienes from 1,6-diynes possessing terminal aryl groups. In contrast, when a 1,6-diyne possessing terminal methyl groups was used as the substrate, [2 + 2 + 2] cyclodimerization rather than transfer-hydrogenative cyclization occurred. Thus, we used cationic ruthenium complexes, $[CpRu(AN)_3]PF_6$ (**1b**, Cp = η^5-C_5H_5, AN = MeCN) and $[Cp^*Ru(AN)_3]PF_6$ (**1c**), as the catalysts, which enabled the transfer-hydrogenative cyclization of various 1,6-diynes possessing terminal aryl, alkenyl, or alkyl groups using a Hantzsch ester (HE, **2**) as an alternative H_2 surrogate (Scheme 1).[7] However, 1,6-diynes possessing terminal alkyl groups were selectively converted into cycloalkenes via the 1,4-hydrogenation of the corresponding exocyclic 1,3-diene intermediates.

We also demonstrated that the exocyclic 1,3-diene products efficiently underwent Diels–Alder reaction with highly electrophilic dienophiles such as *N*-phenylmaleimide, 4-phenyl-1,2,4-triazoline-3,5-dione, or dimethyl acetylenedicarboxylate.[7] Recently, various tandem processes comprising catalytic 1,3-diene formations and subsequent Diels–Alder reactions have been developed for the rapid and diversity-oriented syntheses of complex polycyclic molecules.[8,9] Therefore, we also attempted the tandem ruthenium-catalyzed transfer-hydrogenative cyclization/Diels–Alder reaction of a 1,6-diyne in the presence of HE **2** and *N*-phenylmaleimide. However, this one-pot process was hampered by the undesirable hydrogenation of the dienophile.[10] As a continuation of our study, we then carried out a tandem process including an intramolecular Diels–Alder reaction because such an intramolecular setting would facilitate the [4 + 2] cycloaddition step. Therefore, a less electrophilic dienophile such as an acrylate can be used, thereby suppressing the undesirable hydrogenation of the dienophile. In addition,

Scheme 1. Ruthenium-Catalyzed Transfer-Hydrogenative Cyclization of 1,6-Diynes



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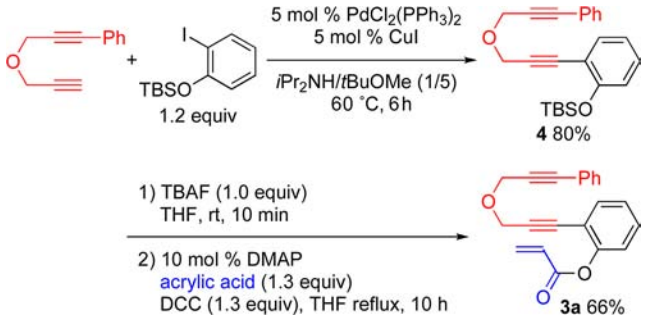
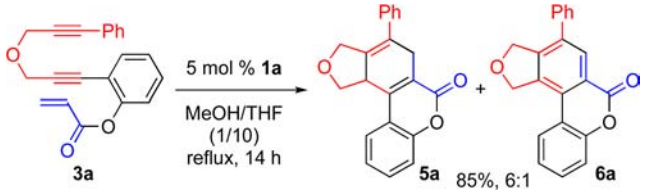
the newly developed tandem process would afford complex polycyclic products from simple acyclic precursors in a single operation. For this purpose, we designed a new enediyne substrate (**3**) consisting of a pendant acrylate dienophile attached to a 1,6-diyne moiety through an *o*-phenol tether. Representative enediyne **3a** was readily obtained by the Sonogashira coupling of monophenylated propargyl ether with *tert*-butyldimethylsilyl (TBS)-protected *o*-iodophenol and subsequent deprotection, followed by condensation with acrylic acid (Scheme 2). Because of the modular nature of this scheme, diverse enediyne substrates were also obtained by replacing the 1,6-diyne and acrylic acid.

Scheme 2. Modular Synthesis of Enediyne Substrate 6a



At the outset, the reaction of **3a** was examined under the previously optimized conditions using catalyst **1a** and MeOH as the H_2 surrogate (Scheme 3). In the presence of 5 mol % **1a**, **3a**

Scheme 3. Cyclization of Enediyne 3a in the Presence of 1a and MeOH

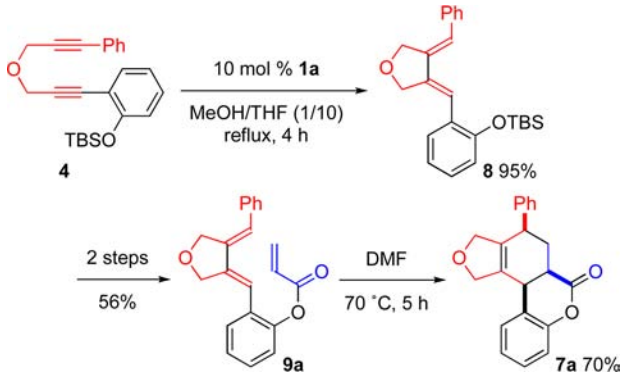


was refluxed in THF for 14 h to afford two new products **5a** and **6a**. According to ^{1}H and ^{13}C NMR, IR, and high-resolution mass analyses (see Supporting Information), **5a** and **6a** could be assigned as the cyclohexadiene and phthalan derivatives, respectively, which are probably formed via the intramolecular [2 + 2 + 2] cycloaddition,[11] followed by alkene isomerization or aromatization rather than the expected tandem process. These characterizations are also in good agreement with the fact that **5a** gradually underwent aromatization upon exposure to air, affording **6a**.

These results indicate that the intramolecular [2 + 2 + 2] cycloaddition is preferred over transfer-hydrogenative cyclization when catalyst **1a** was used with MeOH. Then, the reaction of **3a** under alternative transfer-hydrogenative cyclization conditions was examined using cationic catalyst **1b** and HE (**2**) as the H_2 surrogate (Scheme 4). In the presence of 1 mol % **1b** and 2 equiv of **2**, **3a** was heated in DMF at 70 °C for 5 h, affording the desired tandem reaction product **7a** as the sole product. The structural assignment of **7a** was corroborated by an alternative stepwise synthesis of **7a** from diyne **4**, which is the precursor of **3a** (Scheme 5). In the presence of **1a** and MeOH, **4** uneventfully underwent the transfer-hydrogenative

Scheme 4. Cyclization of 3a in the Presence of 1b and HE 2

Scheme 5. Stepwise Synthesis of 7a from 4



cyclization, affording exocyclic 1,3-diene **8** in 95% yield. Using similar procedures for the synthesis of **3a**, **8** was converted into **9a**, which underwent the intramolecular Diels–Alder reaction in DMF at 70 °C for 5 h to afford **7a** in 70% yield. Therefore, **7a** was unambiguously confirmed as the thermal [4 + 2] cycloadduct obtained from exocyclic 1,3-diene **9a** with the pendant acrylate dienophile. It was confirmed that the cycloaddition of 3,4-dibenzylidenetetrahydrofuran with ethyl acrylate did not take place in DMF at 100 °C within 5 h. It was also shown that **7a** was not an intermediate for the formation of **5a** and **6a**: the isolated **7a** was subjected to the transfer-hydrogenative cyclization conditions using catalyst **1a** and MeOH, yielding neither **5a** nor **6a**.

The substrate scope of the tandem process was further investigated with various enediynes (Table 1). First, the effect of the diyne moiety was examined. Enediynes possessing an electron-donating methoxy or electron-withdrawing fluoro substituent at the para position of the terminal phenyl groups, **3b** and **3c**, were converted into the corresponding tetracyclic products **7b** and **7c** in comparable yields. In the previous study, electron-donating substituents decreased the reaction rates of the transfer-hydrogenative cyclization of 1,6-diynes.[7] However, no such effect was observed for this tandem process, because the second intramolecular Diels–Alder reaction is the rate-determining step. In addition to the phenyl groups, the 2-thienyl group of **3d** was tolerated, affording **7d** in 75% yield. The terminal aryl group was essential for the tandem process; enediyne **10** possessing a terminal methyl group was subjected to the transfer-hydrogenative cyclization conditions (5 mol % **1b**, 2.0 equiv of **2**, DMF, 70 °C, 17 h), affording intractable materials along with unreacted substrate **10**. The use of an alternative catalyst **1c** in THF afforded a similar result.

The effect of the diyne tether was then examined for *p*-toluenesulfonamide derivative **3e** and malonate derivative **3f**. The tandem reaction of **3e** proceeded under the same conditions to afford the expected 3-pyrroline-fused product **7e** in a similar yield (70%). In contrast, the tandem reaction of **3f** was sluggish under the same conditions. Thus, **3f** was subjected to the reaction using an increased loading of **1b** (10

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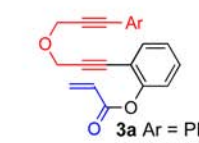
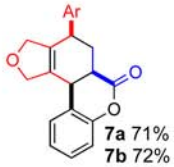
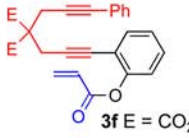
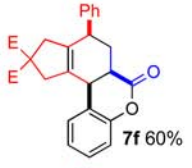
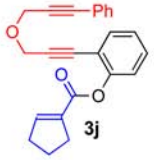
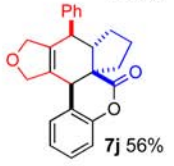
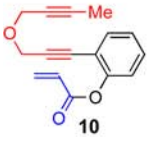
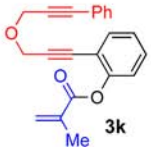
Table 1. Scope of Tandem Process

substrates	conditions	products
 **3a** Ar = Ph **3b** Ar = *p*-MeOC$_6$H$_4$ **3c** Ar = *p*-FC$_6$H$_4$ **3d** Ar = 2-thienyl	1 mol % **1b** **2** (2.0 equiv) DMF, 70 °C, 5 h	 **7a** 71% **7b** 72% **7c** 75% **7d** 75%
 **3e**	1 mol % **1b** **2** (2.0 equiv) DMF, 70 °C, 5 h	 **7e** 70%
 **3f** E = CO$_2$Me	10 mol % **1b** **2** (3.0 equiv) DMF, 70 °C, 7 h	 **7f** 60%
 **3g** R = Me **3h** R = *trans*-CH=CHMe **3i** R = 2-furyl	1 mol % **1b** **2** (2.0 equiv) DMF, 70 °C, 1 h then 120 °C, 3–4 h	 **7g** 77% **7h** 74% **7i** 72%
 **3j**	1 mol % **1b** **2** (2.0 equiv) DMF, 70 °C, 1 h then 120 °C, 16 h	 **7j** 56%
 **3l**	1 mol % **1b** **2** (2.0 equiv) DMF, 70 °C, 4 h	 **7l** 42%
 **10**		
 **3k**		 **9k** 96%

mol %) and **2** (3.0 equiv) for 7 h to afford the desired cyclopentene-fused product **7f**, albeit in a moderate yield (60%). Subsequently, the effect of the dienophile on the reaction efficiency was examined (Table 1). The reaction of enediyne **3g** possessing the crotonate moiety was attempted under the standard conditions (1 mol % **1b**, 2.0 equiv of **2**, DMF, 70 °C, 5 h); however, the ^{1}H NMR analysis of the crude reaction mixture indicated that the second intramolecular Diels–Alder step did not proceed. Therefore, the reaction temperature was raised to 120 °C, after transfer-hydrogenative cyclization was carried out at 70 °C for 1 h. Consequently, the desired tetracyclic product **7g** was obtained in 77% yield. Enediynes **3h** and **3i**, which possess sorbate or 3-(2-furyl)acrylate as the dienophiles, were successfully converted to the corresponding products **7h** and **7i** in similar yields.

Furthermore, interesting pentacyclic compound **7j** was also obtained, albeit in a moderate yield (56%), from enediyne **3j** possessing the cyclopentenecarboxylate dienophile. In this case, a prolonged reaction time of 16 h was required although transfer-hydrogenative cyclization proceeded smoothly under the standard conditions. Therefore, the substitution of the *β*-position to the ester detrimentally effected the efficiency of the Diels–Alder step.[12] This is also true of enediyne **3k** possessing the methacrylate dienophile; this substrate afforded polymeric materials at an elevated temperature of 120 °C, even though its transfer-hydrogenative cyclization under the standard conditions (1 mol % **1b**, 2.0 equiv of **2**, DMF, 70 °C, 1 h) afforded exocyclic 1,3-diene **9k** without difficulty in a high yield. The Diels–Alder reaction of isolated **9k** was also unsuccessful under thermal conditions. Finally, enediyne **3l** was examined as the substrate bearing a doubly activated dienophile. Consequently, the tandem reaction proceeded at 70 °C. However, the desired **7l** was isolated in a moderate yield (42%) because of complex side reactions.

All the polycyclic products were obtained as single diastereomers by this tandem process. The relative stereochemistry of these products was determined by NOE analyses of representative products **7b** and **7g** and was also unambiguously confirmed by a single-crystal X-ray diffraction study of compound **7l** (Figure 1). These data indicate that the

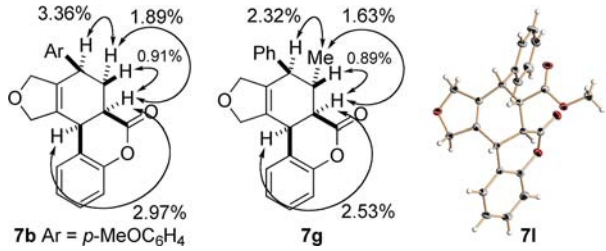
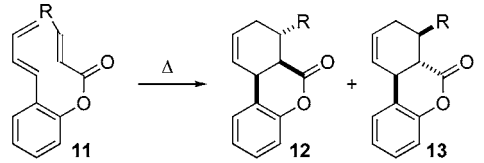


Figure 1. NOE data for **7b** and **7g** and ORTEP drawing of **7l**.

intramolecular Diels–Alder reactions of the exocyclic 1,3-diene intermediates possessing the pendant acrylate dienophiles proceeded via *endo* transition states. In contrast, previously reported reactions of closely related compounds **11** at higher reaction temperatures (110 °C for R = H and 180 °C for R = Me) afforded two stereoisomers **12** and **13** in a ca. 3:7 ratio (Scheme 6).[13] The formations of **12** and **13** were correlated to

Scheme 6. Previously Reported Intramolecular Diels–Alder Reactions of 11



the *endo* and *exo* transition states, respectively, based on density functional theory (DFT) calculations. Therefore, the major pathways of the Diels–Alder reactions of **11** were inferred to be via the *exo* transition states. To gain more insights, we analyzed the transition states for the intramolecular Diels–Alder reactions of exocyclic 1,3-diene intermediate **9g** corresponding to enediyne **3g**, using DFT calculations (Figure S2). The *endo*

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transition state was found to be 2.2 kcal/mol lower in energy than the corresponding *exo* transition state. This energy difference corresponds to an *endo*/*exo* selectivity of ca. 96:4. Therefore, this theoretical prediction that the *endo* pathway is kinetically favorable is qualitatively in good agreement with the experimental results of the exclusive formation of *endo* cycloadducts **7** from **3**. The difference in stereoselectivity between **11** and our system such as **9** can be ascribed to the rigid exocyclic 1,3-diene moiety as well as the aryl terminal group, although the details are unclear at this stage.

In conclusion, we have successfully developed a new tandem process comprising a transfer-hydrogenative cyclization and subsequent intramolecular Diels–Alder reaction. The use of our previously reported catalyst system with a cationic ruthenium catalyst, $[CpRu(AN)_3]PF_6$, and a Hantzsch ester as the H_2 surrogate in DMF effectively converted enediyne substrates containing 1,6-diyne, acrylate dienophile, and phenol tether moieties into dihydrocoumarin-fused polycyclic products. The relative stereochemistry of the tandem reaction products was confirmed by NOE as well as X-ray crystallography. Furthermore, based on DFT calculations, it was reasoned that the intramolecular Diels–Alder reactions of exocyclic 1,3-diene intermediates proceed via *endo* transition states.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and analytical data. 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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