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Ruthenium-Catalyzed Transfer Oxygenative Cyclization of α,ω-Diynes: Unprecedented [2 + 2 + 1] Route to Bicyclic Furans via Ruthenacyclopentatriene

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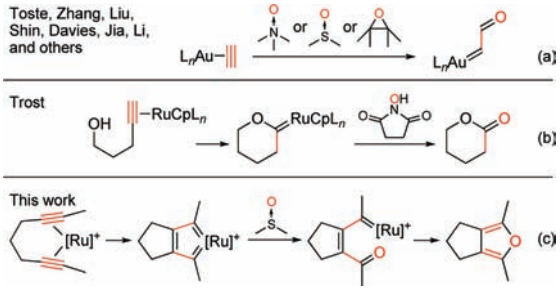
Supporting Information

ABSTRACT: A novel oxygen-atom-transfer process enables the catalytic [2 + 2 + 1] synthesis of bicyclic furans from α,ω-diynes with DMSO. $[CpRu(AN)_3]PF_6$ catalyzed the transfer oxygenative cyclization of diynes with aryl terminal groups, while those of diynes with alkyl terminal groups were effectively promoted by the corresponding Cp* complex. A mechanism for bicyclic furan formation via a ruthenacyclopentatriene was proposed on the basis of both experimental and theoretical studies.

Transition-metal-catalyzed transfer oxygenation of alkynes is an effective method for synthesizing carbonyl compounds. Transfer oxygenation of gold-activated alkynes with *N*-oxides, sulfoxides, and epoxides has emerged as a powerful method to produce α-oxo gold carbene species (Scheme 1a).[1] Since the pioneering studies carried out by

Scheme 1. Transfer Oxygenation of Alkynes Relevant to Carbene Complexes

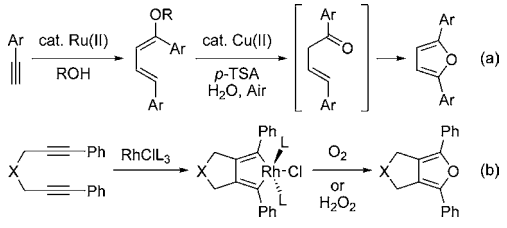


Toste,[1a] Zhang,[1b] and others, fascinating cascade processes initiated by transfer oxygenation have been studied extensively.[2] In contrast, catalytic transfer oxygenation of carbene complexes derived from alkynes has almost been neglected. Trost and Rhee synthesized lactones via Ru-catalyzed oxidative cyclization of alkynols (Scheme 1b).[3] The transfer oxygenation of transient Ru−carbene species with *N*-hydroxysuccinimide is the key step in performing this transformation successfully.

In our recent efforts to develop a new mode of Ru-catalyzed cyclization of 1,6-diynes,[4] we found that the O atom is transferred from dimethyl sulfoxide (DMSO) to the diyne substrates with concomitant cyclization, resulting in the catalytic formation of bicyclic furans (Scheme 1c). In contrast to the above precedents, *two alkyne molecules are simultaneously activated by a single metal center to produce bis(carbenoid) species, and two C−O bonds and one C−C bond are formed in a single transfer oxygenation process.* In addition to the mechanistic novelty, this method is an atom-economical and straightforward route to bicyclic furans under neutral conditions.

Previously, Beller, Dixneuf, and co-workers reported that dienyl ethers formed via Ru-catalyzed alkoxylative dimerization of phenylacetylenes undergo cyclization in the presence of a Cu(II) catalyst and TsOH in air to afford diphenylfurans (Scheme 2a).[5] A similar transformation of diphenylacetylenes

Scheme 2. Previous Syntheses of Furans from Arylalkynes



into tetraphenylfurans has been achieved using a Pd catalyst and zinc Lewis acids under an oxygen atmosphere.[6] *The scope of these furan formations was almost limited to aryl-substituted monoalkynes; only one example of a 1,6-diyne with aryl terminals resulted in a lower yield (32%) under the Pd-catalyzed conditions.*[6b] In addition, Müller's group has shown that bicyclic furans can be obtained in low yields by the oxidation of preformed rhodacyclopentadienes (Scheme 2b).[7] In contrast to these precedents, our method *catalytically converts a wide variety of 1,6- and 1,7-diyne substrates having both aryl and alkyl terminals into bicyclic furans in moderate to high yields.* Here we report the preliminary results of our investigation of this novel oxidative cyclization reaction of α,ω-diynes to produce bicyclic furans. We also propose a possible mechanism for this process on the basis of our experimental and theoretical studies on ruthenacyclopentatrienes.

At the outset, the reaction conditions were optimized for the cyclization of diyne **2a** using Ru catalysts **1** (Table 1).[8] First, we used the pentamethylcyclopentadienyl (Cp*) complex [Cp*RuCl(cod)] (**1a**; cod = 1,5-cyclooctadiene) for the

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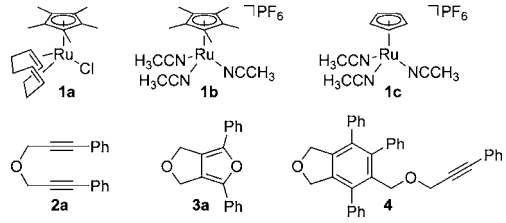
Table 1. Optimization of the Reaction Conditions



run	cat (mol %)	conditions	products (yield/%)[a]
1[b]	**1a** (10)	THF, 70 °C, 12 h	**3a** (4),[c] **4** (36)[c]
2[b]	**1a** (10)[d]	THF, 70 °C, 12 h	**3a** (46),[c] **4** (3)[c]
3[e]	**1a** (10)[d]	THF, 70 °C, 3.5 h	**3a** (71), **4** (trace)
4[e]	**1b** (10)	THF, 70 °C, 24 h	**3a** (19)[c]
5[e]	**1c** (10)	THF, 70 °C, 24 h	**3a** (50)[c]
6[f]	**1c** (10)	THF, 70 °C, 24 h	**3a** (40)[c]
7[e]	**1c** (5)	DMF, 70 °C, 24 h	**3a** (73)
8[e]	**1c** (5)	DMF, 100 °C, 10 h	**3a** (79)
9[e]	**1c** (3)	DMF, 140 °C, 4 h	**3a** (90)

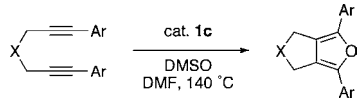
[a]Isolated yields based on 0.3 mmol of **2a**. [b]DMSO (10 equiv) and solvent (1.5 mL). [c]Yield determined by ^{1}H NMR analysis of the crude products; **2a** was returned in 37, 9, 57, 30, and 35% yield for runs 1, 2, and 4–6, respectively. [d]MsOH (20 mol %) was added. [e]DMSO (5 equiv) and solvent (3 mL). [f]DMSO (1.2 equiv) and solvent (3 mL).

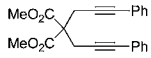
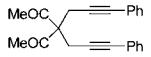
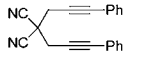
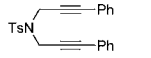
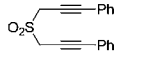
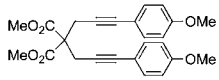
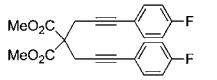
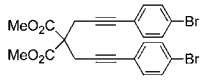
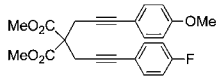
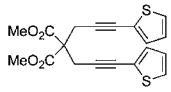
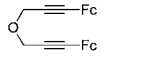
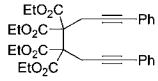
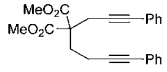
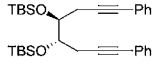
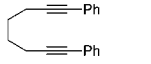
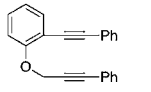
cyclization of **2a** in the presence of 10 mol % catalyst and 10 equiv of DMSO in refluxing THF for 12 h (run 1). The formation of bicyclic furan **3a** was confirmed by ^{1}H NMR analysis of the crude products, although 37% of **2a** remained intact. In addition, the [2 + 2 + 2] self-cycloaddition product **4** was found. Since this reaction was presumed to proceed via a ruthenacyclopentatriene intermediate (see below), methanesulfonic acid (MsOH) (20 mol %) was added to enhance the electrophilicity of the ruthenacycle via protonation.[9] Gratifyingly, this increased the conversion rate of **2a** and afforded the desired **3a** in a higher yield (run 2). Using a reduced amount of DMSO (5 equiv) dramatically increased the reaction rate, and **3a** was isolated in 71% yield (run 3). In contrast to DMSO, pyridine *N*-oxide and PhIO proved to be much less efficient as O-atom donors. The reactions using these reagents immediately yielded black precipitates, and <10% yield of **3a** was detected in the crude reaction mixtures.

Electron-deficient ruthenacycle intermediates produced from cationic Ru complexes were also expected to enhance the reaction rate. In addition, the undesirable self-cycloaddition of the diyne was expected to be suppressed by the use of cationic complexes. In fact, no trace of **4** was detected in the crude products when the cationic complex $[Cp^*Ru(AN)_3]PF_6$ (**1b**; AN = acetonitrile) was used as the catalyst (run 4). However, the reaction was sluggish, and **3a** was formed in a low yield. Next, instead of **1b**, the corresponding cyclopentadienyl (Cp) complex **1c** was investigated as a catalyst, as Cp is less electron-donating than Cp*. As a result, the yield of **3a** improved to 50% under the same conditions (run 5). The product yield was significantly decreased by the use of 1.2 equiv of DMSO (run 6). Finally, to improve the yield of **3a** further, different solvents such as acetone, *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide, and 1,3-dimethyltetrahydropyrimidin-2(1*H*)-one were studied. DMF gave the best results (run 7): the reaction was almost completed with a reduced catalyst loading (5 mol %), and **3a** was isolated in 73% yield. At higher temperatures, the reaction time and the catalyst loading were reduced (runs 8 and 9). Therefore, the following optimal cyclization conditions were used to study the substrate scope: catalyst **1c**, DMSO (5 equiv), DMF solvent, 140 °C.

Various 1,6-diynes with aryl terminal groups were subjected to the optimal cyclization conditions (Table 2). Diynes **2b–d** with quaternary carbon tethers and tosylamide **2e** underwent furan annulation with 5 mol % catalyst, affording the corresponding bicyclic furans in ∼90% yields (runs 1–4). On the other hand, sulfone **2f** required 10 mol % catalyst because

Table 2. Scope of Diynes with Aryl Terminal Groups[a]



Run	Diyne		Time/h	Yield/%[b]
1		**2b**	4	**3b**, 90
2		**2c**	4	**3c**, 93
3		**2d**	5	**3d**, 94
4		**2e**	2	**3e**, 89
5		**2f**	4	**3f**, 87
6		**2g**	3	**3g**, 92
7		**2h**	1	**3h**, 94
8		**2i**	2	**3i**, 93
9		**2j**	1	**3j**, 93
10		**2k**	1	**3k**, 90
11		**2l**	2	**3l**, 57
12		**2m**	6	**3m**, 84
13		**2n**	12	**3n**, 64[c]
14		**2o**	12	**3o**, 70
15		**2p**	12	**3p**, 51[c]
16		**2q**	11	**3q**, 85

[a]**1c** [5 mol % (10 mol % for runs 5, 12–14, and 16; 20 mol % for runs 11 and 15)], **2** (0.3 mmol), DMSO (5 equiv), DMF (3 mL), 140 °C. [b]Isolated yields. [c]Yields of recovered starting materials were determined by ^{1}H NMR analyses: 6% for run 13 and 22% for run 15.

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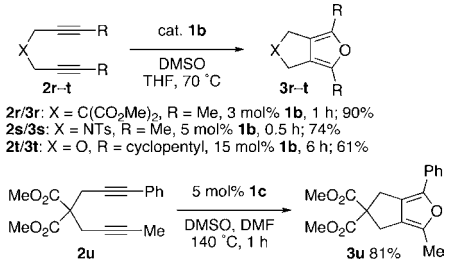
the reaction was sluggish (run 5). The desired **3f** was obtained in 87% yield, and its X-ray structure was determined [see the Supporting Information (SI)]. These results indicate that the Ru-catalyzed transfer oxygenative cyclization tolerates esters, ketones, nitriles, and sulfones.

Next, the influence of the terminal aryl moieties was investigated. Diynes **2g**–**j**, which have electron-donating methoxy or electron-withdrawing halogen substituents or both, were cleanly converted to **3g**–**j** in yields of >90% (runs 6–9). When substrates with strongly electron-withdrawing fluorine substituents were used, the reaction times were notably shortened (runs 7 and 9). Diyne **2k** with thiophene terminal groups underwent cyclization without any difficulty, giving a 90% yield of the interesting product **3k** having a thiophene–furan–thiophene sequence (run 10). The sluggish reaction of **2l** with ferrocenyl (Fc) terminal moieties required a **1c** loading of 20 mol % and gave the expected bis(ferrocenyl)furan **3l** in a moderate yield (run 11).

Moreover, 1,7-diynes also participated in the transfer oxygenative cyclization, albeit with increased catalyst loadings. Diyne **2m** with four ester substituents on the tether efficiently underwent oxygenative cyclization with a 10 mol % catalyst loading, affording **3m** with a fused six-membered ring in 84% yield (run 12). The corresponding diester **2n** and diol derivative **2o** were also subjected to similar conditions (runs 13 and 14); although these reactions were less efficient, the corresponding furans **3n** and **3o** were obtained in good yields (64 and 70%, respectively). Because the reaction of the parent **2p** with no substituent on the tether was very sluggish, the catalyst loading was increased to 20 mol %, which furnished **3p** in a moderate 51% yield. Furthermore, the desired tricyclic furan **3q** was obtained in a high yield (85%) because of the favorable conformational rigidity of the phenylene tether. These results imply that conformational restraint by the tether substituents is significant for the cyclization of 1,7-diynes. In contrast, 1,8-diynes failed to undergo transfer oxygenative cyclization under the optimal conditions.

Next, 1,6-diynes with terminal alkyl groups were examined as substrates (Scheme 3). Malonate-derived diyne **2r** was

Scheme 3. Synthesis of Furans from Diynes with Alkyl Terminal Groups



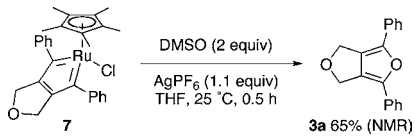
subjected to the above optimal reaction conditions, but the desired furan was obtained in a poor yield, probably because of the poor electron-donating ability of the $[CpRu]^+$ fragment toward the diyne bearing electron-donating methyl terminal groups. After reoptimization of the reaction conditions, we eventually found that the reaction with a 3 mol % loading of the more electron-rich complex **1b** in THF at 70 °C for 1 h afforded **3r** in 90% yield. This improvement is presumably due to the enhancement of oxidative cyclization of diyne **2r** with the electron-rich catalyst **1b**. Similarly, tosylamide analogue **2s** efficiently underwent oxygenative cyclization with 5 mol % **1b**, affording **3s** in 74% yield. Ether derivative **2t** featuring bulky cyclopentyl groups required a higher catalyst loading (15 mol %) and gave the desired bicyclic furan **3t** in 61% yield. The cyclization of diyne **2u** with both alkyl and aryl terminals was carried out using **1c** as the catalyst in DMF at 140 °C to obtain **3u** in 81% yield. In contrast, diynes with terminal alkynes were not compatible with this method.

Our intramolecular [2 + 2 + 1] cyclization has several synthetic advantages. The synthesis of oligoarylenes such as **6** via previous monocyclic furan annulations is difficult, but **6** can be selectively constructed in 87% yield from tetrayne **5** via the Ru-catalyzed double transfer oxygenative cyclization (Scheme 4). Such furan-containing oligoaryls are reported to be efficient hole-transporting materials.[10]

Scheme 4. Double Transfer Oxygenative Cyclization of Tetraynes

In regard to the mechanism of furan formation, the previous catalytic methods involve ketonic intermediates such as β,γ-unsaturated ketones and unsaturated 1,4-diketones that undergo subsequent cyclization under the influence of Cu(II) or Zn salts, respectively. In contrast, in our Ru-catalyzed reaction, furan ring formation is presumed to occur via ruthenacycle intermediates without extra metal catalysts or Brønsted/Lewis acids. To gain insight into this mechanism, we reacted isolated ruthenacyclopentatriene **7** with DMSO (2.0 equiv) in the presence of $AgPF_6$ (1.1 equiv) in THF at 25 °C for 0.5 h and obtained bicyclic furan **3a** in 65% NMR yield (Scheme 5). However, in the absence of the Ag salt, **3a** was scarcely formed within 1 h under the same conditions.

Scheme 5. Reaction of Ruthenacycle 7 with DMSO



These results imply that the reaction proceeds via cationic ruthenacycle intermediates (Figure 1a). A possible catalytic cycle starts with oxidative cyclization of diyne complex **8** to give bicyclic biscarbene **9** with an O-bound DMSO, which then undergoes rate-determining transfer oxygenation to produce keto carbene intermediate **10**. A related transfer oxygenation of a Fischer-type carbene complex with DMSO was reported by Casey and co-workers.[11] Subsequent cyclization of **10** involving the ketone carbonyl group and the remaining carbene carbon generates bicyclic furan complex **11**. Similar cyclizations of oxadienyl carbene complexes yielding furans have been proposed for different types of furan ring formations.[12]

The proposed mechanism was supported by preliminary density functional theory (DFT) calculations on a model system (Figure 1b and Figures S2 and S3 in the SI). The reaction starts with a delocalized ruthenacyclopentatriene complex with an O-bound DMSO (**A**). O-atom transfer from

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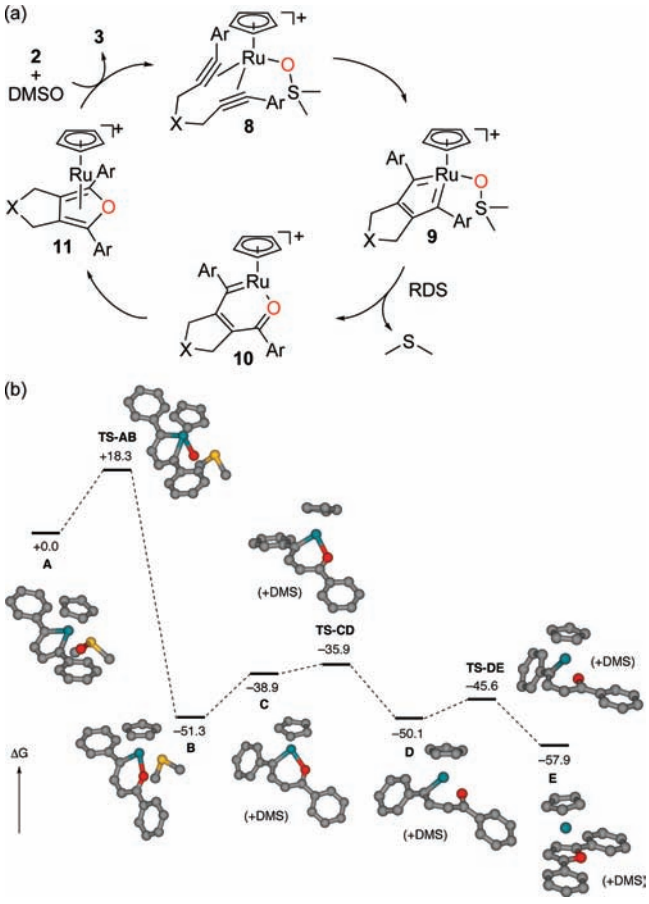

Figure 1. (a) Proposed mechanism. (b) Calculated energy surface with relative Gibbs free energies ΔG (kcal/mol) at 298 K.

DMSO to the carbene carbon of the ruthenacycle to give oxaruthenacyclohexatriene complex **B** with a DMS ligand occurs in a concerted manner (transition state **TS-AB**) with an activation barrier of $\Delta G^{\ddagger}$ = 18.3 kcal/mol, which is larger than that of the oxidative cyclization step ($\Delta G^{\ddagger}$ = 14.1 kcal/mol; Figure S3). After this rate-determining step, which is expected to be highly exergonic (ΔG = −51.3 kcal/mol), extrusion of the DMS ligand produces **C**, which is 12.4 kcal/mol higher in energy. Subsequent isomerization of **C** generates γ-keto carbene complex **D** via transition state **TS-CD** with a small barrier of $\Delta G^{\ddagger}$ = 3.0 kcal/mol. The final furan ring closure from **D** is expected to proceed via **TS-DE** with a similarly small activation barrier of $\Delta G^{\ddagger}$ = 4.5 kcal/mol. The formation of η^5-furan complex **E** (with Ru−O, Ru−Cα, and Ru−Cβ distances of 2.39, 2.35, and 2.32 Å, respectively) from **A** is highly exergonic (ΔG = −57.9 kcal/mol).

In summary, we have successfully developed a novel transfer oxygenative cyclization of diynes with DMSO catalyzed by cationic Ru complexes. For diynes with terminal aryl groups, $[CpRu(AN)_3]PF_6$ was the optimal catalyst, while those with terminal alkyl groups were effectively catalyzed by the corresponding Cp* complex. A mechanism for the formation of bicyclic furans was proposed on the basis of the results obtained by carrying out the stoichiometric reaction of a ruthenacyclopentatriene complex with DMSO and by performing DFT calculations of model ruthenacycles. This novel method is highly useful for the synthesis of bicyclic furans and is complementary to previous monocyclic furan formations.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, compound characterization data, a CIF file, and NMR spectra of the products. 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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