Ruthenium-Catalyzed Intramolecular Cyclization of 3-Butyne-1,2-diols into Furans

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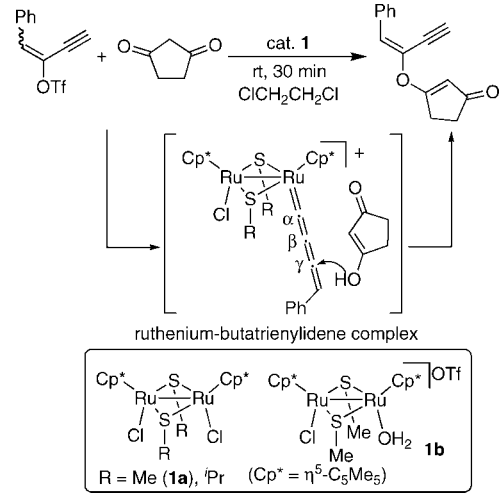
Summary: Ruthenium-catalyzed intramolecular cyclization of 3-butyne-1,2-diols affords the corresponding substituted furans in good to high yields. This catalytic reaction is proposed to proceed via ruthenium−allenylidene complexes as key intermediates.

Quite recently, we have found the novel ruthenium-catalyzed vinylic substitution reactions of vinylic trifluoromethanesulfonates with nucleophiles such as cyclic 1, 3-diketones and alcohols to give the corresponding vinylic-substituted products in good to high yields (Scheme 1).[1] This catalytic reaction is considered to be a new type of vinylic substitution reaction via ruthenium−butatrienylidene complexes as key intermediates[2] and to open up a further aspect of the chemistry of metal−cumulenylidene complexes, in addition to the rich chemistry of carbene,[3] vinylidene,[4] and allenylidene complexes.[5]

As an extension of our study, we attempted the ruthenium-catalyzed reactions of 3-butyne-1,2-diols with simple alcohols as nucleophiles, where the formation of vinylic ethers is expected from reactions of butatrienylidene complex intermediates generated from 3-butyne-1,2-diols with the alcohols. However, no formation of vinylic ethers was observed and instead furans, intramolecular cyclized products, were obtained unexpectedly. This result prompted us to investigate these reactions in detail. A preliminary result of this unpredicted formation of substituted furans is described here.

Heating of 1-phenyl-3-butyne-1,2-diol (**2a**) as a mixture of two diastereoisomers (*anti*-**2a**/*syn*-**2a** = 87/13) in ethanol (0.02 M) in the presence of 5 mol % of the methanethiolate-bridged diruthenium complex $[Cp^*RuCl(\mu_2\text{-}SMe)]_2$ ($Cp^* = \eta^5\text{-}C_5Me_5$; **1a**)[6] and 10 mol% of NH_4BF_4 at 60 °C for 2 h afforded 2-phenylfuran (**3a**) in 65% isolated yield (Scheme 2; Table 1, run 1). When the corresponding cationic diruthenium complex $[Cp^*RuCl(\mu_2\text{-}SMe)_2RuCp^*(OH_2)]OTf$ (**1b**; $OTf = OSO_2CF_3$)[7] was used in place of **1a**, a slightly lower yield of **3a** was obtained (Table 1, run 2). Separately, we confirmed that a mononuclear ruthenium complex such as $[CpRuCl(PPh_3)_2]$ ($Cp = \eta^5\text{-}C_5H_5$)[8] did not promote this cyclization effectively.

Scheme 1



Scheme 2

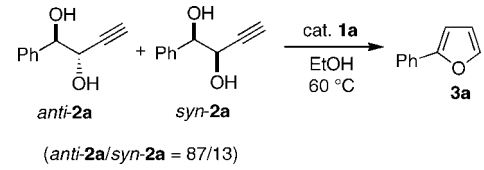


Table 1. Ruthenium-Catalyzed Cyclization of 1-Phenyl-3-butyne-1,2-diol (2a) To Form 2-Phenylfuran (3a)[a]

run	*anti*-**2a**/*syn*-**2a**	cat. (**1**)	solvent	*T* (°C)	time (h)	yield[b] (%)
1	87/13	**1a**	EtOH	60	2	65
2	87/13	**1b**	EtOH	60	2	57
3	>99/<1	**1a**	EtOH	60	2	62
4	>1/<99	**1a**	EtOH	60	2	65
5	87/13	**1a**	MeOH	60	2	59
6	87/13	**1a**	^{i}PrOH	60	2	49
7	87/13	**1a**	$ClCH_2CH_2Cl$	60	2	15
8	87/13	**1a**	EtOH	80	2	47
9	87/13	**1a**	EtOH	40	12	70

[a] All reactions of **2a** (0.30 mmol) were carried out in the presence of **1** (0.015 mmol) and NH_4BF_4 (0.030 mmol, 10 mol %) in solvent (15 mL). [b] Isolated yield.

Interestingly, intramolecular cyclization of diastereomerically pure *anti*-**2a**[9] and *syn*-**2a** gave **3a** in 62% and 65% isolated yields, respectively (Table 1, runs 3 and 4), indicating that the ratio of diastereoisomers in **1a** did not have any effect on the yield of **3a**.

Although **3a** was produced in methanol or 2-propanol as well with a slightly lower yield (Table 1, runs 5 and 6), the reaction did not proceed smoothly in other organic solvents such as 1,2-dichloroethane (Table 1, run 7). The corresponding oligomers were observed as side products when the

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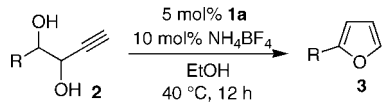
Scheme 3



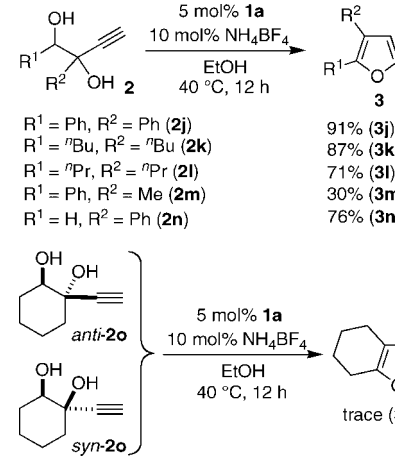
R = *p*-ClC$_6$H$_4$ (**2b**)	90% (**3b**)
R = *p*-BrC$_6$H$_4$ (**2c**)	86% (**3c**)
R = *p*-MeOC$_6$H$_4$ (**2d**)	72% (**3d**)
R = *p*-MeC$_6$H$_4$ (**2e**)	66% (**3e**)
R = 1-naphthyl (**2f**)	71% (**3f**)
R = cyclohexyl (**2g**)	46% (**3g**)
R = ^{n}C$_7$H$_{15}$ (**2h**)	66% (**3h**)

reaction was carried out at a higher temperature such as 80 °C (Table 1, run 8), while the reaction at a lower temperature such as 40 °C gave a higher yield of **3a** with a longer reaction time (Table 1, run 9).

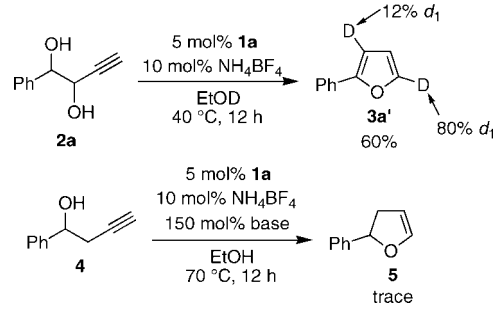
Next, cyclization of various 1-substituted 3-butyne-1,2-diols (**2b**−**h**) in the presence of 5 mol % of **1a** and 10 mol % of NH_4BF_4 was investigated at 40 °C for 12 h (Scheme 3). The corresponding 2-arylfurans (**3b**,**c**) were isolated in excellent yields when a halogen group such as a chloro or bromo moiety was introduced to the benzene ring of 1-aryl-3-butyne-1,2-diols (**2b**,**c**). A similar yield of the corresponding furans was achieved when an electron-donating group such as a methoxyl or methyl moiety is present at the benzene ring (**3d**,**e**). Intramolecular cyclization of 1-alkyl-3-butyne-1,2-diols (**2g**,**h**) afforded the corresponding 2-alkylfurans (**3g**,**h**) in 46% and 66% yields, respectively. On the other hand, no reaction occurred at all when 1,2,4-triphenyl-3-butyne-1,2-diol (**2i**) was used as a starting material, indicating that only 3-butyne-1,2-diols bearing a terminal alkyne moiety are available for the formation of furans.

Cyclization of 1,2-disubstituted 3-butyne-1,2-diols[10] (**2j**−**m**) also proceeded smoothly to give the corresponding 2,3-substituted furans in good to high yields (Scheme 4). Even when 1,2-diol without any substituents at the homopropargylic position (**2n**) was used, 3-phenylfuran (**3n**) was obtained in 76% yield. Unfortunately, no cyclization occurred with either *anti*- or *syn*-1-ethynylcyclohexane-1,2-diol[11] (*anti*-**2o** or *syn*-**2o**) under the same reaction conditions (Scheme 4).

Scheme 4



Scheme 5



To obtain more information on the reaction pathway, we investigated the cyclization of **2a** (*anti*-**2a**/*syn*-**2a** = 87/13) in ethanol-d_1, as shown in Scheme 5. Deuterated furan (**3a′**) was obtained in 60% isolated yield with 12% and 80% deuterium incorporation at the 3- and 5-positions, respectively. Some transition-metal complexes have been known to promote the intramolecular cyclization of homopropargylic alcohols such as 1-phenyl-3-butyn-1-ol (**4**) to give the corresponding dihydrofuran derivatives via metal−vinylidene complexes as key intermeidtaes.[12] When we attempted the cyclization of 1-phenyl-3-butyn-1-ol (**4**) in ethanol under the same reaction conditions, the corresponding cyclic compound **5** was not obtained, even in the presence of a base such as triethylamine, pyridine, diisopropylethylamine, and K_2CO_3, and unreacted **4** was recovered quantitatively. This is because the intermediate complex produced from **1a** and **4** may be too stable to carry out the catalytic reaction. In fact, a ruthenium−alkoxycarbene complex has previously been isolated as a stable complex from the reaction of [Cp*RuCl(μ_2-S^{i}Pr)]$_2$ with 3-butyn-1-ol via a ruthenium−vinylidene complex as an intermediate.[13]

By considering the above experimental results, a reaction pathway is proposed in Scheme 6. Initially, a vinylidene complex (**A**) is formed in the reaction of **1a** with **2a** in the presence of NH_4BF_4. Dehydration of the vinylidene complex **A** leads to an allenylidene complex (**B**), where tautomerization occurs to give a vinylic vinylidene complex (**C**).

(6) Diruthenium complexes such as **1a** have been found to have various catalytic activities toward substitution reactions of propargylic alcohols bearing a terminal alkyne moiety; for recent examples, see: (a) Nishibayashi, Y.; Milton, M. D.; Inada, Y.; Yoshikawa, M.; Wakiji, I.; Hidai, M.; Uemura, S. *Chem. Eur. J.* **2005**, *11*, 1433. (b) Yamauchi, Y.; Onodera, G.; Sakata, K.; Yuki, M.; Miyake, Y.; Uemura, S.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 5175. (c) Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 6488. (d) Matsuzawa, H.; Kanao, K.; Miyake, Y.; Nishibayashi, Y. *Org. Lett.* **2007**, *9*, 5561. (e) Daini, M.; Yoshikawa, M.; Inada, Y.; Uemura, S.; Sakata, K.; Kanao, K.; Miyake, Y.; Nishibayashi, Y. *Organometallics* **2008**, *27*, 2046. (f) Nishibayashi, Y.; Uemura, S. *Curr. Org. Chem.* **2006**, *10*, 135, and references therein. (g) Nishibayashi, Y.; Uemura, S. In *Comprehensive Organometallic Chemistry III*; Crabtree, R. H., Mingos, D. M. P., Eds.; Elsevier: Amsterdam, 2007; Vol. 11 pp 75−122, and references therein.

(7) Cationic diruthenium complexes such as **1b** were revealed to have a catalytic activity toward substitution reactions of propargylic alcohols bearing an internal alkyne moiety; see: (a) Inada, Y.; Nishibayashi, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 15172. (b) Nishibayashi, Y.; Inada, Y.; Yoshikawa, M.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1495. (c) Nishibayashi, Y.; Shinoda, A.; Miyake, Y.; Matsuzawa, H.; Sato, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1835.

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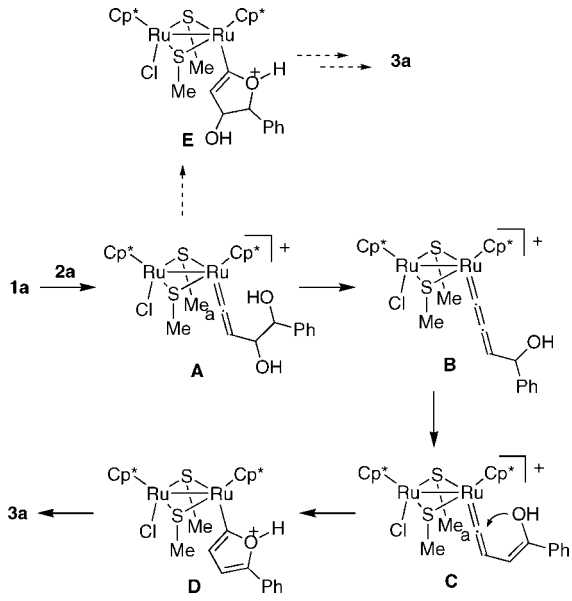
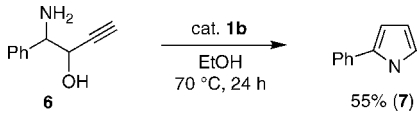
Scheme 6



Intramolecular nucleophilic attack of the hydroxy oxygen atom of the complex **C** results in the formation of **3a** via an alkenyl complex (**D**). Here, the direct intramolecular nucleophilic attack of a hydroxy oxygen atom of the vinylidene complex **A** might be possible as another reaction pathway. However, the result of no intramolecular cyclization of **4** to **5** may support the reaction pathway via ruthenium−allenylidene complex **B** and not via ruthenium−vinylidene complex **E** as key intermediates. This difference is considered to be due to the aromaticity of **3a**.

Finally, we applied this methodology to the formation of pyrroles via intramolecular cyclization of 1-amino-3-butyn-2-ol (**6**).[14] Heating of **6** in ethanol (0.02 M) in the presence of 10 mol % of **1b** at 70 °C for 24 h afforded 2-phenylpyrrole (**7**) in 55% yield (Scheme 7), indicating that our methodology provides a useful synthetic route to the formation of heteroaromatic compounds.[15]

Scheme 7



In summary, we have found that the ruthenium-catalyzed intramolecular cyclization of 3-butyne-1,2-diols gives the corresponding substituted furans in good to high yields. This catalytic reaction can be explained to proceed by proposing ruthenium−allenylidene complexes as key intermediates. Although many types of catalytic transformation to furans and pyrroles from alkyne and allene derivatives have been reported so far,[16,17] the novel synthetic and catalytic method described in this article may add another protocol for the formation of substituted furans and pyrroles by starting from readily available 3-butyne-1,2-diols and 1-amino-3-butyn-2-ol. It should be noted that similar routes have so far been developed using iodine[18] or some transition metals,[19] but with a reaction mechanism completely different from ours. Further work is currently in progress to broaden its synthetic applicability to natural products and develop other types of intramolecular cyclization.

Experimental Section

General Methods. The ^{1}H NMR (270 MHz) and ^{13}C NMR (67.8 MHz) spectra were recorded on a JEOL Excalibur 270 spectrometer using $CDCl_3$. Elemental analyses were performed at the Microanalytical Center of The University of Tokyo. GC-MS analyses were carried out on a Shimadzu GC-MS QP-5000 spectrometer. Mass spectra were measured on a JEOL JMS-700 mass spectrometer. All reactions were carried out under a dry nitrogen atmosphere. Solvents were dried by the usual methods and distilled before use. 3-Butyne-1,2-diols (**2**) and 1-amino-3-butyn-2-ol (**6**)[14] were prepared by the reaction of the corresponding aldehydes[9,20] with ethynylmagnesium bromide. The obtained furans (**3a**−**j**,**m**,**n**)[21] and 2-phenylpyrrole (**7**)[22] were known compounds.

Ruthenium-Catalyzed Intramolecular Cyclization of 3-Butyne-1,2-diols. A typical experimental procedure for the cyclization of diol **2a** in the presence of **1a** is described. To a solution of **1a** (9.6 mg, 0.015 mmol) and NH_4BF_4 (3.1 mg, 0.030 mmol) in anhydrous ethanol (15 mL) was added **2a** (48.7 mg, 0.30 mmol). After the reaction mixture was stirred at 40 °C for 12 h, the solvent was evaporated in vacuo. The crude material was purified by column chromatography (SiO_2, eluent hexane) to give **3a**[21a] (29.4 mg, 0.20 mmol, 70% yield) as a colorless oil.

2,3-Dibutylfuran (3k). Yield: 87%, of a colorless oil. ^{1}H NMR: δ 0.91 (t, J = 7.3 Hz, 6H), 1.18−1.63 (m, 8H), 2.32 (t, J = 7.44 Hz, 2H), 2.55 (t, J = 7.43 Hz, 2H), 6.17 (d, J = 1.8 Hz, 1H), 7.21 (d, J = 1.8 Hz, 1H). ^{13}C NMR: δ 13.8, 13.9, 22.3, 22.4, 24.4, 25.7, 30.8, 32.8, 111.3, 118.8, 139.6, 151.2. HRMS (EI): *m*/*z* calcd for $C_{12}H_{20}O$ [M] 180.1514, found 180.1507.

2,3-Dipropylfuran (3l). Yield: 71%, of a colorless oil. ^{1}H NMR: δ 0.92 (t, J = 7.4 Hz, 6H), 1.48−1.66 (m, 4H), 2.23 (t, J = 7.4 Hz, 2H), 2.53 (t, J = 7.4 Hz, 2H), 6.18 (d, J = 1.9 Hz, 1H), 7.22 (d, J = 1.9 Hz, 1H). ^{13}C NMR: δ 13.76, 13.85, 22.0, 23.7, 26.7, 27.9, 111.3, 118.8, 139.7, 151.2. HRMS (EI): *m*/*z* calcd for $C_{10}H_{16}O$ [M] 152.1201, found 152.1193.

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Supporting Information Available: CIF file giving crystallographic data for *anti*-**2o**. This material is available free of charge via the Internet at http://pubs.acs.org.

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