Homogeneous Catalysis

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# Cyclization by Catalytic Ruthenium Carbene Insertion into $C_{sp^3}$–H Bonds**

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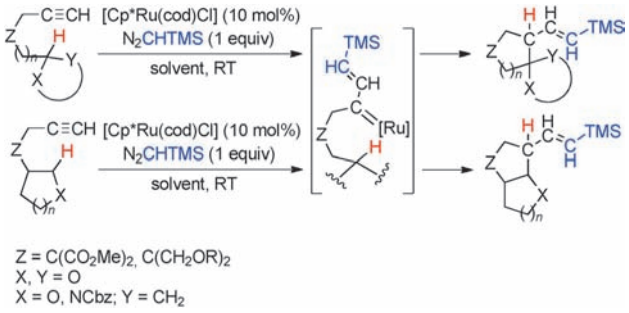
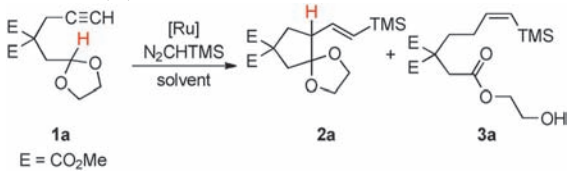
Novel reactions that can selectively functionalize carbon–hydrogen bonds are very important because they offer new strategic approaches in synthesis.[1] A remarkable method for such C–H functionalization involves the insertion of metal carbenes into C–H bonds.[2] The regioselectivity of these C–H insertions is governed by electronic, steric, and conformational factors.[3] Typically, in nonconstrained systems, metal-catalyzed intramolecular C–H insertion reactions predominantly afford five-membered rings (1,5-insertions).[2,4] The formation of smaller and larger rings is achieved only when geometrical constraints or activated C–H bonds are involved.[5] Usually, Rh-[6] and Cu-catalyzed[7] C–H insertions have shown amazing versatility in both intramolecular and intermolecular reactions, but it is still 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 $C_{sp^3}$–H bonds in alkynyl ethers and amines to produce complex spiro or fused bicyclic systems by a tandem 1,5-hydride shift/cyclization sequence.[10] The above methods require temperatures as high as 100–120 °C to achieve good results and under Pt catalysis only 5-*exo* methylene bicyclic structures are formed. We report herein a mild procedure based on a novel tandem Ru-catalyzed carbene addition to terminal alkynes/insertion into $C_{sp^3}$–H bonds in alkynyl acetals, ethers, and amines to form complex spiro and fused bicyclic structures by 1,5- and 1,6-hydride shift/cyclization sequences (Scheme 1).[11]




***Scheme 1.*** Ru-catalyzed transformation of alkynyl derivatives in spiro and fused bicyclic structures. Cbz = benzyloxycarbonyl, cod = 1,5-cyclooctadiene, TMS = trimethylsilyl.

The cyclization of dioxolane **1a** was the first reaction examined under a variety of catalytic conditions (Table 1). After some preliminary experiments,[12] the well-known conditions, established by Dixneuf and co-workers, for the preparation of Ru carbenes starting from alkynes were employed.[13] Thus, a 1,5-hydride shift/cyclization sequence gave the functionalized spiro[5,5] compound **2a** in a moderate yield of 40 % and the linear hydroxyester **3a** as the major isolated product in 50 % yield, by stirring a dioxane solution of **1a** (0.15 M) with 1 equivalent of $N_2CHTMS$ (2 M in hexanes) and 10 mol % of [Cp*Ru(cod)Cl] as catalyst at 60 °C (Table 1, entry 1). A lower overall yield and a similar ratio of **2a** and **3a** were obtained when the reaction was performed in dioxane at room temperature (Table 1, 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 either diethyl ether or MeOH at room temperature (Table 1, entries 3 and 4).[14] However, other typical solvents like THF and toluene gave either lower yields and/or longer reaction times (Table 1, entries 5 and 6).

***Table 1:*** Optimization of Ru-catalyzed 1,5-hydride shift/cyclization sequence in alkynyl dioxolane **1a**.[a]




| Entry | Solvent | *t* [min] | **2a** [%][b] | **3a** [%][b] |
|---|---|---|---|---|
| 1[c] | dioxane | 20 | 40 | 50 |
| 2 | dioxane | 20 | 30 | 28 |
| 3 | $Et_2O$ | 20 | 80 | – |
| 4[d] | MeOH | 2 h | 66 (**2a′**) | – |
| 5 | THF | 20 | 36 | 41 |
| 6 | toluene | 12 h | 40 | – |
| 7[e] | $Et_2O$ | 12 h | 34 | – |

[a] Typical reaction conditions: [Cp*Ru(cod)Cl] (10 mol %), $N_2CHTMS$ (1 equiv), RT, [**1a**] = 0.15 M. [b] Yields of the isolated products. [c] Reaction performed at 60 °C. [d] **2a′** = desilylated **2a** (H instead TMS). [e] 10 mol % of [CpRu(cod)Cl] was used as catalyst.

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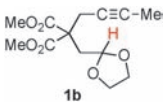
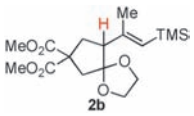
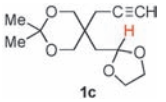
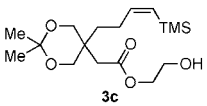
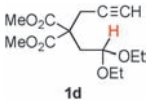
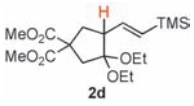
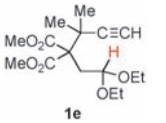
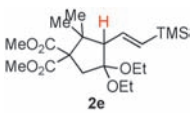
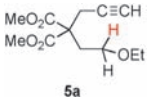
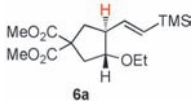
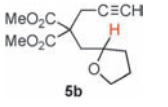
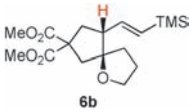
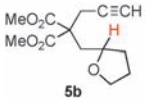
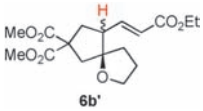
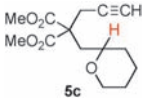
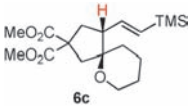
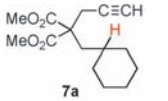
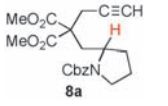
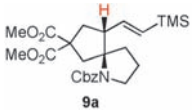
Changes in the electronic and steric nature of the neutral $Ru^{II}$ catalyst on using [CpRu(cod)Cl] strongly affected the course of the reaction resulting in an increase in the reaction time and an a decrease in the conversion and yield (Table 1, entry 7).[15]

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 $C_{sp}$ substituent 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 **3c** being the major isolated product in the case of **1c**, Z = $(CH_2O)_2CMe_2$ (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). Gratifiyngly, 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 tetrahydropyranyl ethers **5b**[19] and **5c** gave the corresponding *trans*-homoallylic ether **6a** and 1-oxaspiro[4,4]nonane and 6-oxaspiro-[4,5]decane **6b** and **6c**, respectively, as a single (or major) diastereoisomer in fairly good yields upon isolation (Table 2, entries 5, 6 and 8). The presence of an ether to activate the $C_{sp^3}$–H for cyclization is mandatory since the hydrocarbon **7a** was totally recovered under all the reaction 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 for a five-membered ring versus 12 h for a six-membered ring), thus highlighting the crucial role of steric hindrance in the reaction (Table 2, entries 6 and 8). When electron-poor $N_2CHCO_2Et$ was used instead of $N_2CHTMS$, cyclization of **5b** was not diastereoselective, thus giving the corresponding spiro derivative **6b'** 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).

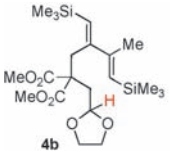
We next turned our attention to the reactivity of C3-linked heterocycles such as tetrahydrofurans **10a** and piperidine **11a** (Table 3).[8,9] To our delight, fused bicyclic tetrahydrofuran **12a** and piperidine **13a** were obtained in fairly good yields (Table 3, entries 1 and 2), thus showing the efficient functionalization of secondary C–H bonds α 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]decane **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 (Table 4, entries 2–4). A comparison of the 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** versus 1,4-dioxaspiro[4,4]nonane **2c**; this result clearly indicates that the conformation of the

***Table 2:*** Ru-catalyzed 1,5-hydride Shift/cyclization sequence in alkynyl acetals **1**, ethers **5** and amines **7**.[a]

| Entry | Substrate | Product | Yield [%][b] |
|---|---|---|---|
| 1 |  **1b** |  **2b** | 25[c] |
| 2 |  **1c** |  **3c** | 61[d] |
| 3 |  **1d** |  **2d** | 61[e] |
| 4 |  **1e** |  **2e** | 40[e] |
| 5 |  **5a** |  **6a** | 53[f] |
| 6 |  **5b** |  **6b** | 79[g] |
| 7 |  **5b** |  **6b'** | 55[h] |
| 8 |  **5c** |  **6c** | 48[i] |
| 9 |  **7a** | – | –[j] |
| 10 |  **8a** |  **9a** | 85 |

[a] Typical reaction conditions: [Cp*Ru(cod)Cl] (10 mol%), $N_2CHTMS$ (1 equiv), RT, 0.5 h–2 h, diethyl ether. [b] Yields of the isolated products. [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°C, 10 h. [f] Dioxane, 60°C, 12 h. [g] Obtained as a 4:1 diastereomeric mixture of *E* isomers. [h] Dioxane, 3 equiv of $N_2CHCO_2Et$, sealed tube, 110°C, 24 h; obtained as a 1:1 diastereomeric mixture of *E* isomers. [i] 1 equiv of $N_2CHTMS$, 12 h. [j] Reaction conditions tried: diethyl ether, RT, dioxane, 60°C, and MeOH, RT.


**4b**

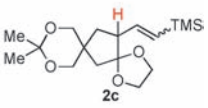
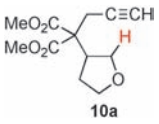
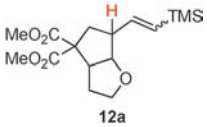
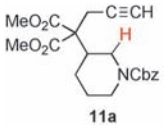
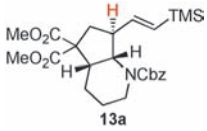
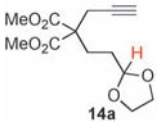
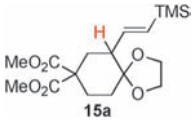
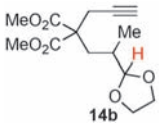
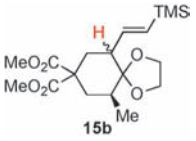
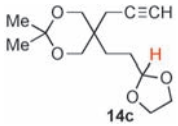
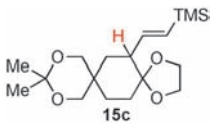
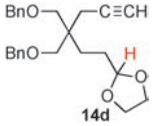
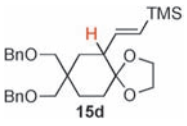

**2c**

***Table 3:*** Ru-catalyzed 1,5-hydride shift/cyclization sequence in alkynyl C3-linked heterocycles **10** and **11**.[a]

| Entry | Substrate | Product | Yield [%][b] |
|---|---|---|---|
| 1 |  **10a** |  **12a** | 51[c]<br>87[d] |
| 2 |  **11a** |  **13a** | 61 |

[a] Typical reaction conditions: [Cp*Ru(cod)Cl] (10 mol%), $N_2CHTMS$ (1 equiv), RT, 0.5 h–2 h, diethyl ether. [b] Yields of the isolated products. [c] Mixture of diastereomers. [d] Dioxane, 60°C.

***Table 4:*** Ru-catalyzed 1,6-hydride shift/cyclization sequence in alkynyl acetals **14**.[a]

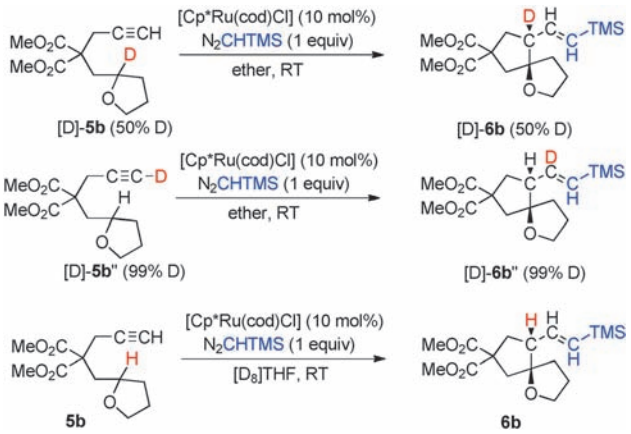
| Entry | Substrate | Product | Yield [%][b] |
|---|---|---|---|
| 1 |  **14a** |  **15a** | 81<br>90[c] |
| 2 |  **14b** |  **15b** | 61[d] |
| 3 |  **14c** |  **15c** | 60 |
| 4 |  **14d** |  **15d** | 51 |

[a] Typical reaction conditions: [Cp*Ru(cod)Cl] (10 mol%), $N_2CHTMS$ (1 equiv), RT, diethyl ether. [b] Yields of the isolated products. [c] Dioxane, 60°C. [d] Mixture of diastereomers (3:1) of *E* isomers.

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 tetrahydrofuranyl ethers [D]-**5b** and [D]-**5b″** (Scheme 2).

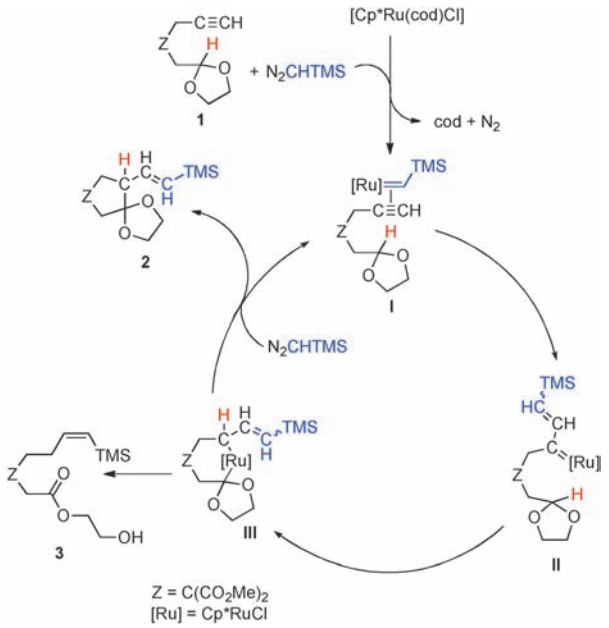
In the reaction of [D]-**5b**, the deuterium atom in the position α to the oxygen was completely transferred to the allylic position of 1-oxaspiro[4,4]nonane [D]-**6b**, thus supporting a mechanism involving a hydride transfer. On the other hand, the cyclization of deuterated alkyne [D]-**5b″** afforded the 1-oxaspiro[4,4]nonane [D]-**6b″** in which the deuterium was incorporated selectively at the β vinylic




***Scheme 2.*** Deuterium labeling experiments. THF = tetrahydrofuran.

position. In addition, deuterium was not incorporated into the cyclized product **6b** when the reaction of **5b** was conducted in $[D_8]THF$.[21,22]

Although more mechanistic investigations 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*Ru(cod)Cl] easily loses its cod ligand in the presence of alkyne **1** and $N_2CHSiMe_3$, thus leading to ruthenium carbene species **I**.[13,23] Oxidative coupling to give a metallacyclobutene,[24] with a subsequent ring opening of this species would lead to the Ru vinyl carbene **II**.[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 **III**. A final reductive elimination would give rise to the spiro compound **2** with recovery of the catalytic $Ru^{II}$ species in the presence of




***Scheme 3.*** Mechanistic hypothesis for the Ru-catalyzed intramolecular carbene insertion into $C_{sp^3}$–H bonds.

$N_2CHSiMe_3$. 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 **III** assisted by the heteroatom (dioxane at 60 °C in **1a** or by geometrical requirement in **1c**) followed by hydrolysis of the resulting intermediate could explain the formation of major hydroxyesters **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 into $C_{sp^3}$–H bonds. These cyclizations, which could be applied mainly to terminal alkynes, enable the efficient conversion of secondary or tertiary $C_{sp^3}$–H bonds into new C–C bonds under practical reaction 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 equiv), $N_2CHTMS$ (0.136 mL, 0.273 mmol, 1 equiv, 2 M in hexane) in diethyl ether (2 mL) was added the catalyst [Cp*RuCl(cod)] (10 mg, 0.027 mmol, 0.1 equiv). The resulting solution was stirred at room temperature for 20 min until disappearance of starting material (monitored by TLC and GC/MS). The reaction was quenched with a saturated aqueous solution of $NH_4Cl$ (2 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$ and evaporated to dryness. The crude residue was purified by column chromatography on silica gel using a mixture of *n*-hexane/EtOAc (8:2) as eluent to afford **2a** (74 mg, 80 %) as a yellowish oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 5.95$ (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 ppm (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 172.4$ (CO), 171.8 (CO), 142.8 (CH), 133.7 (CH), 116.4 (C), 65.4 ($CH_2$), 65.0 ($CH_2$), 55.0 (C), 53.0 (CH), 52.9 ($CH_3$), 52.8 ($CH_3$), 43.3 ($CH_2$), 36.8 ($CH_2$), −1.3 ppm (3 × $CH_3$). MS (ESI): *m*/*z* (%): 365 ($[M+Na]^+$, 100), 298 (13), 214 (14). HRMS (ESI): *m*/*z* calcd for $C_{16}H_{27}O_6Si$: 343.1577 $[M+H]^+$ found: 343.1579.

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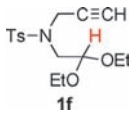
[14] Neglibible variation in time and yield was observed on using 2 M $N_2CHTMS$ in diethyl ether.

[15] Similar effects have been found in other Ru carbene reactions, see ref. [13g].

[16] No cyclization was observed with **1f**.

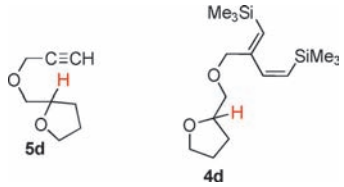



**1f**

[17] Cyclization in the presence of molecular sieves (4 Å) gave rise to a lower overall yield (68%) with a slightly minor proportion of **3c** (44%).

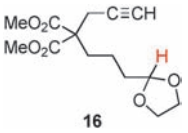
[18] E. V. Anslyn, D. A. Dougherty, *Modern Physical Organic Chemistry*, University Science Books, **2006**.

[19] The nature of Z is crucial since cyclization was not observed when **5d** was employed, but silyl conjugated Dixneuf's diene **4d** was obtained in low yield. See the Supporting Information for details.




**5d** **4d**

[20] Unfortunately, a 1,7-hydride shift/cyclization sequence was not observed when dioxolane **16** was subjected to the typical and modified reaction conditions, and starting material was recovered unchanged.




**16**

[21] 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 the Supporting Information for details.

[22] In addition, cyclization of acetal **1a** in $CD_3OD$ gave rise to monodeuterated **2a′** as a 1:1 mixture of *E* and *Z* isomers (60% combined yield). See the Supporting Information for details.

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