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Efficient Synthesis of Functionalized Furans via Ruthenium-Catalyzed Cyclization of Epoxyalkyne Derivatives

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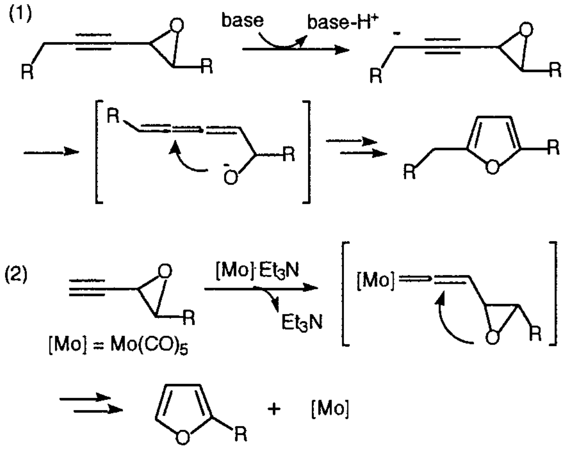
Abstract: Ruthenium catalyst TpRuPPh$_3$(CH$_3$CN)$_2$Cl is found to effect the cyclization of epoxyalkynes to furans in the presence of Et$_3$N. The reactions worked well for various epoxyalkynes with suitable oxygen and nitrogen functionalities with low loading of catalyst. It failed with disubstituted epoxyalkynes. The mechanism was elucidated by a deuterium labeling experiment that suggested that the mechanism involved a ruthenium−vinylidenium intermediate.

Furan is an important subunit in many naturally occurring compounds.[1] It is also an important reaction intermediate in organic synthesis.[2] The metal-catalyzed synthesis of furan derivatives has attracted considerable attention.[1−3] Several methods have been developed that focused exclusively on palladium catalytic systems including (1) cyclization of alkynones,[4] (2) coupling of propargyl carbonates with acetoacetates,[5] (3) coupling of aryl or allyl halides with allenyl ketones,[6a,b] and (4) addition of phenol to a tethered alkyne group.[6c,d] The synthesis of furans from allenyl ketones can also be achieved by Rh(I) or Ag(I) catalyst.[7] The direct transformation of γ-ethynylallyl alcohol to furan was catalyzed by a ruthenium or palladium catalyst.[8] Epoxyalkyne is easily prepared by epoxidation of the corresponding enyne, and one-step synthesis of furans from this substrate is a convenient and useful route. There are two known pathways for such transformations: (1) KH- or KOBu^t-catalyzed transformation via a cumulene anion[9] (Scheme 1, eq 1) and (2) Mo(CO)$_5$·Et$_3$N-catalyzed cyclization via molybdenum vinylidene species (Scheme 1).[10] The former is for use with an internal alkyne whereas the latter is suitable for a terminal alkyne. Although the molybdenum system can be performed under mild conditions, a high loading of catalyst (15 mol %) is required to complete the reaction.[9] In this study, we report an efficient ruthenium-catalyzed synthesis[11] of furan derivatives from various epoxyalkynes with suitable oxygen and nitrogen functionalities.

Scheme 1. Synthesis of Furans from Epoxyalkynes



Among various ruthenium complexes, we found that TpRuPPh$_3$(CH$_3$CN)Cl (Tp = trispyrazolylborate)[12] **(1a)** and TpRuPPh$_3$(CH$_3$CN)$_2$BF$_4$[13] **(1b)** effected the cyclization of epoxyalkyne **2**; the optimum conditions were given in Table 1. The reactions were performed by heating epoxide **2** (1.0 M) with catalyst **1a** or **1b** in CH$_2$ClCH$_2$Cl at 80 °C for 12 h (Table 1, entries 1−5). In the absence of base, compounds **1a** and **1b** did not show pronounced catalytic activities even though 10 mol % of these catalysts was employed. The catalytic activities of catalysts **1a** and **1b** were significantly enhanced in the presence of Et$_3$N. The desired furan **3** was obtained in

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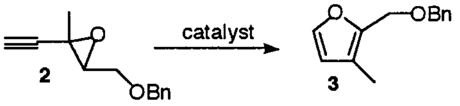
Table 1. Conditions for Ruthenium-Catalyzed Synthesis of Furans[a]



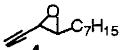
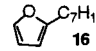
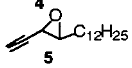
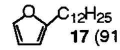
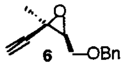
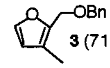
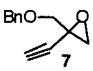
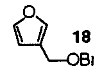
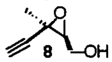
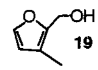
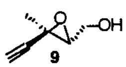
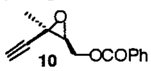
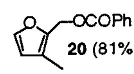
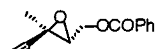
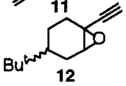
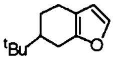
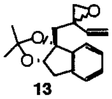
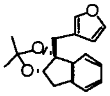
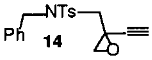
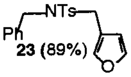
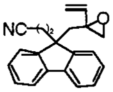
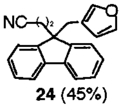
entry 1	catalyst	solvent	base	yields[e]
1	**1a** (10 mol%)	DCE[b]	—	48%
2	**1a** (10 mol%)	DCE	Et_3N (50 mol%)	91%
3	**1a** (2.0 mol%)	DCE	Et_3N (50 mol%)	91%
4	**1b** (10 mol%)	DCE	Et_3N (50 mol%)	30 %
5	**1b** (10 mol%)	DCE	—	5 %
6	**1a** (2.0 mol%)	CH_3CN[c]	Et_3N (50 mol%)	N.R.
7	**1a** (2.0 mol%)	EtOH[b]	Et_3N (50 mol%)	N.R.
8	**1a** (2.0 mol%)	THF[d]	Et_3N (50 mol%)	14%
9	$RuCl_2(PPh_3)_3$[f]	DCE	Et_3N (50 mol%)	49%
10	$CpRuCl(PPh_3)_2$	DCE	Et_3N (50 mol%)	5%
11	$TpRuCl(PPh_3)_2$	DCE	Et_3N (50 mol%)	N.R.
12	$TpRuCl(COD)_2$	DCE	Et_3N (50 mol%)	N.R.

[a] Concentration of compound **2** is prepared to be 1.0 M (a) 80 °C, 12 h for entries 1−5, 9−12. [b] 80 °C, 24 h. [c] 70 °C, 72 h. [d] Yields were reported after purification from TLC-plate. [e] 2.0 mol% catalyst was used in entries 9−12.

91% yield when 2.0 mol % of catalyst **1a** and Et_3N (50 mol %) were used. This catalytic reaction is highly dependent on the solvent. Catalyst **1a** became less active or actually inactive if CH_3CN (0% yield), THF (14% yield), or ethyl alcohol (0% yield) was used as the solvent (Table 1, entries 6−8). We also examined catalytic reactions for various ruthenium complexes to study the key factors in this catalytic activity. $RuCl_2(PPh_3)_3$ (2.0 mol %) gave furan **3** in 49% yield (Table 1, entry 9). On the other hand, it was much less active for $CpRuCl(PPh_3)_2$ (5% yield) and became inactive for $TpRuCl(PPh_3)_2$ and TpRu-$(COD)_2Cl$. The poor activities of $TpRu(PPh_3)_2Cl$ and $CpRuCl(PPh_3)_2$ suggest that basicity and a labile CH_3-CN in catalyst **1a** is crucial for cyclization.

We prepared a series of epoxyalkynes **4**−**15** bearing various functionalities. In a standard procedure, the substrate (1 M) was heated with catalyst **1a** in 1,2-dichloroethane (80 °C), with the optimum conditions given in Table 2. Most of the catalytic reactions were achieved with 1−2 mol % of catalyst **1a**. The reported yields of furans are after purification on a silica column. Entries 1 and 2 of Table 2 show the syntheses of 2-substituted furans **16** (84%) and **17** (91%), respectively, which were achieved by a small amount of catalyst **1a** (1 mol %). This catalyst works well with *cis*-epoxide **6** to give furan **3** in 71% yield and can also be used for the synthesis of 3-substituted furan **18** (67% yield). For substrates **8** and **9** which each have an alcohol functionality, furan **19** was obtained in respective yields of 86% and 83%. Similarly, the benzoate derivative **20** was produced efficiently from epoxides **10** and **11** (Table 2, entries 7 and 8). This catalytic reaction also works well for the synthesis of fused furan **21** from cyclohexene oxides **12**. We also prepared a complex molecule **13** to examine its feasibility in catalytic reaction, and the corresponding furan **22** was obtained in 78% yield. This reaction was extended to the synthesis of furan **23** (89% yield) bearing a tosylamino group (entries **11**). The catalytic activity of **1a** was completely inhibited by the nitrile group in compound **15**, even though 10 mol % of **1a** was used. The corresponding furan **24** was obtained in 45% yield by using ruthenium cationic species **1b** (10 mol %) in the presence of Et_3N (0.5 equiv).

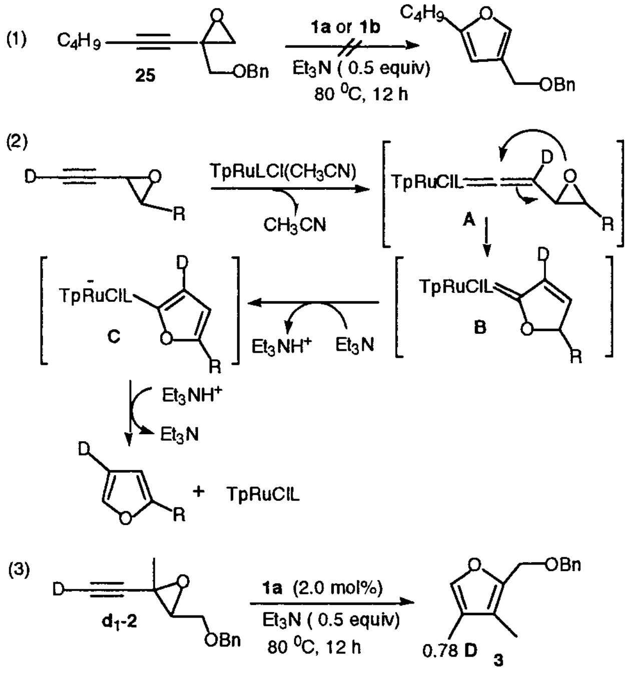
Table 2. Conditions for Ruthenium-Catalyzed Synthesis of Furans[a]

Entry	Epoxyalkyne[a]	conditions	furans (Yields)
1	 **4**	**1a** (1.0 mol%), 12 h Et_3N (50 mol%)	 **16** (84%)
2	 **5**	**1a** (1.0 mol%), 12 h Et_3N (50 mol%)	 **17** (91%)
3	 **6**	**1a** (2.0 mol%), 12 h Et_3N (50 mol%)	 **3** (71%)
4	 **7**	**1a** (2.0 mol%), 12 h Et_3N (50 mol%)	 **18** (67%)
5	 **8**	**1a** (2.0 mol%), 12 h Et_3N (50 mol%)	 **19** (86%)
6	 **9**	**1a** (2.0 mol%), 12 h Et_3N (50 mol%)	**19** (83%)
7	 **10**	**1a** (2.0 mol%), 12 h Et_3N (50 mol%)	 **20** (81%)
8	 **11**	**1a** (2.0 mol%), 12 h Et_3N (50 mol%)	**20** (88%)
9	 **12**	**1a** (2.0 mol%), 24 h Et_3N (50 mol%)	 **21** (88%)
10	 **13**	**1a** (5.0 mol%), 24 h Et_3N (50 mol%)	 **22** (78%)
11	 **14**	**1a** (2.0 mol%), 12 h Et_3N (50 mol%)	 **23** (89%)
12	 **15**	**1b** (10 mol%), 24 h Et_3N (50 mol%)	 **24** (45%)

[a] Concetration of epoxyalkynes was prepared at 1.0−1.1 M. [b] The yields of furans were reported after purification from the TLC plate.

While catalyst **1a** is not suitable for furan synthesis using disubstituted epoxyalkyne **25** under the same conditions; its terminal alkyne analogue **7** gave furan **20** in 67% yield (Table 2, entry 4). This suggests that the mechanism of cyclization (Scheme 2, eq 2) is analogous to that with $Mo(CO)_5{\cdot}Et_3N$ proposed by McDonald and Schlutz.[10] Several $TpRuL_2Cl$ complexes formed ruthenium-vinylidene complexes upon treatment with a terminal alkyne.[13] Intramolecular attack of species **A** at its central carbon gave ruthenium-furylidene **B**, and subsequently ruthenium-furyl anion **C**. The high basicity of species **C** is expected promote protonation with Et_3NH^+ to form furan and an active $TpRuCl(PPh_3)$ species. To confirm the reaction mechanism, we prepared a deuterated sample **d_1-2,** which was converted to **3** with deuterium (78%) at the C_3-carbon, consistent with the proposed mechanism. The bulky Tp ligand of **1a** has two important

Scheme 2. Mechanism for Catalytic Cyclization



features in this catalytic reactions:[12] (1) it facilitates dissociation of CH_3CN and (2) it increases the basicity of ruthenium center to offer stabilization of ruthenium–furylidene **B**.

In summary, we have reported a new ruthenium system to effect the cyclization of terminal epoxyalkynes to furan derivatives. This catalytic reaction requires less catalyst than the previous molybdenum system.[10] This reaction is compatible with oxygen and nitrogen functionalities tethered in complex molecules. Further modification of the catalyst and the application of this reaction are under investigation.

Experimental Section

Unless otherwise noted, all reactions were carried out under a nitrogen atmosphere in oven-dried glassware using standard syringe, cannula, and septa apparatus. Benzene, diethyl ether, tetrahydrofuran, and hexane were dried with sodium benzophenone and distilled before use. 1,2-Dichloroethane was dried over CaH_2 and distilled before use. $TpRuPPh_3(CH_3CN)Cl$,[11] $TpRuPPh_3(CH_3CN)_2PF_6$,[11] TpRu(COD)Cl,[12a] and $TpRu(PPh_3)_2Cl$[11] were prepared according to the methods in the literature. *trans*-3-Methyl-2-penten-4-yn-1-ol, *cis*-3-methyl-2-penten-4-yn-1-ol, $RuCl_2(PPh_3)_3$, and $CpRu(PPh_3)_2Cl$ were obtained commercially without purification. Compounds **8**, **9**, and **19** were reported previously.[9] Spectral data of compounds **4**–**7**, **10**–**18**, and **20**–**25** in repetitive experiments are provided in the Supporting Information.

Synthesis of *trans*-3-Benyloxymethyl-2-ethynyl-2-methyl-2-oxirane (2). To a THF solution (30 mL) of *trans*-3-methyl-2-penten-4-yn-1-ol (3.00 g, 31.2 mmol) was added NaH (1.24 g, 31.2 mmol), and the mixture was stirred for 4 h at 23 °C. To this solution was added benzyl bromide (5.31 g, 31.2 mmol), and the solution was stirred for 12 h at 25 °C before addition of a saturated NH_4Cl solution. The organic layer was extracted with diethyl ether, concentrated, and eluted through a short silica column (hexane/ether = 5/1) to give its benzyl derivative as a colorless oil (4.15 g, 22.5 mmol). To a CH_2Cl_2 solution (50 mL) of this benzyl ether (2.00 g, 10.7 mmol) was added *m*-chloroperoxybenzoic acid (3.70 g, 21.5 mmol), and this white suspension was stirred for 24 h at 26 °C before treatment with an aqueous $NaHCO_3$ solution. The organic layer was extracted with diethyl ether, concentrated, and eluted through a basic alumina column with diethyl ether as the eluent affording the epoxide **2** (1.52 g, 7.50 mmol) as a colorless oil: IR (neat) 2208 (m), 1610 (w); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.26 (5 H, m, Ph), 4.56 (2 H, ABq, $J = 12.0$ Hz), 3.64 (1H, dd, $J = 11.2, 5.6$ Hz), 3.53 (1H, d, $J = 11.2, 5.6$ Hz), 3.40 (1H, t, $J = 5.6$ Hz), 2.29 (1H, s), 1.47 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 128.4, 127.8, 83.6, 73.3, 70.2, 67.5, 62.2, 49.9, 18.3; HRMS calcd for $C_{13}H_{14}O_2$ 202.0944, found 202.0935.

Experimental Procedures for Catalytic Reactions. Synthesis of 3-Benzyloxymethyl-3-methylfuran (3). To a dichloroethane (0.30 mL) solution of epoxide **2** (100 mg, 0.49 mmol) were added $TpRuCl(PPh_3)(CH_3CN)Cl$ (6.47 mg, 0.010 mmol) and Et_3N (25 mg, 0.25 mmol). The mixture was heated at 80 °C for 12 h. The solution was concentrated and eluted through a silica column to afford compound **3** as a colorless oil (91 mg, 0.45 mmol): IR (neat) 2210 (m), 1608 (w), 1600 (w); ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (1H, s), 7.31–7.28 (5 H, m, Ph), 6.22 (1 H, s), 4.53 (2 H, s), 4.46 (2 H, s), 2.03 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 142.0, 138.4, 128.6, 128.0, 127.8, 119.2, 113.1, 71.9, 62.0, 49.9, 10.0; HRMS calcd for $C_{13}H_{14}O_2$ 202.0944, found 202.0941.

Acknowledgment. Financial support of this work by the National Science Council, Taiwan, is gratefully acknowledged.

Supporting Information Available: Spectral data of compounds **4**–**7**, **10**–**18**, and **20**–**25** in repetitive experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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