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# Unexpected C–C bond cleavage of epoxide motif: Rhodium(I)-catalyzed tandem heterocyclization/[4 + 1] cycloaddition of 1-(1-alkynyl)oxiranyl ketones†

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**A rhodium(I)-catalyzed tandem heterocyclization and formal [4 + 1] cycloaddition of 1-(1-alkynyl)oxiranyl ketones was developed, which provides a general, efficient and practical route to highly substituted furo[3,4-b]furan-3(2*H*)-ones, wherein the epoxide motif undergo unexpected C–C bond cleavage rather than the classical C–O bond cleavage.**

Transition metal-mediated C–C bond activation has received much attention in recent years.[1] There have been lots of reports about metal-catalyzed C–C bond cleavage among the small carbocyclic compounds such as cyclobutanes,[2] cyclobutanones[3] and their oxime derivatives,[4] cyclobutanols,[5] cyclobutenediones,[6] cyclopropanes,[1h,i,7] methylenecyclopropanes,[1j,8] cyclopropanols,[9] and cyclic 2-azidoalcohol derivatives.[10] In contrast, the metal-catalyzed selective C–C bond cleavage of small heterocyclic compounds is rarely explored,[11] since the carbon-heteroatom bond is easier to break.

Epoxides, the highly strained three membered ethers, have been extensively used as building blocks in organic synthesis. However, the dominant chemistry of epoxides is ring opening *via* C–O bond cleavage.[12] For example, alkynyl oxirane scaffold has been reported by Murakami and co-workers to react with arylboronic acids in the presence of rhodium catalyst leading to α-allenols *via* the C–O bond cleavage.[13i] The metal-catalyzed carbonylation of simple epoxide with CO generally undergo a C–O bond insertion to afford β-lactones.[13] Recently, Liu and his co-workers have explored a very impressive $Co_2(CO)_8$-mediated tandem [5 + 1]/[2 + 2 + 1] cycloadditions of *cis*-epoxy eneynes, leading to tricyclic δ-lactones in high yields, in which the ring opening of epoxide mode is still C–O bond cleavage.[13h] Very recently, we also developed a rhodium-catalyzed tandem carbonylative cyclization reaction of 1-(1-alkynyl)cyclopropyl ketones to afford highly substituted 5, 6-dihydro-cyclopenta[*c*]furan-4-ones.[14a] During this study and as a continuation of our ongoing efforts to develop rhodium-catalyzed reactions,[14] we became interested in the chemistry of 1-(1-alkynyl)oxiranyl ketones **1** (such as **1a**),[15] which is readily available from the corresponding 2-(1-alkynyl)-alk-2-en-1-ones *via* stereoselective epoxidation. It is envisaged that under the catalysis of rhodium complex, ketone **1a** might undergo a tandem heterocyclization and formal [4 + 1] cycloaddition to produce bicyclic lactone **2a** *via* C–O bond cleavage of the epoxide motif. Herein we want to document an efficient rhodium-catalyzed tandem heterocyclization/formal [4 + 1] cycloaddition of 1-(1-alkynyl) oxiranyl ketones *via* an unexpected C–C bond cleavage of epoxide motif, which provides an rapid access to highly substituted furo[3,4-b]furan-3(2*H*)-ones.

We began our study by examining of (1-alkynyl)oxiranyl ketone **1a** with CO under the catalysis of various rhodium catalysts (Table 1). The reaction did not occur (Table 1, entry 1) under normal conditions (1 atm of CO (balloon), DCE, 70 °C) using a $[Rh(CO)_2Cl]_2$ catalyst, which is the commonly used and most effective catalyst in rhodium-catalyzed reactions. Fortunately, it was found that the reaction proceeds smoothly under the catalysis of 5 mol% of $[RhCl(CO)(PPh_3)_2]$, affording 70% yield of furo[3,4-b]furan-3(2*H*)-one **3a** rather than the expected bicyclic lactone **2a** after 12 h, indicating a novel unexpected C–C bond cleavage of epoxide motif was involved (Table 1, entry 2). Different solvents (Table 1, entries 3–5) and silver salts (Table 1, entries 6–7) such as $AgSbF_6$ and AgOTf were further tested, but failed to improve the yield. The reaction did not occur at lower temperature (Table 1, entry 8). A mixture of $CO/N_2$ (1/4) gas led to a trace amount of product (Table 1, entries 8–9). The oftused catalyst $[Rh(COD)Cl]_2$ itself failed to catalyze this reaction either (Table 1, entry 10). However, the combination of 1 : 1 ratio of $[Rh(COD)Cl]_2$ with ligands S-Phos (**L1**), Ruphos (**L2**) or Davephos (**L3**) resulted in excellent yields (Table 1, entries 11–13). Among which S-phos (**L1**) derived rhodium catalyst gave a quantitative yield. Interestingly, when the ratio of rhodium and **L1** was 1 : 2, the reaction was slowed down, affording the desired product in only 51% NMR yield (Table 1, entry 14).

Under the optimal reaction conditions, a wide variety of 1-(1-alkynyl)oxiranyl ketones **1** were examined and the results are summarized in Table 2. The ketone substituent $R^1$ can be either an aromatic or alkyl group. For those substrates with aromatic $R^1$, the reactions normally gave the corresponding

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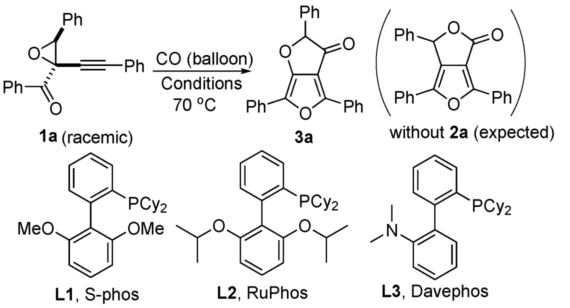
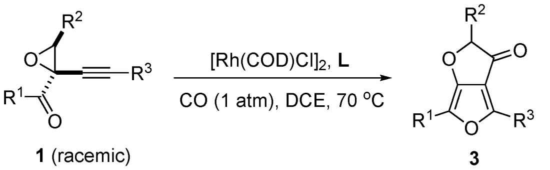
**Table 1** Optimization of reaction conditions[a]



| Entry | Conditions | $T$ (h) | Yield (%)[b] |
|---|---|---|---|
| 1 | $[\{Rh(CO)_2Cl\}_2]$, DCE | 12 | NR |
| 2 | $[RhCl(CO)(PPh_3)_2]$, DCE | 12 | 78(70) |
| 3 | $[RhCl(CO)(PPh_3)_2]$, THF | 24 | <5 |
| 4 | $[RhCl(CO)(PPh_3)_2]$, $CH_3CN$ | 18 | 10 |
| 5 | $[RhCl(CO)(PPh_3)_2]$, Toluene | 12 | NR |
| 6 | $[RhCl(CO)(PPh_3)_2]/AgSbF_6$ (1 : 1), DCE | 10 | 21 |
| 7 | $[RhCl(CO)(PPh_3)_2]$/AgOTf (1 : 1), DCE | 10 | <5 |
| 8[c] | $[RhCl(CO)(PPh_3)_2]$, DCE | 24 | NR |
| 9[d] | $[RhCl(CO)(PPh_3)_2]$, DCE | 36 | <5 |
| 10 | $[Rh(COD)Cl]_2$, DCE | 12 | NR |
| 11 | $[Rh(COD)Cl]_2$/**L1**, (1 : 1), DCE | 11 | 100(99) |
| 12 | $[Rh(COD)Cl]_2$/**L2**(1 : 1), DCE | 13 | 98(90) |
| 13 | $[Rh(COD)Cl]_2$/**L3** (1 : 1), DCE | 40 | 99(94) |
| 14 | $[Rh(COD)Cl]_2$/**L1**(1 : 2), DCE | 36 | 51 |

[a] Unless otherwise noted, reactions were performed with 0.4 mmol of **1a** and 5.0 mol% of catalysts in DCE at 70 °C. [b] NMR yield, the number in the parentheses is the isolated yield. [c] 60 °C. [d] 1 atm of mixture gas ($CO/N_2$ = 1 : 4) was used.

**Table 2** Scope of 1-(1-alkynyl)oxiranyl ketones **1**[a]



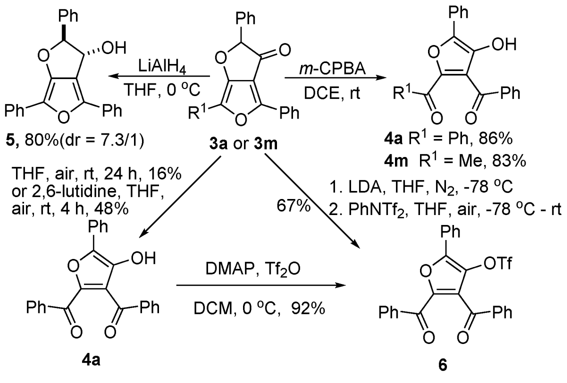
| Entry | $R^1/R^2/R^3$ (**1**) | $T$ (h) | Yield[b] of Product (%) |
|---|---|---|---|
| 1 | Ph/4-$MeOC_6H_4$/Ph (**1b**) | 12 | **3b** (72) |
| 2 | Ph/4-$ClC_6H_4$/Ph (**1c**) | 17 | **3c** (91) |
| 3 | Ph/1-naphthyl/Ph (**1d**) | 22 | **3d** (81) |
| 4 | Ph/styryl/Ph (**1e**) | 13 | **3e** (58) |
| 5 | Ph/Ph/4-$MeOC_6H_4$ (**1f**) | 11 | **3f** (95) |
| 6 | Ph/Ph/3,5-$(CF_3)_2C_6H_4$ (**1g**) | 40 | **3g** (86) |
| 7 | Ph/Ph/1-naphthyl (**1h**) | 40 | **3h** (90) |
| 8 | Ph/Ph/*n*-Bu (**1i**) | 48 | **3i** (69) |
| 9 | Ph/Ph/Cyclohexenyl (**1j**) | 11 | **3j** (88) |
| 10 | 4-$MeOC_6H_4$/Ph/Ph (**1k**) | 16 | **3k** (79) |
| 11 | 4-$ClC_6H_4$/Ph/Ph (**1l**) | 17 | **3l** (98) |
| 12[c] | Me/Ph/ Ph (**1m**) | 18 | **3m** (86) |
| 13[c] | Me/Ph/4-$MeOC_6H_4$ (**1n**) | 36 | **3n** (67) |
| 14[c] | Me/Ph/cyclohexenyl (**1o**) | 42 | **3o** (58) |
| 15[c] | Me/4-$ClC_6H_4$/Ph (**1p**) | 36 | **3p** (61) |

[a] Unless otherwise noted, reactions were performed with 0.4 mmol of **1** and 5.0 mol% of $[Rh(COD)Cl]_2$/**L1**(1 : 1) in the presence of 1 atm of CO (balloon) in DCE at 70 °C. [b] Isolated yields. [c] 10.0 mol% of $[Rh(COD)Cl]_2$/**L3** were used.

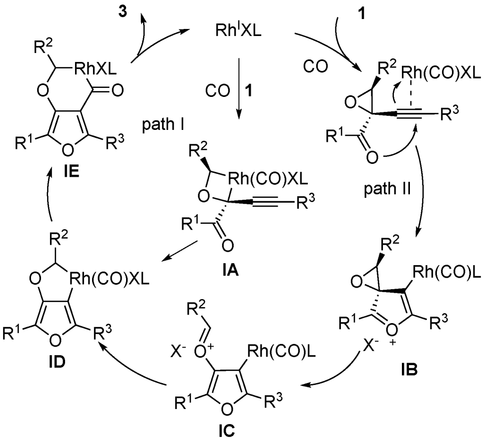
cycloadducts in good to excellent yields (Table 2, entries 1–11); for alkyl-substituted substrates, the reactions required higher catalyst loading (10 mol% of 1 : 1 ratio of $[Rh(COD)Cl]_2$/**L3**) (Table 2, entries 12–15), in which the relatively lower yields resulted from the air sensitivity of the products during the purification by column chromatography. Substituent $R^2$ on the epoxide moiety can be either aromatic or styryl group, producing the corresponding products in moderate to excellent yields (Table 2, entries 1–4). For example, the reaction of ketone **1e** with a styryl group proceeded smoothly to afford **3e** in 58% yield (Table 2, entry 4), which can readily undergo further functional group transformation. Substituent $R^3$ groups on the alkyne moiety can be aromatic, alkenyl and alkyl groups and moderate to excellent yields of the products can be obtained in the reactions (Table 2, entries 5–10 and 13–14).

Synthetic applications of the products were showcased by the conversion of the representative **3a** and **3m** (Scheme 1). Treatment of **3a** and **3m** by 1.1 equiv. of *m*-CPBA in DCE at r.t. gave the corresponding tetrasubstituted furans **4a** and **4m** in 86% and 83% yields, respectively. Interestingly, **3a** can be oxidized by the air slowly and the presence of 2,6-lutidine can accelerate this transformation due to the enole form which will make the whole system be more electron-rich.[17] It is noteworthy that on treatment of **3a** with LDA followed by $PhNTf_2$ in THF, a tetrasubstituted furan-3-yl triflate **6** could be obtained rather than the corresponding heterobicyclic furo[3,4-b]furan-3-yl triflate. Although we can see a new dot in the TLC plate during the reaction, attempts to isolate this intermediate failed as it was quickly to be oxidized by air during the work-up.[17] Product **6** can also be obtained in excellent yield by an alternative more simple operation ($Tf_2O$, $Et_3N$, and cat. DMAP). The structure of **4m** was established by spectroscopic analysis and further confirmed by single-crystal X-ray analysis.[16] 2,3-Dihydrofuro[3,4-b]furan-3-ol **5** can be obtained in 80% yield from **3a** by $LiAlH_4$ reduction in THF.

Two plausible reaction pathways are depicted in Scheme 2. In path I, chemoselective oxidative addition of the C–C bond of epoxy motif of 1-(1-alkynyl)oxiranyl ketone **1** would generate rhodaoxetane **IA**, which would undergo a rapid cycloisomerization to form intermediate **ID**. Insertion of carbon monoxide generates fused furan derivative rhoda-pyranone **IE**, followed by reductive elimination to furnish the heterobicyclic product **3** and regenerate the rhodium catalyst. An alternative pathway is shown as path II, The rhodium(I) coordination of the triple bond of **1** enhances the electrophilicity of alkyne. Subsequent nucleophilic attack of the carbonyl oxygen to



**Scheme 1** Synthetic applications of representative **3a** and **3m**.



**Scheme 2** Plausible mechanism.

the rhodium (I)-activated alkyne would form the oxonium-containing vinyl-rhodium intermediate **IB**, which would then undergo C–C bond cleavage to generate intermediate **IC**. Subsequent cyclometallation would lead to intermediate **ID**, which could undergo the same process to give the heterobicyclic product **3** as was shown in path I.

In summary, we have demonstrated a rhodium(I)-catalyzed tandem heterocyclization and formal [4 + 1] cycloaddition reaction of 1-(1-alkynyl)oxiranyl ketones, leading to highly substituted furo[3,4-b]furan-3(2*H*)-ones in moderate to excellent yields. It is noteworthy that this reaction represents the first example of rhodium-catalyzed C–C bond cleavage of epoxide instead of the well known C–O bond cleavage process. This new approach can be successfully extended to construct other various heterobicyclic frameworks. Further studies on the reaction scope, mechanism, and synthetic applications of this new process are being pursued in this lab.

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16 CCDC 796889 (**4m**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge form www.ccdc.cam.ac.uk/ data_request/cif.

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