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Tetrahedron Letters 44 (2003) 7151–7154

TETRAHEDRON
LETTERS

Regio- and stereocontrolled dimerisation of allenic alcohols via introduction of an acetoxy group using ruthenium catalysis

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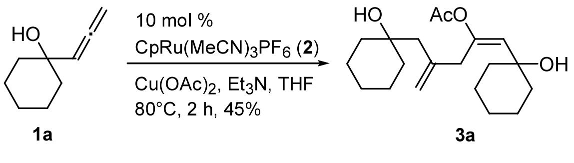
Received 3 June 2003; revised 25 July 2003; accepted 25 July 2003

Abstract—Acetate-introduced dimers of allenes can be produced from the ruthenium catalysed reaction of allenic alcohols with AcOH. Incorporation of acetate component is activated in the presence of $Cu(OAc)_2$ and amine, and various allenic alcohols can be transformed to the corresponding dimers in a regio- and stereoselective manner.

Ruthenium-catalysed dimerisations have been extensively explored as one of the most useful methods of constructing new C–C bonds, and a variety of reactions using alkynes,[1] olefins[2] and conjugated dienes[3] have been reported. However, in spite of the interesting and versatile reactivity of allenes with ruthenium complexes,[4] no examples of ruthenium catalysed dimerisation of allenes have been previously reported.[5,6] During the course of our studies of ruthenium catalysed reactions using allenes[7] we discovered that acetoxy-introduced dimers[8] were formed via the reaction of allenic alcohols in the presence of $Cu(OAc)_2$. We report here our preliminary results describing this novel type of dimerisation reaction using ruthenium catalysis.

When 1,2-propadienylcyclohexanol (**1a**) is treated with 10 mol% $CpRu(MeCN)_3PF_6$ (**2**),[9] 2.5 equiv. $Cu(OAc)_2$ and Et_3N in THF at 80°C for 2 h, a dimerised compound **3a** containing an acetoxy group is obtained in a regio- and stereoselective manner at a yield of 45% (Scheme 1). This structure, including its stereochemistry, was determined unambiguously using spectroscopic methods.



Scheme 1.

Table 1 shows optimisation of the reaction conditions. We first examined the reactions using diverse metal acetates (entries 2–4). The reaction using $Zn(OAc)_2$ also produces **3** at a moderate yield of 33% (entry 2), while both $Mn(OAc)_3$ and LiOAc deactivate the catalyst resulting in poor yields (entries 3 and 4). Improved results were obtained, however, when pyridine and $^iPr_2NEt$ were used instead of Et_3N (entries 5 and 6).

Table 1. Optimisation studies in the ruthenium-catalysed dimerisation reaction of **1a** to give **3a**[a]

Entry	Acetate source	Amine	Solvent	Yield (%)
1[b]	$Cu(OAc)_2$	Et_3N	THF	45
2[c]	$Zn(OAc)_2$	Et_3N	THF	33
3[c]	$Mn(OAc)_3{\cdot}3H_2O$	Et_3N	THF	8[e]
4[c]	LiOAc	Et_3N	THF	8[e]
5[b]	$Cu(OAc)_2$	Pyridine	THF	46
6[b]	$Cu(OAc)_2$	$^iPr_2NEt$	THF	54
7[b]	$Cu(OAc)_2$	–	THF	36
8[b]	$Cu(OAc)_2$	Et_3N	Dioxane	49
9[b]	$Cu(OAc)_2$	Et_3N	Acetone	48
10[b]	$Cu(OAc)_2$	Et_3N	DMF	54
11[d]	$Cu(OAc)_2$	$^iPr_2NEt$	DMF/H_2O[f]	65
12[d]	$Cu(OAc)_2/AcOH$[g]	$^iPr_2NEt$	DMF	65
13[d]	AcOH	$^iPr_2NEt$	DMF	32

[a] Reactions were carried out using 1.2–2.5 equiv. acetate source in the presence of 10 mol% 2, 3 equiv. of amine for 2–4 h in a sealed tube.

[b] Reactions were carried out in a 0.3 M solution at 80°C.

[c] Reactions were carried out in a 0.3 M solution at 50°C.

[d] Reactions were carried out in a 0.5 M solution at 50°C.

[e] Considerable amounts of starting material remained.

[f] The ratio of $DMF:H_2O$ is 10:1.

[g] 10 mol% $Cu(OAc)_2$ and 1.5 equiv. AcOH were used.

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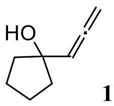
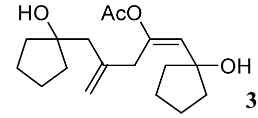
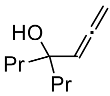
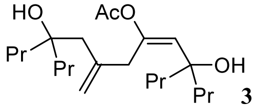
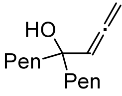
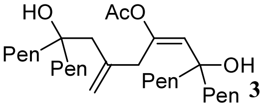
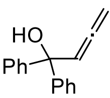
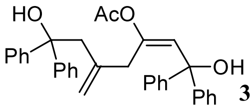
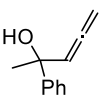
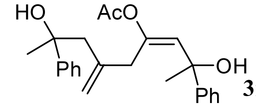
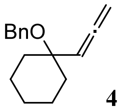
0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01807-0

Additionally, the reactivity decreased in the absence of amine (entry 7). Attempts using different solvents (entries 8–10) reveal that DMF is a better solvent for this reaction (entry 10). The highest yield is obtained, however, when the reaction is carried out in the presence of 10 mol% **2**, 1.2 equiv. $Cu(OAc)_2$ and $^{i}Pr_2NEt$ in DMF/H_2O (10/1) at 50°C (65% yield, entry 11). Furthermore, it is clear that when using catalytic amounts of $Cu(OAc)_2$ (10 mol%) and AcOH (1.5 equiv.) as the acetate source, the reaction proceeded successfully without loss of reactivity (entry 12). The yield decreased to 32% in the absence of $Cu(OAc)_2$ (entry 13).

A variety of allenic alcohols were subjected to the dimerisation reaction under our optimized reaction conditions using catalytic amounts of $Cu(OAc)_2$ and AcOH (Table 2).[10] The cyclopentyl derivative **1b** in this reaction produced the acetate-introduced dimer **3b** at a 63% yield (entry 1). Allenic alcohols **1c** and **1d**, having propyl and pentyl groups, respectively, were transformed to the corresponding acetates **3c** and **3d** in yields of 73 and 70%, respectively (entries 2 and 3). Substrates **1e** and **1f** possessing diphenyl and methylphenyl substituents, respectively, gave products **3e** and **3f** in yields of 62 and 71%, respectively (entries 4 and 5). The reaction of **4**, in which the hydroxy group is protected by a benzyl group, does not produce the corresponding dimer (entry 6). It is clear therefore, that these reactions proceed in a high regio- and stereoselective manner to produce a sole isomer.

Table 2. Ruthenium-catalysed dimerisation reaction of allenic alcohols with $Cu(OAc)_2$–AcOH combination[a]

entry	substrate	product	yield (%)
1	 **1b**	 **3b**	63[b]
2	 **1c**	 **3c**	73[c]
3	 **1d**	 **3d**	70[c]
4	 **1e**	 **3e**	62[b]
5	 **1f**	 **3f**	71[c,d]
6	 **4**	—	0

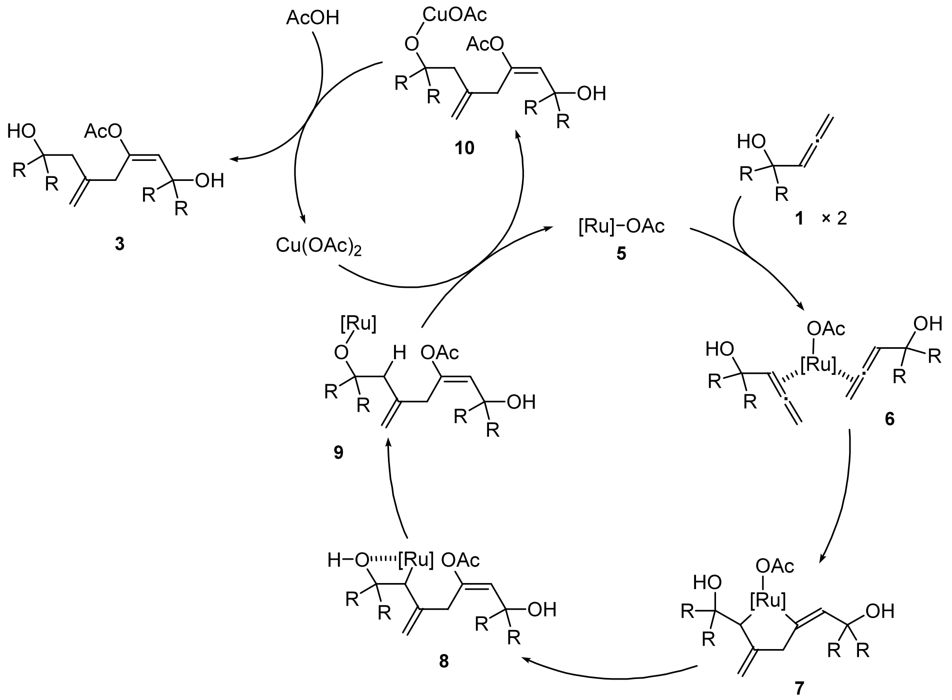
[a] All reactions were carried out in the presence of 10 mol % of **2**, 10 mol % $Cu(OAc)_2$, 3 eq. $^{i}Pr_2NEt$ and 1.5 eq of AcOH in DMF at 50°C for 2-24 h. [b] The stereochemistry of products are determined by ^{1}H-NOESY. [c] The stereochemistry of products are tentatively assigned by analogy of ^{1}H-NMR spectrum of other products. [d] Products are obtained as 1 : 1 mixture of diastereomer.

A possible mechanism underlying the ruthenium-catalysed dimerisation process in the presence of $Cu(OAc)_2$ and AcOH is shown as Scheme 2. It is presumed that the reactive species of the reaction is cyclopentadienyl-ruthenium acetate **5**, initially formed by reaction of $CpRu(MeCN)_3PF_6$ with $Cu(OAc)_2$. Complex **5** coordinates with two molecules of allenic alcohol **1** to give ruthenacycle **7** via **6** at the first step. Reductive elimination of ruthenium from **7** forms an oxygen–sp^2 carbon bond leading to the alkyl ruthenium complex **8**, which would be transformed to **9** by the action of the hydroxy group. Transmetalation of **9** with $Cu(OAc)_2$ produces copper alkoxide **10** and ruthenium acetate **5**, and the resulting complex **10** would finally be converted to the acetate-introduced dimer **3** and $Cu(OAc)_2$ by reaction with AcOH. Thus, the ruthenium catalyst **5** and $Cu(OAc)_2$ are regenerated to perform a catalytic cycle. The requirement of the hydroxy group for the reaction would indicate that its chelation to a ruthenium complex is an important factor in forming intermediates **7** and **9**. Although the role of amine in the dimerisation is not clear, it is presumed that it acts as a base or a ligand for the ruthenium or copper catalyst to enhance the reactivity. In this reaction, ruthenacycle **7** would be formed by the coupling between terminal and central carbons of two allene molecules. This type of coupling pattern has never been previously shown for the dimerisation of allenes using late transition metals.[11]

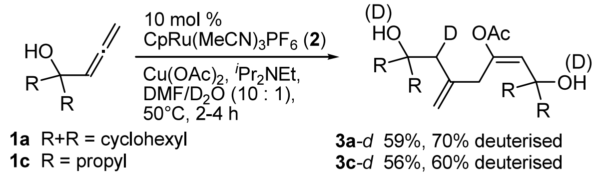
To confirm this proposed reaction mechanism, the reaction was performed in the presence of D_2O. When dimerisations of **1a** and **1c** were carried out in a mixture of DMSO and D_2O (10:1), dimer **3a**-*d* and **3c**-*d* are obtained at a yield of 59% (70% deuterised) and 56% (60% deuterised), respectively (Scheme 3).[12] This result indicates that the dimerisation reactions proceed via intermediate **8**.

When **11**, which is substituted with methyl group at the 1-position of the allenyl group, is subjected to the reaction, non-acetoxy dimer **12**[13] is selectively obtained in 58% yield (Scheme 4). The reaction would proceed via formation of symmetrical ruthenacycle **13** because of steric hindrance of the allenic methyl group, and then proton transfer from the δ-carbon atom to the α′-carbon atom would give the cross-conjugated triene **12**.[14]

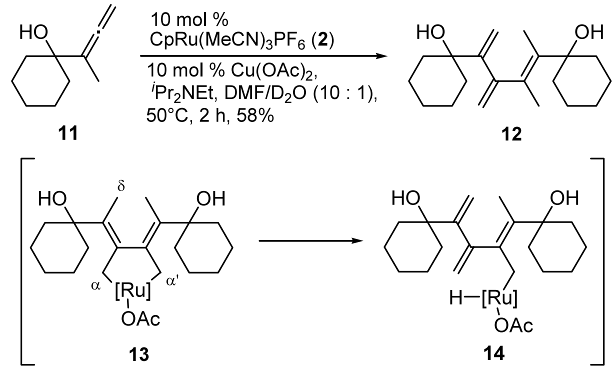
In conclusion, we have developed a novel type of ruthenium catalysed dimerisation of allenic alcohols. This reaction enables the regio- and stereoselective construction of highly functional dienes with an incorporated acetoxy group on the sp^2 carbon. The methodology should provide opportunities to utilise



Scheme 2. Proposed reaction mechanism.



Scheme 3.



Scheme 4.

these products in the development of a variety of new reactions. Mechanistic studies and investigation of further applications of this reaction are now being undertaken.

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10. General procedure for the ruthenium-catalysed dimerisation of allenic alcohols. Reaction of **1a** with $Cu(OAc)_2$/AcOH (entry 12 in Table 1): To a stirred solution of 1-(1,2-propadienyl)-1-cyclohexanol (**1a**) (57.3 mg, 0.414 mmol) in DMF (0.828 mL) was added $CpRu(MeCN)_3PF_6$ (**2**) (17.8 mg, 0.041 mmol), $Cu(OAc)_2$ (7.4 mg, 0.041 mmol), $^{i}Pr_2NEt$ (0.216 mL, 1.24 mmol) and AcOH (0.035 mL, 0.621 mmol) at rt, and the stirring was continued for 4 h at 50°C. After filtration of the reaction mixture using small amount of silica gel, the mass was washed with AcOEt. The combined filtrates were washed with water and brine, and the residue upon workup was chromatographed on silica gel with hexane–Et_2O (85:15 v/v) as eluent to give dimer **3a** (45.5 mg, 65%) as a colorless oil. **3a**: $R_f = 0.26$ (50% Et_2O in hexane); IR (neat) 3439, 2930, 2856, 1732, 1678, 1637, 1447, 1371, 1221, 1171, 1136, 1103, 1063, 1038, 986, 964, 903 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.36 (1H, s), 5.00 (1H, d, $J = 2.1$ Hz), 4.81 (1H, d, $J = 2.1$ Hz), 3.76 (1H, brs), 3.40 (2H, s), 2.90 (1H, brs), 2.26 (2H, s), 2.09 (3H, s), 1.80–1.20 (20H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 147.2, 141.8, 127.0, 117.4, 71.5, 70.0, 39.6, 39.6, 39.3, 37.6, 37.6, 37.6, 25.8, 25.4, 22.3, 22.3, 22.2, 22.2, 21.0; MS *m*/*z* 276 ($M^+ - C_2H_4O_2$); HRMS *m*/*z* calcd for $C_{18}H_{28}O_2$ 276.2088 ($M^+ - C_2H_4O_2$), found 276.2117.
11. This type of dimerisation has been reported using a stoichiometric amount of titanium complex, see Ref. 4d.
12. The d-content of the products were determined by ^1H NMR integration of deuterised methylene signals (δ 2.24 for **3a**-*d*, δ 2.26 for **3a**, δ 2.21 for **3c**-*d*, δ 2.23 for **3c**).
13. Structure of **12** was determined by COSY, NOESY and C–H COSY.
14. This type of dimerisation has been reported using palladium complex, see Ref. 4c.