Ruthenium-catalysed multiple component transformations: one-step stereoselective synthesis of functional dienes from alkynes and carboxylic acids

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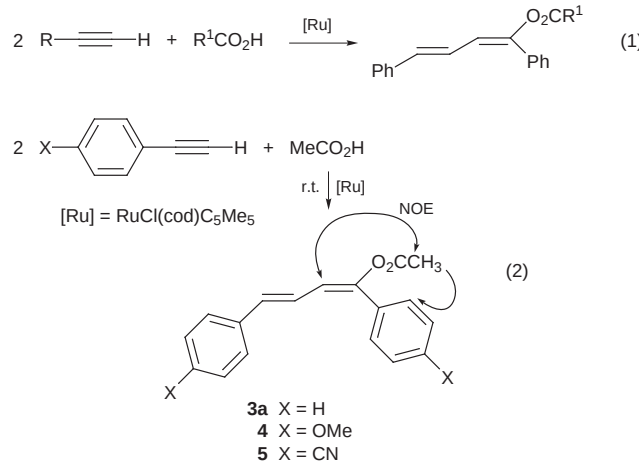
The precatalyst RuCl(cod)C_5Me_5 allows the head-to-head oxidative dimerization of terminal alkynes and the concommittent 1,4-addition of carboxylic acid to afford (1*E*,3*E*)-1-acyloxy-1,3-dienes in one step under mild conditions.

The development of catalysis towards the selective combination of several simple substrates to afford in one step a unique functional molecule in high yield constitutes an important contribution to the discovery of new synthetic methods for environmental impact. These reactions require toxic reagents to be banished, high selectivity and atom economy to avoid costly separations. Multiple component reactions selectively combining several molecules into only one[1,2] *via* the formation of more than two bonds constitute an important challenge for chemists. Recently, ruthenium catalysts, in particular, have been shown to promote the one-step addition of three simple substrates. Representative examples deal with the selective formation of polycyclic compounds,[3] bicyclic phenols,[4] tricyclic hydroquinones[5] or cyclopentenones *via* the catalytic trifunctional Pauson–Khand reaction.[6] The combination of functional arene derivatives with alkene and carbon monoxide *via* the activation of the inert (sp^2)C–H bond has led to aryl ketones.[7] 1,5-Diketones and (*E*)-vinyl chlorides can also be obtained in one step by three component addition of alkyne, unsaturated ketone and water,[8] or NH_4Cl,[9] respectively. The combination of two molecules of acetylene and acrylonitrile has just been achieved by a ruthenium catalyst and affords the heptatrienenitrile.[10]

We have shown recently that the catalyst precursor RuCl(cod)C_5Me_5 promotes the oxidative coupling of C≡C and C=C bonds of alkynes and allyl alcohol to generate either γ,δ-aldehydes[11] or performs the three-component synthesis of methylenetetrahydropyran acetal derivatives.[12] We now report a novel regio- and stereo-selective, three-component catalytic synthesis of functional 1,3-dienes, by one-step combination of two molecules of terminal alkynes and one of carboxylic acid to easily afford (1*E*,3*E*)-1,4-disubstituted-1-acyloxybuta-1,3-dienes [eqn. 1)].

The reaction of 2.5 mmol phenylacetylene with 1.25 mmol acetic acid in the presence of 5 mol% of RuCl(cod)C_5Me_5 (**A**) in 1 mL dioxane affords, after 20 h at room temperature 90% of only the (1*E*,3*E*)-1,4-diphenyl-1-acyloxybuta-1,3-diene **3a** stereoisomer [eqn. (2)]. This reaction corresponds to the highly regioselective head-to-head coupling of terminal alkynes with stereoselective 1,4-addition of the proton and the carboxylate. The stereochemistry of **3a** was established by NMR and NOE experiments.† The addition of $MeCO_2D$ to 2 equiv. of phenylacetylene, catalysed by 5% of **A**, afforded the corresponding PhCD=CH–CH=C(OAc)Ph derivative **3b** and showed the selective 1,4-addition of acetic acid to the conjugated diene skeleton.

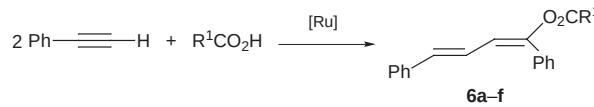
The efficiency of the reaction drastically depends on the nature of the solvent. After 15 h the previous reaction leading to **3a**, performed at room temperature led to 37, 41, 49, 75 and 77% phenylacetylene conversion in toluene, CH_2Cl_2, MeCN, THF and dioxane, respectively. The corresponding addition of acetic acid to *p*-methoxyphenylacetylene and *p*-cyanophenylacetylene led to 85% of **4** and 81% of **5**, but after 42 and 0.5 h,



respectively, at room temperature [eqn. (2)], showing that an electron-withdrawing group on the phenyl ring drastically favours the reaction. The reaction also proceeds with alkylacetylenes but with a lower efficiency as hex-1-yne and oct-1-yne are transformed, under the **3a** formation conditions, into (1*E*,3*E*)-RCH=CH–CH=C(OAc)R **1** (R = Bu^n, 20%) and **2** (R = C_6H_{13}, 40%).

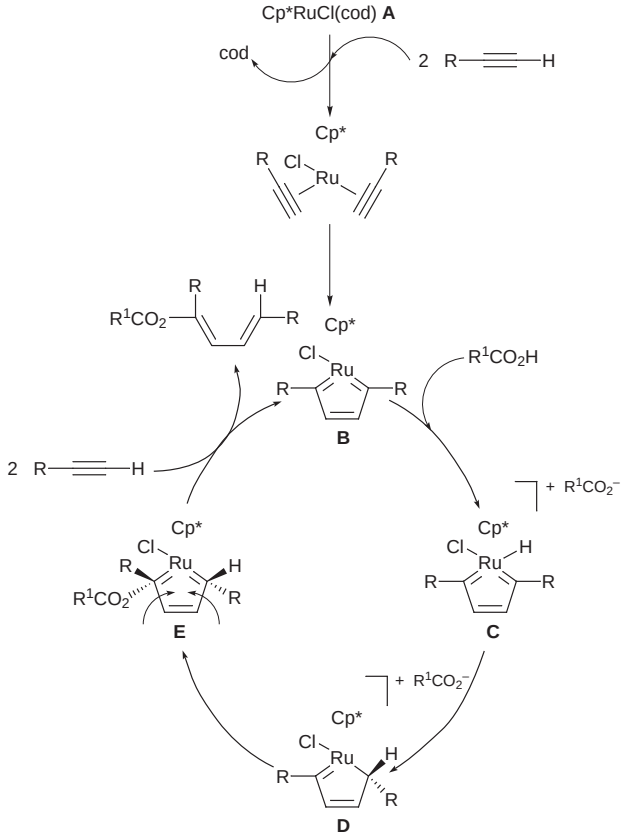
A variety of carboxylic acids have been added to phenylacetylene in the presence of catalyst **A** at room temperature and the corresponding dienes **6** were obtained (Scheme 1). It thus appears that strong carboxylic acids give a low yield of diene (**6a**: 30%), and the weaker acids ($pK_a > 4$) afford quantitative yields after 16–18 h of catalytic reaction at room temperature (**6d**–**6f**).

It has been shown recently that RuCl(cod)C_5R_5 precursors react with terminal alkynes to give, after cod ligand displacement, a complex resulting from the head-to-head, oxidative coupling of two molecules of alkyne at the ruthenium site[10,13,14] to give either a bis-carbene derivative[13,14] or, when a phosphine ligand is coordinated, a ruthenacyclopentadiene.[10] Moreover, we have shown that the addition of two equivalents of phenylacetylene to precursor **A** led to the formation and isolation of the metallacycle **B**, with a bis-carbene structure



	R^1	*t*/h	Yield (%)
a	$CHCl_2$	15	30
b	CH_2CN	18	85
c	H	20	62
d	CH_2OMe	18	95
e	Ph	16	98
f	Bu^t	16	91

Scheme 1 *Reaction conditions*: alkyne (2.5 mmol), catalyst **A** (0.125 mmol), acid (1.25 mmol), dioxane (1 ml), stirred at room temperature for various reaction times (15–20 h).



Scheme 2

(Scheme 2) which was previously obtained *via* a different route.[14] Consequently, Scheme 2 provides a possible mechanism leading to the formation of dienes **3**–**6**. Protonation of bis-carbene intermediate **B** can lead to the species **D**, *via* known carbene ligand insertion into a M–H bond.[15] The direct protonation of the carbene atom of **B** to afford **D** in one step cannot be ruled out. The species **E** arising from carboxylate addition to **D** is expected to generate (1*E*,3*E*)-dienes **3**–**6**. In support of this mechanism we have shown that the isolated complex **B** catalyses the formation of **3a** under conditions reported in Scheme 1 and that the substitution of acetic acid by NaO_2CMe in THF does not lead to any transformation of either phenylacetylene or complex **B**.

The above catalytic reaction represents a new example of multiple component addition of type 2A + B → C, performed under mild conditions with atom economy. It offers potential for the stereoselective preparation of functional dienes by 1,4-addition to the ruthenacycle intermediate resulting from oxidative coupling of two alkyne molecules at the ruthenium centre.

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Notes and references

† *Selected data* for **3a** Ph–C^4H=C^3H–C^2H=$C^1(O_2CCH_3)$Ph: δ_H ($CDCl_3$, 300 MHz) 2.23 (s, 3H, O_2CCH_3), 6.30 (d, 1H, *J* 11.2, H^2), 6.68 (d, 1H, *J* 15.6, H^4), 6.98 (dd, 1H, J_1 11.2, J_2 15.6, H^3), 7.3–7.5 (m, 10H, Ph). δ_H(C_6D_6, 300 MHz) 1.71 (s, 3H, O_2CCH_3), 6.31 (d, 1H, *J* 11.1, H^2), 6.49 (d, 1H, *J* 15.1, H^4), 7.00–7.16 (m, 9H, Ph + H^3), 7.46–7.54 (m, 2H, Ph). NOE experiments show the relative *cis* position of H2 and the O_2CCH_3 group. In $CDCl_3$, the irradiation at δ 2.23 leads to an increase in 2% of the signal at δ 6.30 (H2). In C_6D_6, irradiation at δ 1.71 leads to an increase in 1.5% of the signal of the two *ortho* protons of the phenyl group between δ 7.46 and 7.54 and an increase in 2% of the signal at δ 6.31 (H2). But the irradiation at δ 6.31 (H3) has no influence on the signals at δ 7.46 and 7.54 or δ 1.71.

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