Ru Carbene Insertion C_{sp3}-H Bonds

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Cyclization by Catalytic Ruthenium Carbene Insertion into sp^3 C–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 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_{sp3}–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 alkynyl 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 ºC 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_{sp3}–H bonds in alkynyl 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 ºC a dioxane solution of **1a** (0.15 M) in the presence of 1 equiv of N_2CHTMS (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 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** 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, 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 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 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_2CHCO_2Et was used instead N_2CHTMS, no diastereoselective cyclization of **5b** occurred giving rise to 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 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 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 (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 tetrahydrofuranyl ethers **5b-*d*$_1$** and **5b-*d*$_2$** (Scheme 2).

In the reaction of **5b-*d*$_1$**, the deuterium atom in the position α to the oxygen was completely transferred to the allylic position of 1-oxaspiro[4,4]nonane **6b-*d*$_1$**, thus supporting a mechanism involving a hydride transfer. On the other hand, the cyclization of deuterated alkyne **5b-*d*$_2$** afforded the 1-oxaspiro[4,4]nonane **6b-*d*$_2$** in which the deuterium was incorporated selectively at the β 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*Ru(cod)Cl easily loses its cod ligand in the presence of alkyne **1** and $N_2CHSiMe_3$ leading to a ruthenium carbene species **I**.[13],[23] Oxidative coupling to give a metallacyclobutene[24] followed by opening of this species would lead to the ruthenium 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**. Final reductive elimination would give rise to the spiro compound **2** with recovery of the catalytic Ru(II) species in the presence of $N_2CHSiMe_3$. 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 ºC 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 of C_{sp3}–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_2CHTMS (0.136 mL, 0.273 mmol, 1 eq, 2M in hexane) in diethyl ether (2 mL) was added the catalyst Cp*RuCl(cod) (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_4Cl (2 mL) and extracted with diethyl ether (3 x 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 hexane/EtOAc (8:2) as eluent to afford 2a (74 mg, 80%) as a yellowish oil. 1H NMR (400 MHz, CDCl3), 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, CDCl3), δ (ppm): 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 (3xCH_3). MS, m/z (% relative

intensity): 365 (M++Na, 100), 298 (13), 214 (14). HRMS (ESI) calculated for $C_{16}H_{27}O_6Si$ [M++1]: 343.1577 found: 343.1579.

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[14] Neglibible variation in time and yield was observed on using 2M 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**.

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

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[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 Supporting Information for details.

[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.

[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 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 Supporting Information for details.
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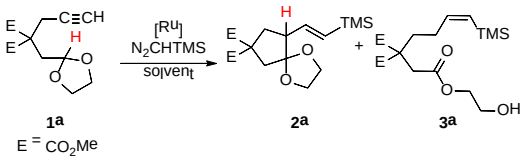
Scheme 1. Ru-Catalyzed Transformation of Alkynyl Derivatives in Spiro and Fused Bicyclic Structures.

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**.[a]

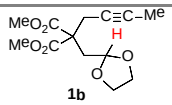
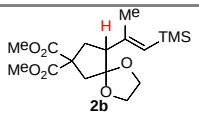
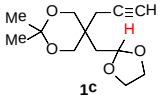
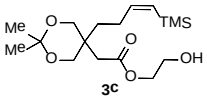


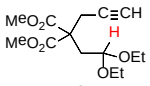
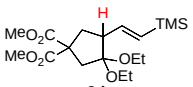
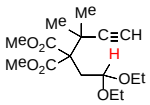
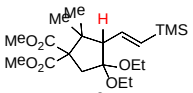
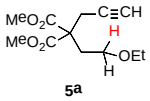
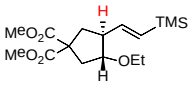
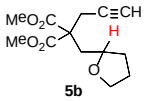
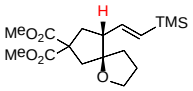
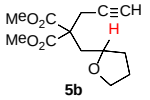
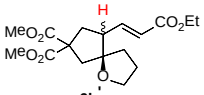
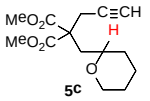
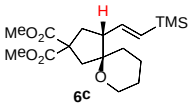
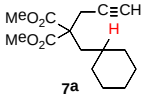
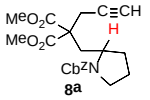
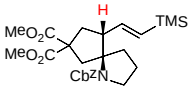
1a E = CO_2Me **2a** **3a**

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	-

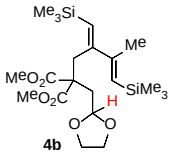
[a] *Typical conditions*: Cp*Ru(cod)Cl (10 mol%), N_2CHTMS (1 eq), rt, [**1a**] = 0.15 M. [b] Isolated yields. [c] Reaction performed at 60 ºC. [d] **2a'** = desilylated **2a** (H instead TMS). [e] 10 mol % of CpRu(cod)Cl was used as catalyst.

Table 2. Ru-catalyzed 1,5-Hydride Shift/Cyclization Sequence in Alkynyl Acetals **1**, Ethers **5** and Amines **7**.[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 conditions*: Cp*Ru(cod)Cl (10 mol%), N_2CHTMS (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, 12h. [g] Obtained as a 4:1 diastereomeric mixture of *E* isomers**.** [h] Dioxane, 3 eq of N_2CHCO_2Et, sealed tube, 110 ºC, 24h; obtained as a 1:1 diastereomeric mixture of *E* isomers. [i] 1 eq of N_2CHTMS, 12 h. [j] Ether, rt; dioxane, 60 ºC; MeOH, rt.


4b

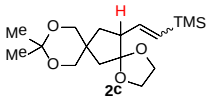
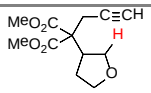
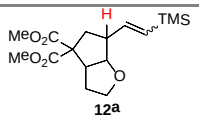
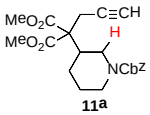
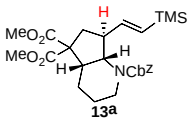
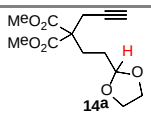
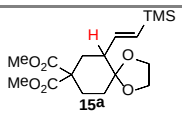

2c

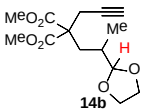
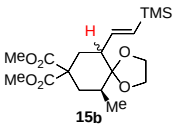
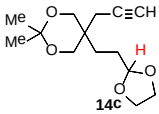
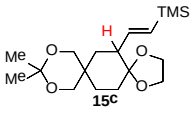
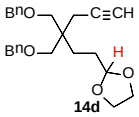
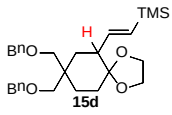
Table 3. Ru-catalyzed 1,5-Hydride Shift/Cyclization Sequence in Alkynyl C(3)-Linked Heterocycles **10** and **11**.[a]

Entry	Substrate	Product	Yield (%)[b]
1	 **10a**	 **12a**	51[c] 87[d]
2	 **11a**	 **13a**	61

[a] *Typical conditions*: Cp*Ru(cod)Cl (10 mol%), N_2CHTMS (1 eq), rt, 0.5 h - 2h, diethyl ether. [b] Isolated yields. [c] Mixture of diastereomers. [d] Dioxane, 60 ºC.

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

Entry	Substrate	Product	Yield (%)[b]
1	 **14a**	 **15a**	81 90[c]

2	 14b	 15b	61[d]
3	 14c	 15c	60
4	 14d	 15d	51

[a] *Typical conditions*: Cp*Ru(cod)Cl (10 mol%), N_2CHTMS (1 eq), rt, diethyl ether. [b] Isolated yields. [c] Dioxane, 60 ºC. [d] Mixture of diastereomers (3:1) of *E* isomers.

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_Ru_ Carbene _Insertion_ C_{sp3}-H Bonds

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

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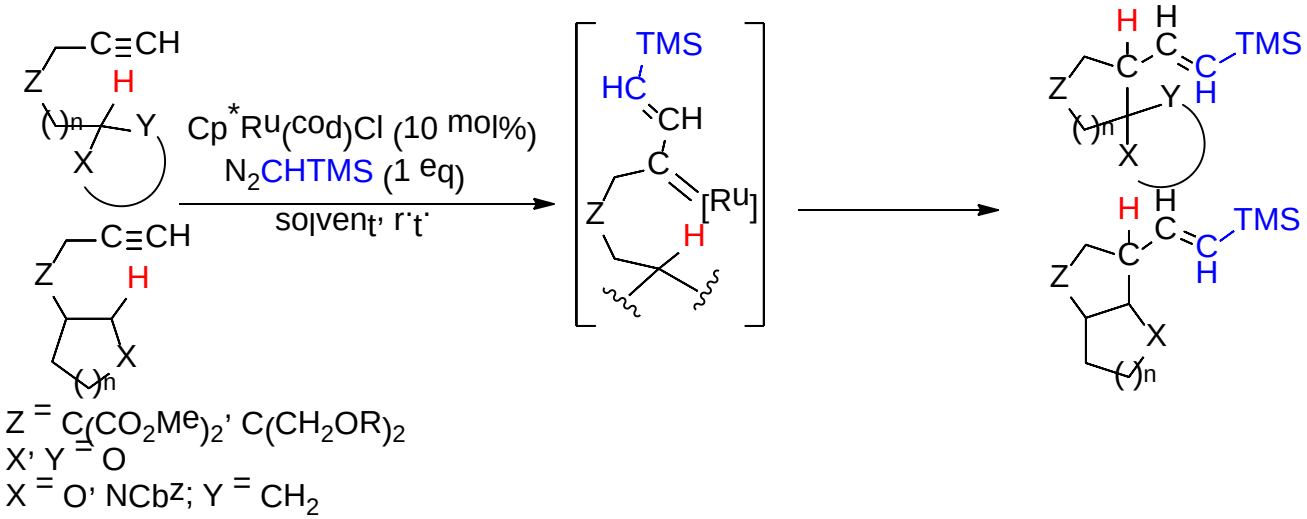
Cyclization by Catalytic Ruthenium Carbene Insertion into sp^3 C–H Bonds

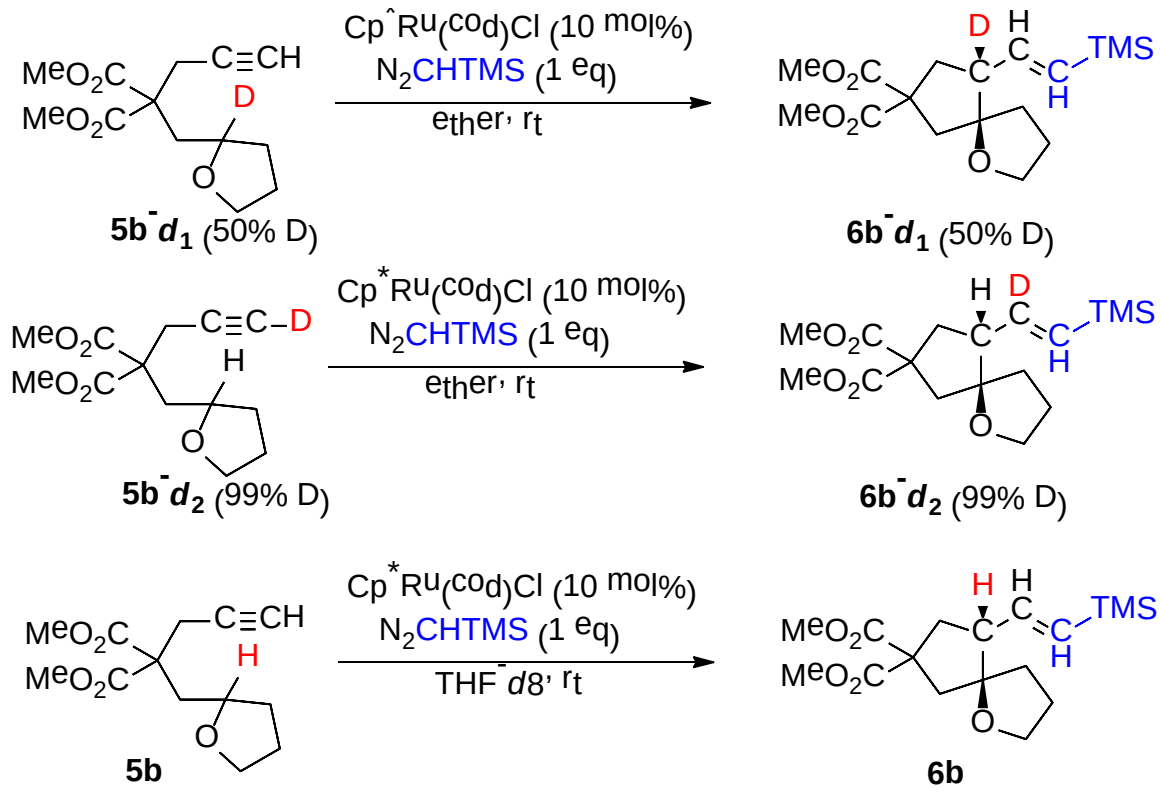
A novel tandem Ru-catalyzed carbene addition to terminal alkynes/insertion of Csp3–H bonds in alkynyl acetals, ethers and amines has been accomplished under mild conditions. This cascade provides an efficient approach to form complex spiro and fused bicyclic structures in 1,5- and 1,6-hydride shift/cyclization sequences from vinylcarbene Ru intermediates.

Keywords: Alkynyl derivatives · Cyclization · Insertion C_{sp3}-H bonds · Ruthenium carbenes · Spirocycles

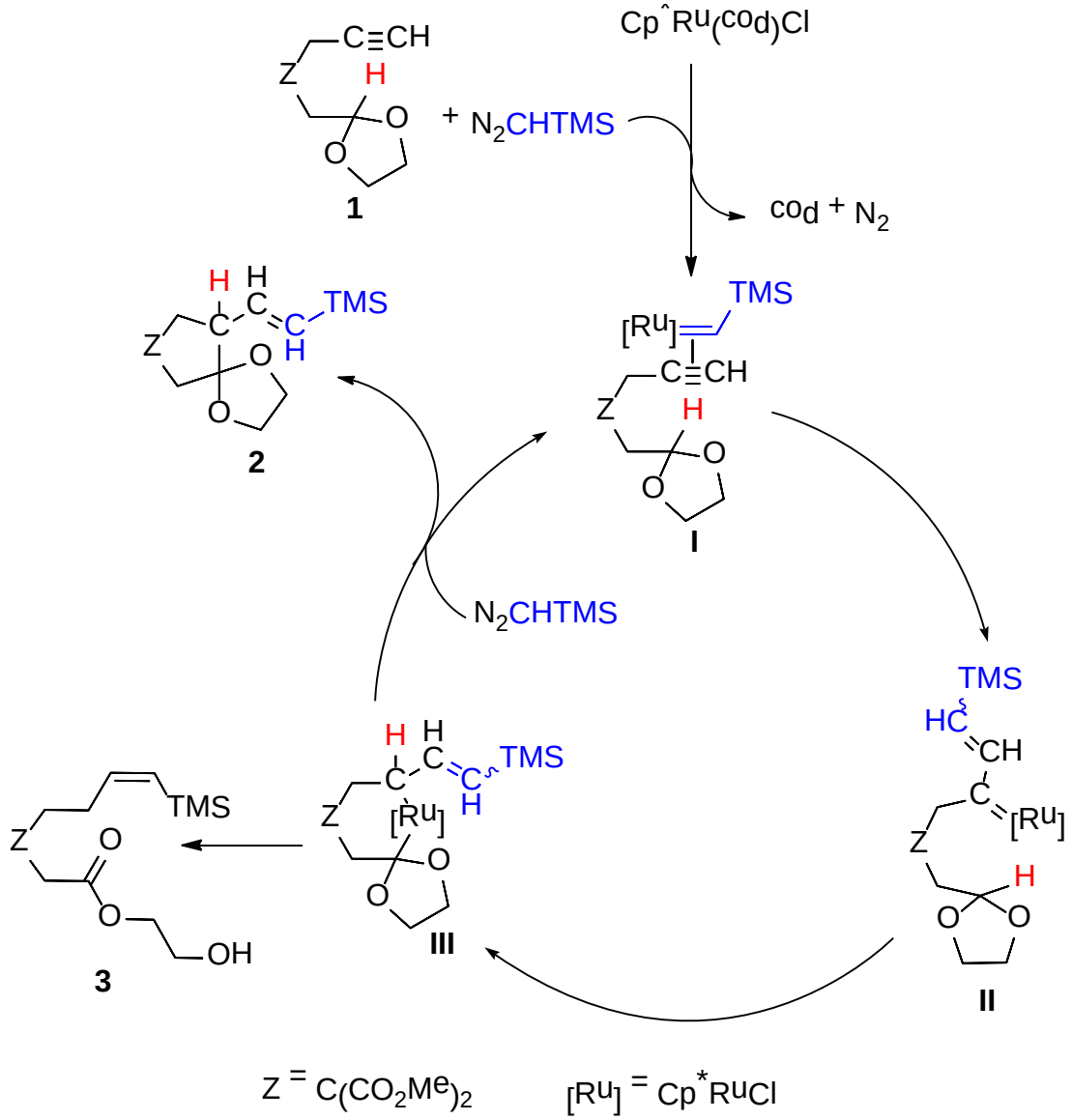
Graphical material



Scheme 1.


Cp^Ru(cod)Cl (10 mol%)
N2CHTMS (1 eq)
ether, rt
MeO2C
MeO2C
C≡CH
D
O
5b-d1 (50% D)
D
H
C
C
TMS
H
6b-d1 (50% D)
Cp*Ru(cod)Cl (10 mol%)
N2CHTMS (1 eq)
ether, rt
C≡C–D
H
5b-d2 (99% D)
H
D
6b-d2 (99% D)
Cp*Ru(cod)Cl (10 mol%)
N2CHTMS (1 eq)
THF-d8, rt
C≡CH
H
5b
H
H
6b

Scheme 2.



Scheme 3.

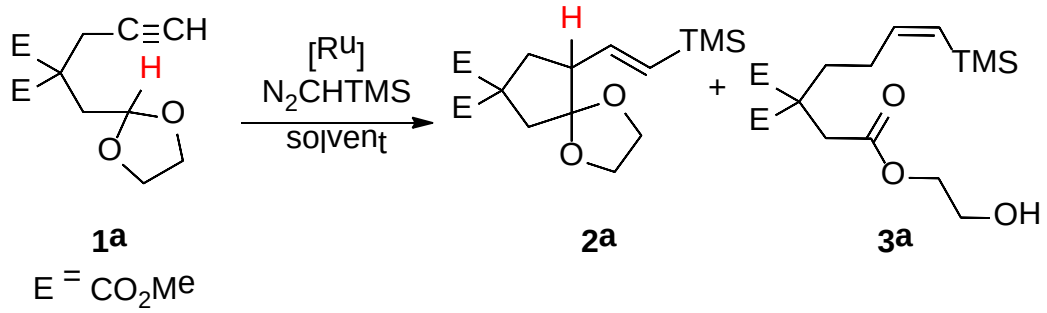
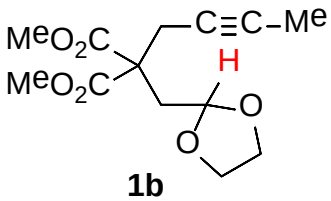
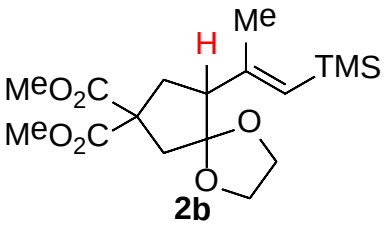


Table 1 Figures.



1b



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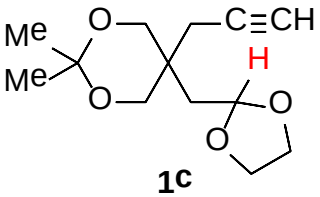

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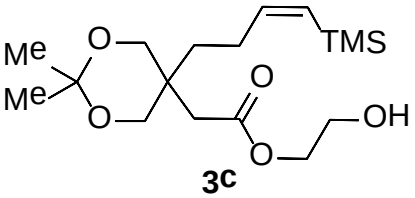
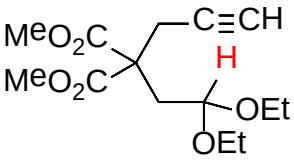


3c



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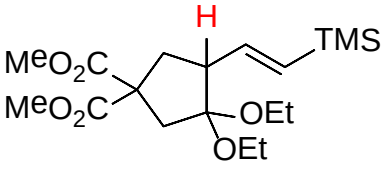

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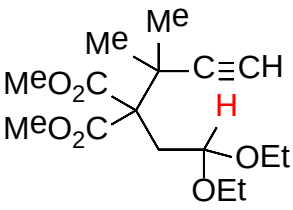

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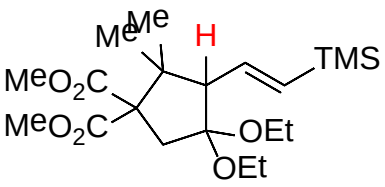

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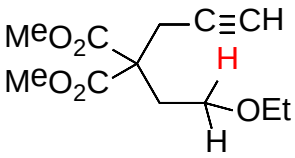

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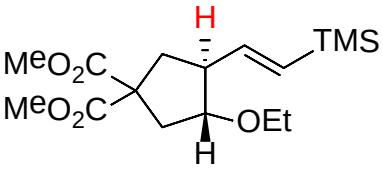

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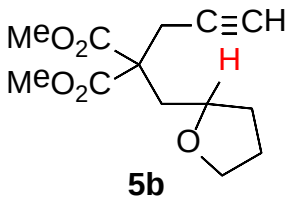

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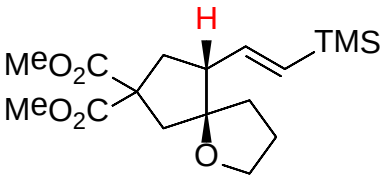

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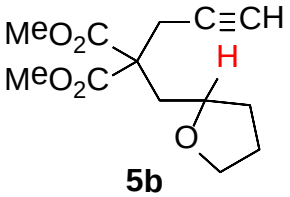

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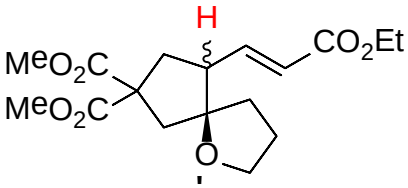

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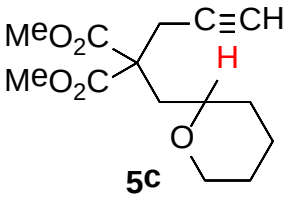

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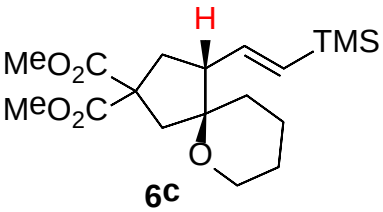

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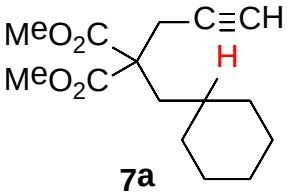

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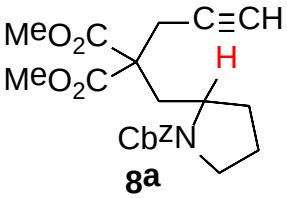

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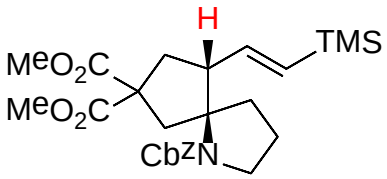

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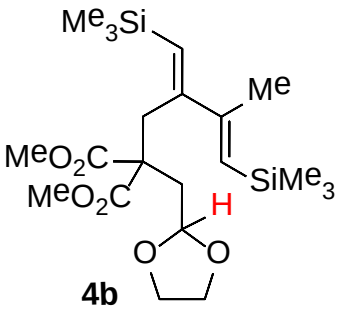

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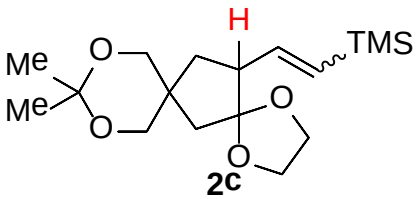

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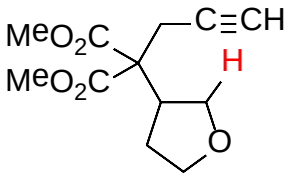

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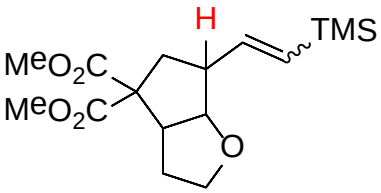

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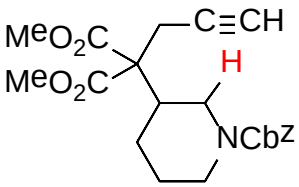

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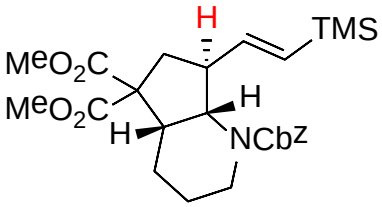

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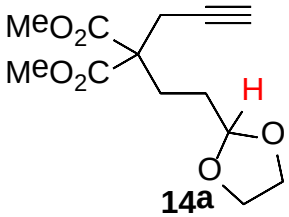

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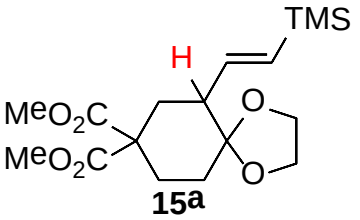

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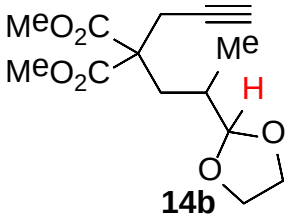

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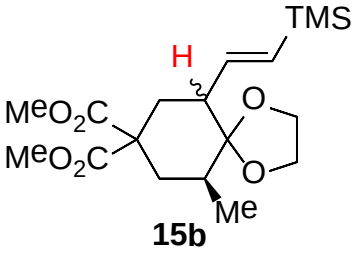

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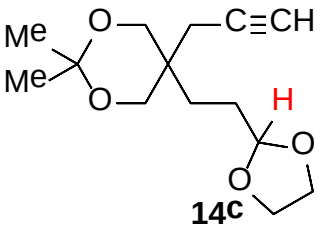

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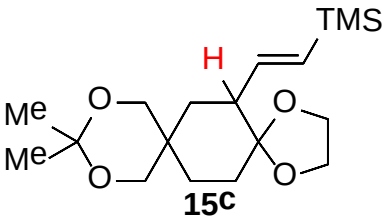

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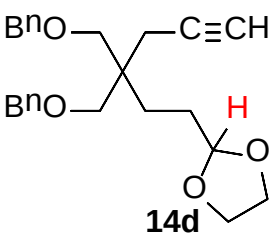

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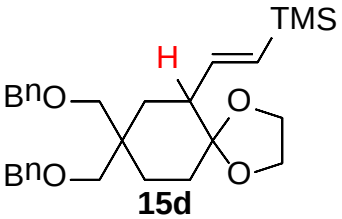

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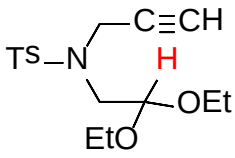

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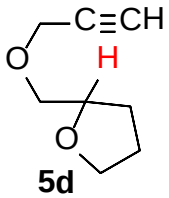
Footnote 16 Figure



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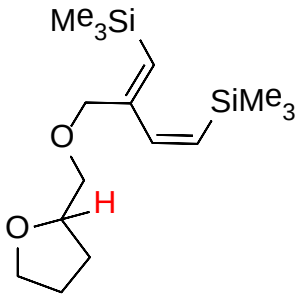

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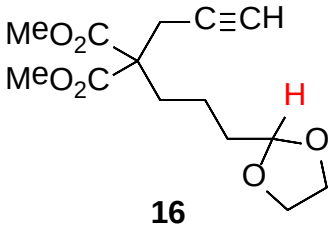

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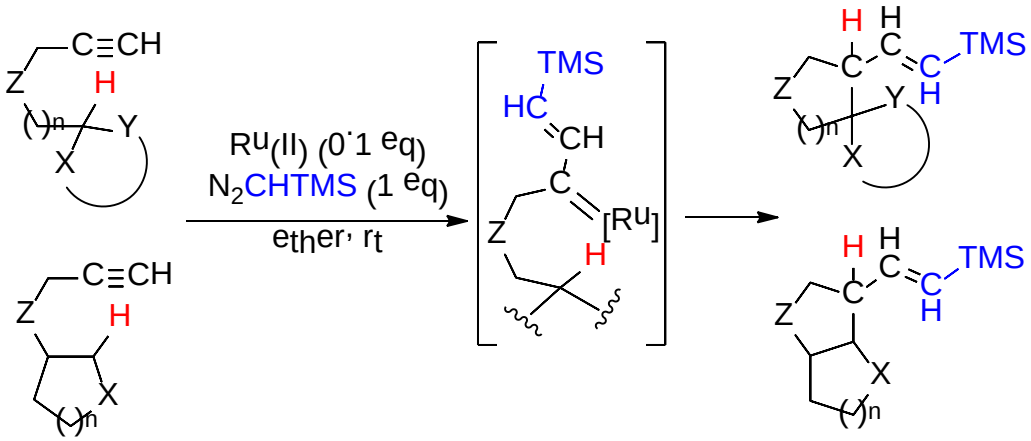
Footnote 20 Figure



TOC graphic.