Solvent-Controlled Switching of Cycloisomerization to Transposition in the Ag/Cu-Promoted Reaction of Terminal α-Allenols [†]

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Abstract: We report herein a study on the Ag/Cu-catalyzed reactivity of α-allenols. The focus was the development of new methodologies for cyclization and/or transposition of this moiety. By simple solvent switch, the divergent preparation of dihydrofurans and 3-halo-3-alkenals in a controlled manner has been reached.

Keywords: allene; dihydrofurans and 3-halo-3-alkenals

1. Introduction

For a long time, it was thought that allenes were highly unstable compounds and for this reason, their chemical and synthetic applications were not well established.

In recent years, chemistry of these compounds has attracted the attention of many chemists giving rise to many studies due to the presence of a cumulated diene in the structure of the compound [1–3].

There are different properties of the allenes, the following are included in them: (1) allenes are the starting point of a large number of synthetic routes, due to the possibility of housing up to four substituents in their structure; (2) the electronic density as well as the reactivity of each carbon of the allenes can be modulated as a function of the substituent; (3) the inherent axial chirality allows the stereoselective synthesis of optically active allenes, just like the transfer of chirality from the allenes to the final product.

Transition-metal catalyzed nucleophile addition to allene group is a very useful tool for the synthesis of functionalized molecules containing heteroatoms in an atom efficient manner [4–9]. This reactivity has a benefit because of regiochemistry can be controlled using different metals or changing the substituents or the length of the chain between allene and heteroatom in the intramolecular case. The metal can coordinate to one or the other double bonds of the allene, promoting the exo- or endo- attack to the terminal or internal carbons to form different size heterocycles. Five- and six-membered rings are often preferred, but bigger rings have been obtained by modulating the substitution in the starting material and the metal employed.

The electrophilic addition of allenes with "X+" is very attractive since 2-haloallylic halides or alcohols are usually formed.

Ma et al. [10,11] described the electrophilic interaction of allenols where they explained the formation of 3-halo-3-alkenals by means of a new synthetic protocol, using α-allenols and X+ as the reaction substrate.
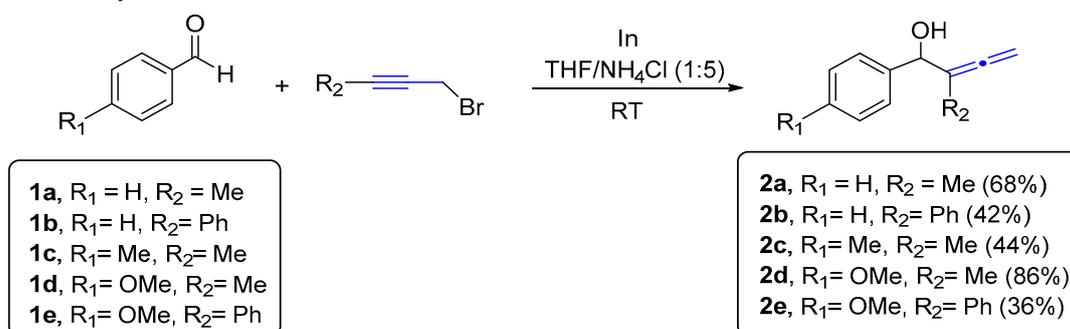
On the other hand, non-aromatic oxacycles are structural units that are extensively encountered in a number of biologically active natural products and functional molecules, and therefore their stereocontrolled synthesis remains an intensive research area [12–18].

Dihydrofurans are one of the most studied oxacycles [19–23] which can be found in different applications such as pharmaceuticals, flavor and fragrance compounds [17].

The main aim of this project is the development of new methodologies for the cyclization and/or transposition of allenols which allow to obtain non-aromatic oxacycles in a regiocontrolled manner, as well as 3-halo-3-alkenals.

2. Results and Discussion

In order to synthesize starting materials, the allenylation reaction was carried out on the aldehydes **1** (Scheme 1). Experiments were performed according to previous conditions developed in our research group [24,25]. Briefly, Barbier-type conditions [26] were used where aldehydes **1** reacted with differently substituted propargyl bromides, using indium and THF/NH$_4$Cl mixture (1:5) as a metal promoter and solvent, respectively. In this way, α-allenols **2** were prepared with total regioselectivity.

1a, R$_1$ = H, R$_2$ = Me
1b, R$_1$= H, R$_2$= Ph
1c, R$_1$= Me, R$_2$= Me
1d, R$_1$= OMe, R$_2$= Me
1e, R$_1$= OMe, R$_2$= Ph

2a, R$_1$ = H, R$_2$ = Me (68%)
2b, R$_1$= H, R$_2$= Ph (42%)
2c, R$_1$= Me, R$_2$= Me (44%)
2d, R$_1$= OMe, R$_2$= Me (86%)
2e, R$_1$= OMe, R$_2$= Ph (36%)

Scheme 1. Synthesis of α-allenols [24,25].

First, the treatment of allenol **2c** with different Cu (II)- and Ag (I)-based salts in DCE was carried out, which provided the 2,5-dihydrofuran **3c** as the only reaction product resulting from a 5-endo-trig oxycyclization process. As we can see in Figure 1 and Table 1, the highest yield of the product was achieved by employing AgF and CuBr$_2$ at room temperature in DCE.

However, surprisingly, the treatment of the same α-allenol under the same catalytic conditions, but using CH$_3$CN as solvent instead DCE provided 3-halo-3-alkenal **4c** as the only reaction product.
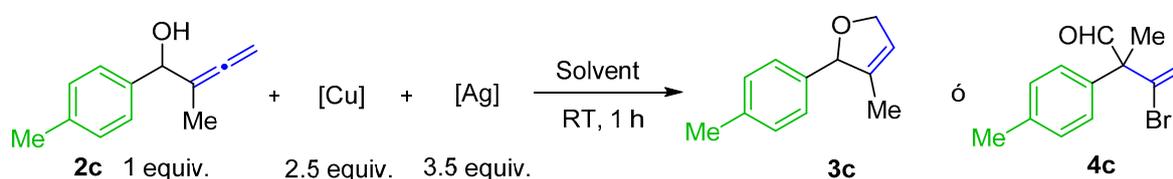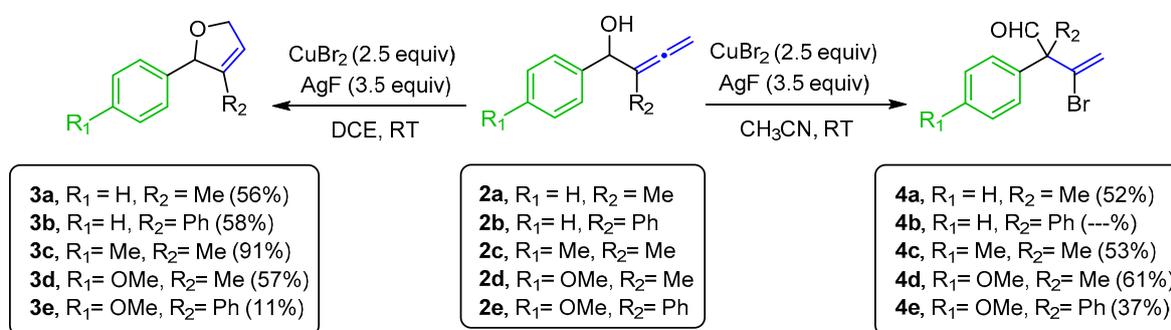

2c 1 equiv.　　2.5 equiv.　3.5 equiv.　　　　　　　　**3c**　　　　　　　**4c**

Figure 1. Synthesis of 2,5-dihydrofuran **3c** and 3-halo-3-alkenal **4c.**

Table 1. Optimization of reaction conditions for the formation of 2,5-dihydrofurans **3** and 3-halo-3-alkenals **4**.

| [Cu]	[Ag]	Solvent	Conv. 3:4	Yield (%)	
CuBr$_2$	Et$_3$N·HF	CH$_3$CN	0:100	45	
CuBr$_2$	AgF	CH$_3$CN	0:100	73	⬅ 4
CuBr$_2$	-	CH$_3$CN	0:100	41	
-	AgF	CH$_3$CN	100:0	40	
CuBr$_2$	AgF	DCE	100:0	91	⬅ 3
Cu(OAc)$_2$	AgF	DCE	100:0	54	
CuBr$_2$	-	DCE	0:100	38	

For this reason, the scope of this divergent reactivity was explored using different α-allenols (Scheme 2). In the event, both protocols gave rise to 2,5-dihydrofurans **3** and 3-halo-3-alkenals **4** respectively.

3a, R$_1$ = H, R$_2$ = Me (56%)
3b, R$_1$= H, R$_2$= Ph (58%)
3c, R$_1$= Me, R$_2$= Me (91%)
3d, R$_1$= OMe, R$_2$= Me (57%)
3e, R$_1$= OMe, R$_2$= Ph (11%)

2a, R$_1$ = H, R$_2$ = Me
2b, R$_1$= H, R$_2$= Ph
2c, R$_1$= Me, R$_2$= Me
2d, R$_1$= OMe, R$_2$= Me
2e, R$_1$= OMe, R$_2$= Ph

4a, R$_1$ = H, R$_2$ = Me (52%)
4b, R$_1$= H, R$_2$= Ph (---%)
4c, R$_1$= Me, R$_2$= Me (53%)
4d, R$_1$= OMe, R$_2$= Me (61%)
4e, R$_1$= OMe, R$_2$= Ph (37%)

Scheme 2. Preparation of 2,5-dihydrofurans **3** and 3-halo-3-alkenals **4**.

This protocol allowed to obtain a family of 2,5-dihydrofurans and 3-halo-3-alkenals by changing both aromatic substitution and internal position of the allene. It should be noted that compound **4b** could not be isolated because a complex reaction mixture was obtained.

The possible pathway for the formation of 2,5-dihydrofurans **3** requires an initial coordination of the silver at the double terminal bond of the allene. Next, a 5-endo-trig oxycyclization followed by proton release and protonation of the C-Ag bond liberates the 2,5-dihydrofuran product **3** (Scheme 3).
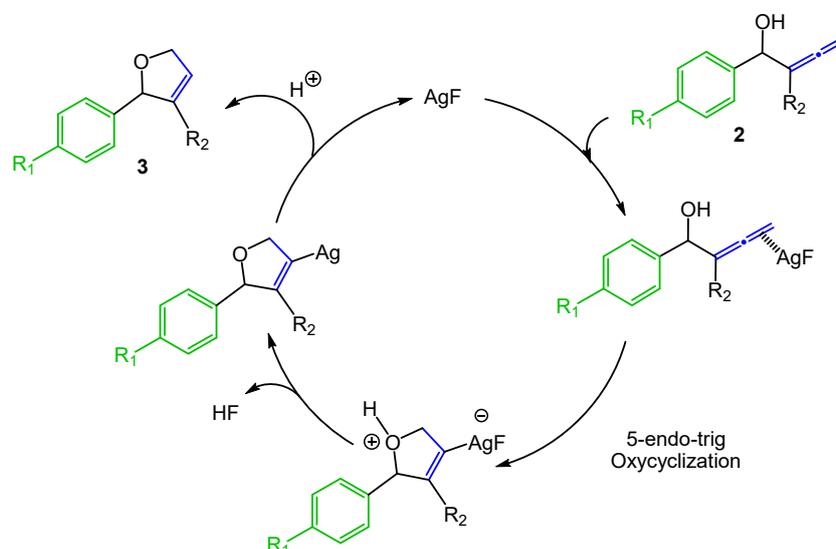
Scheme 3. Possible mechanism for the formation of 2,5-dihydrofurans **3**.

A possible explanation for the formation of the 3-halo-3-alkenals **4** is shown in Scheme 4. It has been proven that the formation of the 3-halo-3-alkenals is a radical process. In this study, the involvement of radicals has been demonstrated through the inhibition of the formation of the corresponding 3-halo-3-alkenal when TEMPO was added to the reaction medium.
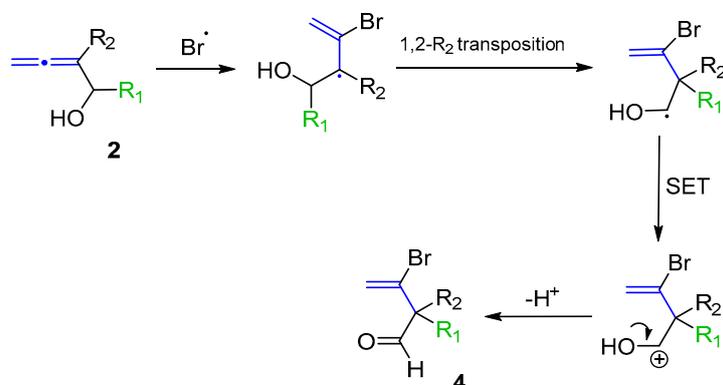
Scheme 4. Possible mechanism for the formation of 3-halo-3-alkenals **4**.

3. Experimental Section

General methods: ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-30 spectrometer. NMR spectra were recorded in CDCl$_3$, except otherwise stated. Chemical shifts are given in ppm relative to TMS (1H, 0.00 ppm), or CDCl$_3$ (1H, 7.27 ppm; ^{13}C, 77.0 ppm). Low and high resolution mass spectra were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electrospray mode (ES) unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. All commercially available compounds were used without further purification.

3.1. General Procedure for the Preparation of α-allenols 2a-e

These precursors were readily obtained as described in the literature [24,25].

3.2. General Procedure for the Preparation of 2,5-Dihydrofurans **3a–e** *and 3-halo-3-alkenals* **4a–e**

CuBr$_2$ (2.5 mmol) and AgF (3.5 mmol) was added to a well stirred solution of α-allenol (1 mmol) in DCE or CH$_3$CN (5 mL). After disappearance of the starting material (TLC) the mixture was extracted with ethyl acetate (3 × 5 mL). The organic extract was washed with brine, dried (MgSO$_4$) and concentrated under reduced pressure.
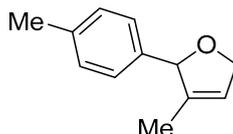
Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds **3** and **4**.
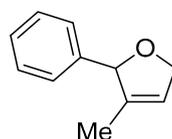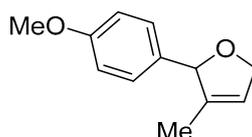

2,5-dihydrofuran **3a**. From 54 mg (0.34 mmol) of the corresponding α-allenol, and after chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **3a** (30 mg, 56%) as a yellow oil; ^1H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 7.23 (m, 5H), 5.56 (q, 1H, *J* = 1.66 Hz), 5.40 (m, 1H), 4.72 (m, 2H), 1.48 (m, 3H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 141.5, 138.5, 128.4 (2CH), 127.9 (CH), 126.8 (2CH), 120.7 (CH), 90.5 (CH), 75.5 (CH$_2$), 12.5 (CH$_3$); IR (CHCl$_3$, cm^{-1}): υ = 2925, 2854, 1727, 701.
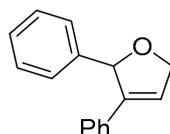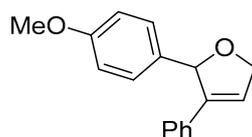
2,5-dihydrofuran 3b. From 50 mg (0.23 mmol) of the corresponding α-allenol, and after chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **3b** (29 mg, 58%) as a yellow oil; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 7.41 (m, 2H), 7.13 (m, 8H), 6.24 (m, 1H), 6.03 (c, 1H, *J* = 1.91 Hz), 4.80 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 141.9, 141.5, 133.3, 128.7 (2CH), 128.5 (2CH), 128.2 (CH), 128.1 (2CH), 127.9 (CH), 127.8 (2CH), 126.9 (CH), 88.4 (CH), 75.3 (CH$_2$); IR (CHCl$_3$, cm^{-1}): υ = 2925, 2854, 1721, 754.
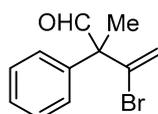

2,5-dihydrofuran 3c. From 15 mg (0.09 mmol) of the corresponding α-allenol, and after chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **3c** (14 mg, 91%) as a yellow oil; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 7.17 (s, 4H), 5.65 (q, 1H, *J* = 1.64 Hz), 5.47 (m, 1H), 4.79 (m, 2H), 2.36 (s, 3H), 1.57 (m, 3H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 138.6, 138.4, 137.6, 129.1 (2CH), 126.8 (2CH), 120.6 (CH), 90.3 (CH), 75.3 (CH$_2$), 21.1 (CH$_3$), 12.5 (CH$_3$); IR (CHCl$_3$, cm^{-1}): υ = 2925, 2854, 1726, 748.

2,5-dihydrofuran 3d. From 50 mg (0.26 mmol) of the corresponding α-allenol, and after chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **3d** (29 mg, 57%) as a yellow oil; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 7.21 (m, 2H), 6.90 (m, 2H), 5.65 (q, 1H, *J* = 1.55 Hz), 5.46 (m, 1H), 4.76 (m, 2H), 3.81 (s, 3H), 1.56 (m, 3H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 159.4, 138.5, 133.6, 128.2 (2CH), 120.7 (CH), 113.8 (2CH), 90.1 (CH), 75.1 (CH$_2$), 55.2 (CH$_3$), 12.5 (CH$_3$); IR (CHCl$_3$, cm^{-1}): υ = 2924, 2853, 1513, 1247.
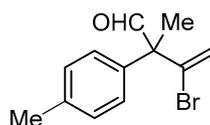

2,5-dihydrofuran 3e. From 51 mg (0.20 mmol) of the corresponding α-allenol, and after chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **3e** (5 mg, 11%) as a yellow oil; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 7.17 (m, 7H), 6.77 (m, 2H), 6.39 (m, 1H), 6.01 (m, 1H), 4.82 (m, 2H), 3.69 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 159.5, 140.8, 133.1, 132.8, 129.0 (2CH), 128.9 (CH), 128.4 (2CH), 127.6 (CH), 126.5 (CH), 122.9 (CH), 114.1 (2CH), 87.7 (CH), 75.0 (CH$_2$), 55.2 (CH$_3$); IR (CHCl$_3$, cm^{-1}): υ = 2925, 2853, 1513, 1252.
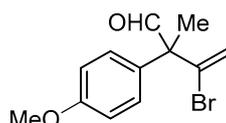

3-Halo-3-alkenal 4a. From 50 mg (0.31 mmol) of the corresponding α-allenol, and after chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **4a** (39 mg, 52%) as a yellow oil; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 9.74 (s, 1H), 7.28 (m, 5H), 5.75 (dd, 2H, *J* = 22.47, 2.75 Hz), 1.63 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 197.7 (CHO), 138.0,

135.1, 129.0 (2CH), 128.0 (CH), 127.6 (2CH), 120.5 (CH_2), 62.3, 20.9 (CH_3); IR (CHCl$_3$, cm^{-1}): υ = 2926, 2854, 1731, 1263.

3-Halo-3-alkenal 4c. From 50 mg (0.29 mmol) of the corresponding α-allenol, and after chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **4c** (38 mg, 53%) as a yellow oil; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 9.79 (s, 1H), 7.20 (m, 4H), 5.82 (dd, 2H, *J* = 20.91, 2.74 Hz), 2.37 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 197.6 (CHO), 137.8, 135.4, 134.9, 129.7 (2CH), 127.5 (2CH), 120.3 (CH_2), 62.0, 21.0 (CH_3), 20.7 (CH_3); IR (CHCl$_3$, cm^{-1}): υ = 2926, 2854. 1728, 1268.

3-Halo-3-alkenal 4d. From 50 mg (0.27 mmol) of the corresponding α-allenol, and after chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **4d** (43 mg, 61%) as a yellow oil; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 9.76 (s, 1H), 7.23 (m, 2H), 6.95 (m, 2H), 5.80 (dd, 2H, *J* = 22.54, 2.72 Hz), 3.83 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 197.4 (CHO), 159.2, 135.8, 129.7, 128.9 (2CH), 120.2 (CH_2), 114.3 (2CH), 61.7, 55.3 (CH_3), 20.6 (CH_3); IR (CHCl$_3$, cm^{-1}): υ = 2923, 2853, 1718, 1252.
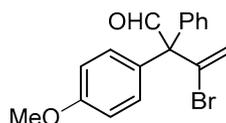
3-Halo-3-alkenal 4e. From 50 mg (0.20 mmol) of the corresponding α-allenol, and after chromatography of the residue using hexanes/ethyl acetate (95:5) as eluent gave compound **4e** (23 mg, 37%) as a yellow oil; ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 10.12 (s, 1H), 7.39 (m, 3H), 7.25 (m, 2H), 7.13 (m, 2H), 6.92 (m, 2H), 5.86 (dd, 2H, *J* = 93.17, 2.29 Hz), 3.83 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 196.4 (CHO), 159.2, 137.2, 133.4, 131.4 (2CH), 130.1 (2CH), 128.7 (CH), 128.5 (2CH), 128.0 (CH), 124.4 (CH_2), 113.9 (2CH), 70.9, 55.3 (CH_3); IR (CHCl$_3$, cm^{-1}): υ = 2925, 2854, 1730, 1299.

4. Conclusions

In this project, we have investigated new methodologies for obtaining 2,5-dihydrofurans as well as 3-halo-3-alkenals starting from 2,3-allenoles with a bimetallic system Ag/Cu.

Surprisingly we found that, for the same reaction conditions, when changing the solvent, the product obtained changed.

Author Contributions: M.T.-P. and H.A. planned and conducted experiments. M.T.-P. analyzed the data for the compounds and compiled most of the Supplementary Information. T.M.d.C. analyzed data to support the mechanistic proposal. P.A. designed and directed the project. M.T.-P. wrote the manuscript. T.M.d.C. and P.A. contributed to discussion.

Conflicts of Interest: The authors declare no conflict of interest.

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