Cyclization by Catalytic Ruthenium Carbene Insertion into sp\(^3\) C–H Bonds

Fermin Cambeiro, Susana López, Jesús A. Varela, and Carlos Saá*

Novel reactions that can selectively functionalize carbon-hydrogen bonds are very important because they offer new strategic approaches in synthesis.[1] A remarkable methodology for such carbon-hydrogen functionalization involves the insertion of metal carbenes into C–H bonds.[2] The regioselectivity in these C–H insertions is governed by electronic, steric and conformational factors.[3] Typically, in non-constrained systems, metal-catalyzed intramolecular C–H insertion reactions predominantly afford five-membered rings (1,5-insertions).[2,4] Formation of lower and higher rings is achieved only when geometrical constraints or activated C–H bonds are involved.[5] Usually, Rh[6]– and Cu[7]-catalyzed C–H insertions have shown amazing versatility in both intramolecular and intermolecular reactions, but it would be a challenging goal to discover other metals and tethers that facilitate the construction of rings by C\(^sp^3\)-H functionalization. Recently, special attention has been paid to Pt[8]– and Au-catalyzed[9] intramolecular coupling between terminal unactivated alkynes and sp\(^3\) C–H bonds in alkenyl ethers and amines to produce complex spiro or fused bicyclic systems in a tandem 1,5-hydride shift/cyclization sequence.[10] The above methods require temperatures as high as 100–120 °C for good performance and Pt only allows the formation of 5-exo methylene bicyclic structures. We report herein a mild procedure based on a novel tandem Ru-catalyzed carbene addition to terminal alkynes/insertion of C\(^sp^3\)-H bonds in alkenyl acetals, ethers and amines to form complex spiro and fused bicyclic structures in 1,5- and 1,6-hydride shift/cyclization sequences (Scheme 1).[11]

Cyclization of dioxolane 1a was the first reaction examined under various catalytic conditions (Table 1). After some preliminary experimentation,[12] the well-known Dixneuf’s conditions for the preparation of Ru carbenes starting from alkynes were employed.[13] Thus, a 1,5-hydride shift/cyclization sequence to give the functionalized spiro[5,5] compound 2a gave a moderate yield of 40% on stirring at 60 °C a dioxane solution of 1a (0.15 M) in the presence of 1 equiv of N2CHTMS (2M in hexanes) and 10 mol% Cp*Ru(cod)Cl as catalyst (entry 1), with the linear hydroxyester 3a being the major isolated product in 50% yield. Lower overall yield and similar amounts of 2a and 3a were obtained when the reaction was performed in dioxane at rt (entry 2). Gratifyingly, the desired spiro compound 2a or its desilylated analogue 2a’[13e,g] were isolated in fairly good yields (66-80%) when the reactions were carried out in diethyl ether or MeOH at rt (entries 3 and 4).[14] However, other typical solvents like THF and toluene gave either lower yields and/or longer reaction times (entries 5 and 6). Changes in the electronic and steric nature of the neutral Ru(II) catalyst on using CpRu(cod)Cl strongly affected the course of the reaction by increasing the time duration and decreasing conversion and yield (entry 7).[15]

More challenging substituted dioxolanes 1 were also examined (Table 2). Thus, spiro compound 2b was obtained in low yield when the formation of the putative Ru carbene was hindered by a C-sp carbene in dioxolane 1b (Table 2, entry 1). The nature of Z (see Scheme 1) had a significant effect on the course of the reaction,[16] with hydroxyester 3e the major isolated product in the case of 1c, Z = (CH\(_2\)O)\(_2\)CMe\(_2\) (Table 2, entry 2).[17] The course of the reaction was also influenced by stereoelectronic effects on the activated C–H bond.[18] Thus, rigid cyclic acetal 1a afforded a higher yield of spiro compound 2a (Table 1, entry 3) in comparison to the linear acetals 1d and 1e (Table 2, entries 3 and 4). Gratifyingly, a diastereoselective C-H activation of ethers took place to give smoothly the
corresponding functionalized cyclic compounds. Thus, cyclization of acyclic ether 5a and cyclic tetrahydrofuranyl and tetrahydropropenyl ethers 5b\(^{[19]}\) and 5c gave the corresponding \(\text{trans}\)-homolytic ether 6a and 1-oxaspiro[4,4]nonane and 6-oxaspiro[4,5]decanes 6b and 6c, respectively, as one single (or major) diastereoisomer in fairly good isolated yields (Table 2, entries 5, 6 and 8). The presence of an ether to activate the Csp3–H for cyclization is mandatory since the hydrocarbon 7a was totally recovered under all conditions tried (Table 2, entry 9). Note also the dramatic effect of the ring size of the cyclic ether on the reaction time (20 min vs 12 h), which stresses the crucial role of steric hindrance in the reaction (Table 2, entries 6 and 8). By contrast, when electron-poor N\(\text{NCH}^+\text{CO}_2\text{Et}\) was used instead N\(\text{NCHTMS}\), no diastereoselective cyclization of 5b occurred giving rise to the corresponding spiro derivative 6b\(^i\) in lower yield (Table 2, entry 7).\(^{[13]}\) Interestingly, pyrrolidine 8a also underwent smooth cyclization to give 1-azaspiro[4,4]nonane 9a as a single diastereomer in rather good yield (Table 2, entry 10).

We next turned our attention to the reactivity of C(3)-linked heterocycles such as tetrahydrofurans 10a,b and piperidine 11a (Table 3).\(^{[8,9]}\) To our delight, fused bicyclic tetrahydrofuran 12a and piperidine 13a were obtained in fairly good yields (entries 1 and 2), thus showing the efficient functionalization of secondary C–H bonds \(\alpha\) to a heteroatom (O, N). Remarkably, a single diastereoisomer of bicyclic piperidine 13a containing three consecutive stereocenters was obtained.

Gratifyingly, a new 1,6-hydride shift/cyclization process took place when dioxolane 14a was smoothly converted into the 1,4-dioxaspiro[4,5]decanes 15a in excellent yield (Table 4, entry 1). This new tandem process also efficiently occurred in the case of substituted dioxolane 14b and dioxolanes 14c,d to afford the corresponding 1,4-dioxaspiro[4,5]decanes 15b–d in relatively good yields (entries 2–4). Comparison of cyclizations of dioxolanes 1c (Table 2, entry 2) and 14c (Table 4, entry 3) shows the easier formation of the 1,4-dioxaspiro[4,5]decane 15c vs 1,4-dioxaspiro[4,4]nonane 2c, which clearly indicates that the conformation of the metallic intermediate plays a definitive role during the course of the reaction.\(^{[20]}\)

In an effort to gain further insights into the mechanism of these tandem sequences, a series of deuterium labeling experiments were conducted. We focused on the cyclization of deuterium labeled tetrahydrofuran ethers 5b–d\(^i\) and 5b–d\(^{ii}\) (Scheme 2).

In the reaction of 5b–d\(^i\), the deuterium atom in the position \(\alpha\) to the oxygen was completely transferred to the allylic position of 1-oxaspiro[4,4]nonane 6b–d\(^i\), thus supporting a mechanism involving a hydride transfer. On the other hand, the cyclization of deuterated alkyne 5b–d\(^{ii}\) afforded the 1-oxaspiro[4,4]nonane 6b–d\(^{ii}\) in which the deuterium was incorporated selectively at the \(\beta\) vinylic position. In addition, deuterium was not incorporated into the cyclized product 6b when the reaction of 5b was conducted in THF\(-d_8\).\(^{[21,22]}\)

Although more mechanistic probes would be desirable to clarify the role of the solvent in the catalytic cycle, the labeling studies strongly support the initial mechanistic hypothesis shown in Scheme 3. The complex Cp*\(\text{Ru}^+\text{cod}^+\)Cl easily loses its cod ligand in the presence of alkyn 1 and N\(\text{NCHSiMe}_3\) leading to a ruthenium carbene species 1\(^{[10,11]}\).\(^{[23]}\) Oxidative coupling to give a metallacylobutene\(^{[24]}\) followed by opening of this species would lead to the ruthenium vinyl carbene 11.\(^{[25]}\)

The electrophilic Ru carbene could induce a 1,5-hydride shift that would lead to the formation of a transient oxonium ion, which would in turn interact with the nucleophilic ruthenium to afford the metallacycle 111. Final reductive elimination would give rise to the spiro compound 2 with recovery of the catalytic Ru(II) species in the presence of N\(\text{NCHSiMe}_3\). A similar catalytic pathway could be envisaged for the 1,6-hydride shift/cyclization sequence leading to the 1,4-dioxaspiro[4,5]decanes 15. For dioxolanes 1, competitive opening of metallacycle 111 assisted by the heteroatom (dioxane at 60 ºC in 1a or by geometrical requirement in 1c) followed by hydrolysis of the resulting intermediate could explain the formation of major hydroxysters 3, as found experimentally.

In summary, we have shown that a series of readily available linear alkynyl acetals, ethers and amines can be transformed into spirobicycles and fused bicyclic structures by means of a Ru-catalyzed intramolecular carbene insertion of Csp3–H bonds. These cyclizations, which could be applied mainly to terminal alkynes, allow the efficient conversion of secondary or tertiary sp\(^3\) C–H bonds into new C–C bonds under practical conditions. Deuterium labeling experiments support a mechanistic hypothesis involving an initial 1,5- or 1,6-hydride shift onto a Ru vinyl carbene followed by cyclization. This investigation opens up opportunities for the development of new Ru-catalyzed cyclizations and we are currently studying this area in our laboratories.

**Experimental Section**

Typical experimental procedure: In a round-bottomed flask containing 1a (70 mg, 0.273 mmol, 1 eq), N\(\text{NCHTMS}\) (0.136 mL, 0.273 mmol, 1 eq, 2M in hexane) in diethyl ether (2 mL) was added the catalyst Cp*\(\text{Ru}^{+}\text{cod}^+\)Cl (10 mg, 0.027 mmol, 0.1 eq). The resulting solution was stirred at room temperature for 20 min until disappearance of starting material (TLC, GC/MS). The reaction was quenched with a saturated aqueous solution of NH\(_4\)Cl (2 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic layers were dried over anhydrous Na\(_2\)SO\(_4\) and evaporated to dryness. The crude residue was purified by column chromatography on silica gel using a mixture of hexane/EtOAc (8:2) as eluent to afford 2a (74 mg, 80%) as a yellowish oil. 1H NMR (400 MHz, CDCl\(_3\), δ (ppm)): 5.95 (dd, J=18.7, 7.2 Hz, 1H), 5.77 (d, J=18.7 Hz, 1H), 3.93-3.80 (m, 4H), 3.71 (s, 6H), 2.80-2.72 (m, 1H), 2.56-2.42 (m, 3H), 2.25 (dd, J=13.4, 12.2 Hz, 1H), 0.02 (s, 9H), 13C NMR, DEPT (100 MHz, CDCl\(_3\), δ (ppm)): 172.4 (CO), 171.8 (CO), 142.8 (CH), 133.7 (CH), 116.4 (C), 65.4 (CH\(_2\)), 65.0 (CH\(_3\)), 55.0 (C), 53.0 (CH), 52.9 (CH\(_3\)), 52.8 (CH\(_3\)), 43.3 (CH\(_2\)), 36.8 (CH\(_3\)), -1.3 (3xCH\(_3\)). MS, m/z (% relative


A 4:1 diastereomeric mixture of E isomers is obtained in the three experiments (see Table 2, entry 6), only the major diastereomer is shown. See Supporting Information for details.

In addition, cyclization of acetal 1a in CD$_3$OD gave rise to monodeuterated 2a’ as a 1:1 mixture of E and Z isomers (60% combined yield). See Supporting Information for details.


a) For the stereochemical course of opening of metallacyclobutene intermediates, see ref 13g; b) For a review on ruthenium vinyl carbene intermediates in enyne metathesis, see: S. T. Diver, Coord. Chem. Rev. 2007, 251, 671-701.

Scheme 1. Ru-Catalyzed Transformation of Alkynyl Derivatives in Spiro and Fused Bicyclic Structures.

Scheme 2. Deuterium Labeling Experiments.

Scheme 3. Mechanistic Hypothesis for the Ru-catalyzed Intramolecular Carbene Insertion of C$_{sp3}$–H Bonds.

Table 1. Optimization of Ru-catalyzed 1,5-Hydride Shift/Cyclization Sequence in Alkynyl Dioxolane 1a.[H]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>t (min)</th>
<th>2a (%)</th>
<th>3a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[h]</td>
<td>dioxane</td>
<td>20</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>dioxane</td>
<td>20</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>Et$_2$O</td>
<td>20</td>
<td>80</td>
<td>-</td>
</tr>
<tr>
<td>4[h]</td>
<td>MeOH</td>
<td>2 h</td>
<td>66 (2a’)</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>20</td>
<td>36</td>
<td>41</td>
</tr>
<tr>
<td>6</td>
<td>toluene</td>
<td>12 h</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>7[h]</td>
<td>Et$_2$O</td>
<td>12 h</td>
<td>34</td>
<td>-</td>
</tr>
</tbody>
</table>

[a] Typical conditions: Cp*Ru(cod)Cl (10 mol%), N$_2$CHTMS (1 eq), rt. [1a] = 0.15 M. [b] Isolated yields. [c] Reaction performed at 60 ºC. [d] 2a’ = desilylated 2a (H instead TMS). [e] 10 mol % of CpRu(cod)Cl was used as catalyst.

Table 2. Ru-catalyzed 1,5-Hydride Shift/Cyclization Sequence in Alkynyl Acetals 1, Ethers 5 and Amines 7.[i]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1b</td>
<td>2b</td>
<td>25[c]</td>
</tr>
<tr>
<td>2</td>
<td>1c</td>
<td>3c</td>
<td>61[d]</td>
</tr>
</tbody>
</table>
Table 3. Ru-catalyzed 1,5-Hydride Shift/Cyclization Sequence in Alkynyl C(3)-Linked Heterocycles 10 and 11.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate 10a" /></td>
<td><img src="image2" alt="Product 12a" /></td>
<td>51[c] 87[d]</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Substrate 11a" /></td>
<td><img src="image4" alt="Product 13a" /></td>
<td>61</td>
</tr>
</tbody>
</table>

[a] Typical conditions: Cp*Ru(cod)Cl (10 mol%), N₂CHTMS (1 eq), rt, 0.5 h – 2 h, diethyl ether. [b] Isolated yields. [c] A small amount of silyl conjugated diene 4b (11%) was also obtained (see ref 13). [d] Spiro derivative 2c was also obtained in 20% yield as an E/Z mixture (5:1). [e] Dioxane, 60 ºC, 10 h. [f] Dioxane, 60 ºC, 12 h. [g] Obtained as a 4:1 diastereomeric mixture of E isomers. [h] Dioxane, 3 eq of N₂CHCO₂Et, sealed tube, 110 ºC, 24h; obtained as a 1:1 diastereomeric mixture of E isomers. [i] 1 eq of N₂CHTMS, 12 h. [j] Ether, rt; dioxane, 60 ºC; MeOH, rt.

Table 4. Ru-catalyzed 1,6-Hydride Shift/Cyclization Sequence in Alkynyl Acetals 14.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image5" alt="Substrate 14a" /></td>
<td><img src="image6" alt="Product 15a" /></td>
<td>81 90[d]</td>
</tr>
</tbody>
</table>

[a] Typical conditions: Cp*Ru(cod)Cl (10 mol%), N₂CHTMS (1 eq), rt, 0.5 h - 2h, diethyl ether. [b] Isolated yields. [c] Mixture of diastereomers. [d] Dioxane, 60 ºC.
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**Keywords:** Alkynyl derivatives · Cyclization · Insertion C\textsubscript{sp3}-H bonds · Ruthenium carbenes · Spirocycles

**Graphical material**

A novel tandem Ru-catalyzed carbene addition to terminal alkynes/insertion of Csp\textsubscript{3}–H bonds in alkynyl acetals, ethers and amines has been accomplished under mild conditions. This cascade provides an efficient approach to form complex spiro and fused bicyclic structures in 1,5- and 1,6-hydride shift/cyclization sequences from vinylcarbene Ru intermediates.

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Scheme 1.
Scheme 2.
Scheme 3.

Table 1 Figures.
Table 2 Figures.
Table 3 Figures.

Table 4 Figures.
Footnote 16 Figure

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TOC graphic.