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Smart ruthenium catalysts for the selective catalytic transformations of alkynes

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Abstract

Easy to produce and to handle ruthenium catalyst precursors have been used for the activation of a variety of terminal alkynes. The *anti-Markovnikov* addition is performed in the catalytic synthesis of vinylcarbamates from terminal alkynes, CO_2 and secondary amines *via* ruthenium vinylidene species, with catalysts of type $RuCl_2(PR_3)$(arene) (**A**) and that of carboxylic acids to alkyl-C≡CH, aryl-C≡CH, HC≡C-C(Me)=CH_2 and HC≡C-CH=CHOMe is performed by catalyst $Ru(\eta^3\text{-}CH_2C(Me)CH_2)_2(Ph_2P(CH_2)_nPPh_2)$ $\mathbf{F_4}$ (n = 4) to produced (*Z*)-alken-1-yl esters, whereas the use of catalyst $\mathbf{F_2}$ (n = 2) is necessary to reach high regioselectivity in the formation of (*Z*)-alken-1-yl esters from HC≡C-$SiMe_3$ and HC≡CCR_2OMe. By contrast the latter ($\mathbf{F_2}$) allows the isomerisation of HC≡CCR_2OH compounds into unsaturated aldehydes O=CH-CH=CR_2 and the reaction is shown to proceed *via* an anti-Markovnikov adduct. The use of electron-rich complex, containing a labile (cod) ligand, $RuCl(cod)(C_5Me_5)$ (**G**) offers the regioselective coupling C-Cof allyl alcohol with alkynes to produce γ,δ-unsaturated aldehydes and with propargylic alcohols to afford 5-methylene tetrahydropyrane derivatives.

Introduction

The needs to save energy, and at the same time protect our environment, motivate chemists to create selective, low cost, catalytic processes in order to offer new routes to high value chemicals without the formation of by-products, separations or the use of toxic reagents. In the last decade, especially ruthenium complexes have shown their power in the promotion of unknown combinations of substrates leading to the development of new synthetic methodologies.

Ruthenium catalysts have recently shown, in the field of the **activation** of **alkynes**, their versatility for the selective formation of carbon-heteroatom or carbon-carbon bonds (ref.1, 2). Since the discovery of the one-step formation of alkenylcarbamates (ref. 3), ruthenium-vinylidene species directly generated from terminal alkynes have been recognized as catalytic intermediates in the dimerisation of alkynes into enynes (ref. 4) or butatrienes (ref. 5), in the cyclization of dienylalkynes (ref. 6) or in the coupling of alkynes with allylic alcohols to generate unsaturated carbonyl compounds (ref. 7).
In the above reactions the advantage of ruthenium catalysts appears to be both its tolerance towards functional groups, especially oxygen-containing groups, and its ability to activate C≡C bonds for the selective combination of two substrates with atom economy (ref. 2, 8).

Our study of stoichiometric activations of terminal alkynes and prop-2-yn-1-ols by a variety of organo-ruthenium(II) complexes (ref. 9,10) has made possible an evaluation of the tunable **electrophilicity** of the latter for the activation of the HC≡C bond and their use as catalyst precursors for regioselective additions to the C≡C bond.

Here we review some examples of regioselective C-O and C-C bond formation reactions which are promoted by easy to handle ruthenium catalysts, and using terminal alkynes and prop-2-yn-1-ols as building blocks.

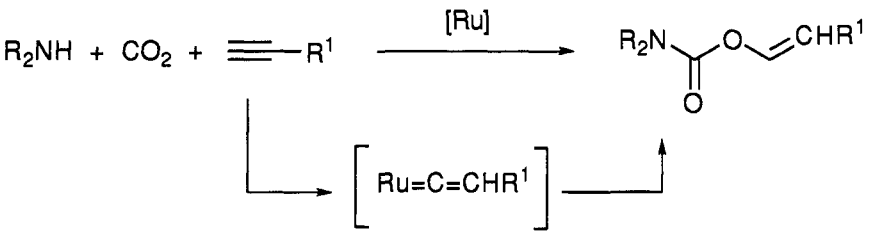
1. Regioselective *anti*-Markovnikov addition of O-H bonds to terminal alkynes

Electrophilic ruthenium catalysts of type $RuCl_2(PR_2)$(arene) (**A**), $[Ru(O_2CH)(CO)_2(PR_3)]_2$ (**B**), $[Ru(O_2CH)(CO)_2(PPh_2(CH_2)_nR]_2$ (**C**) $RuCl_2$(tetrahydropyrimidine)(arene) (**D**) or bis-carbene$[RuCl_2(arene)]_2$ (**E**) have been shown to activate alkynes and promote Markovnikov additions in the formation of C-O bonds to selectively produce enol esters or furanes (ref. 11).

The challenge is now to perform regioselective ***anti*-Markovnikov addition** to the C≡CH bond of terminal alkynes. This has been achieved for a variety of alkynes HC≡C-alkyl, HC≡C-Aryl, C≡C-$C(R)=CH_2$, HC≡C-$CR_2(OR)$ and HC≡C-CR_2OH and led, according to the nature of the alkyne, to the formation of (Z)-alk-1-en-1-yl esters, dienes, or α,β-unsaturated aldehydes.

1.1 Synthesis of alkenyl carbamates

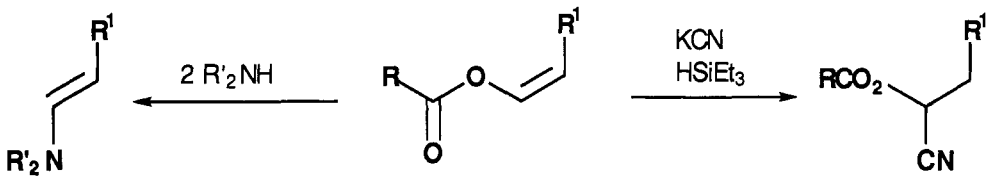
The evidence for the *anti*-Markovnikov addition to terminal alkynes goes back to the catalytic synthesis of alkenyl carbamates in one step from terminal alkyne, secondary amine and CO_2 (50 bar). We discovered this reaction in the search for the use of CO_2 as a substitute for phosgene derivatives and we used the assistance of a variety of ruthenium(II) catalysts, especially $RuCl_2(PR_3)$(arene) derivatives (eq.1, ref. 12).



To explain the regioselective addition of the *in situ* formed ammonium carbamate only to the terminal carbon of the alkyne we postulated the formation of an activated vinylidene-ruthenium intermediate [Ru=C=CHR] (ref. 3,12). Indeed such vinylidene complexes are readily obtained from a variety of metal complexes and terminal alkynes and the carbon atom linked to the metal is the electrophilic site of the moiety M=C=CHR (ref. 13). We showed that $RuCl_2(PR_3)$(arene) derivatives **A** readily produced vinylidene-ruthenium species with terminal alkynes when a vacant site could be generated under mild conditions (ref. 9).

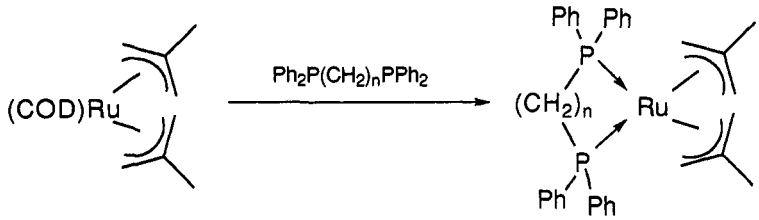
1.2 Synthesis of (Z)-alk-1-en-1-yl esters

The *anti*-Markovnikov addition of carboxylic acid to terminal alkynes would lead to alken-1-yl esters which are of interest to directly generate protected aldehydes from terminal alkynes. These alkenyl esters are actually key-precursors for the access to enamines (ref. 14, eq. 2) or cyanohydrin esters (ref. 15, eq. 2).



eq. 2

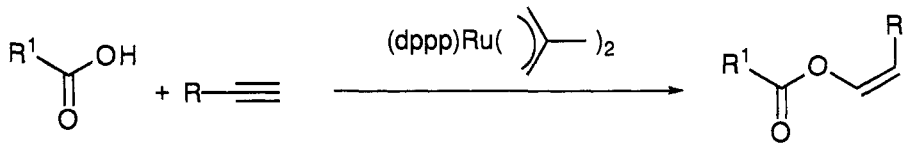
In order to reverse the addition of carboxylates to the substituted carbon atom of alkynes, we have studied the catalytic activity of a series of closely related ruthenium catalysts possessing two key-powers :
- labile hydrocarbon ligands : allyl ligands were selected
- electron-releasing bidentate ligands : diphosphines were selected in order to maintain the *cis*-position of the ancillary coordinating groups and as donating groups to favour the formation of a vinylidene ligand, which is known to be more electron-withdrawing than the η^2-alkyne ligand (ref. 16). Complexes of the type $Ru(\eta^3\text{-}CH_2CMe{=}CH_2)_2(Ph_2P(CH_2)_nPPh_2)$ were prepared with n= 1 (**F_1**), 2 (**F_2**), 3 (**F_3**) and 4 (**F_4**) (eq. 3, ref.17) on the basis of the synthesis of bis-allyl ruthenium derivatives.



eq. 3

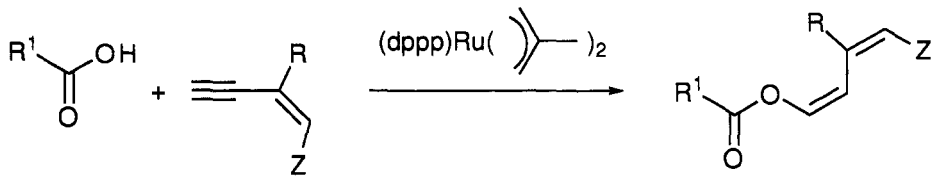
n= 1 (F_1), 2 (F_2), 3 (F_3), 4 (F_4)

The above four catalysts (**F**) have been evaluated for the activation of alkylacetylene (hex-1-yne) and arylacetylene (phenylacetylene) towards a variety of carboxylic acids and only the catalyst (F_4) (dppb)Ru(methallyl)$_2$ led to an excellent regioselective *anti*-Markovnikov addition. Moreover a high stereoselectivity (> 95 %) was observed as the (*Z*)-alk-1-en-1-yl esters corresponding to the *trans*-addition to the C≡C bond were obtained in excellent yields (eq.4, ref 18).



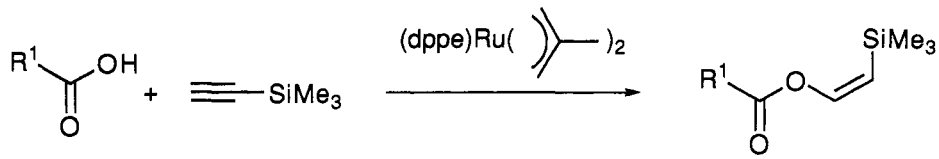
eq. 4

The same complex F_4 was the only efficient catalyst for the addition of carboxylates to the carbon atom C1 of isopropenylacetylene and 4-methoxybut-3-en-1-yne (eq. 5, ref 17), thus offering a route to a variety of functional dienes.



eq. 5

By contrast for the activation of trimethylsilylacetylene catalyst F_4 was useless, whereas catalyst F_2 (dppe)Ru(methallyl)$_2$ led to good yields of the *anti*-Markovnikov addition product (eq. 6, ref 19) without cleavage of the carbon-silicon bond.



eq. 6

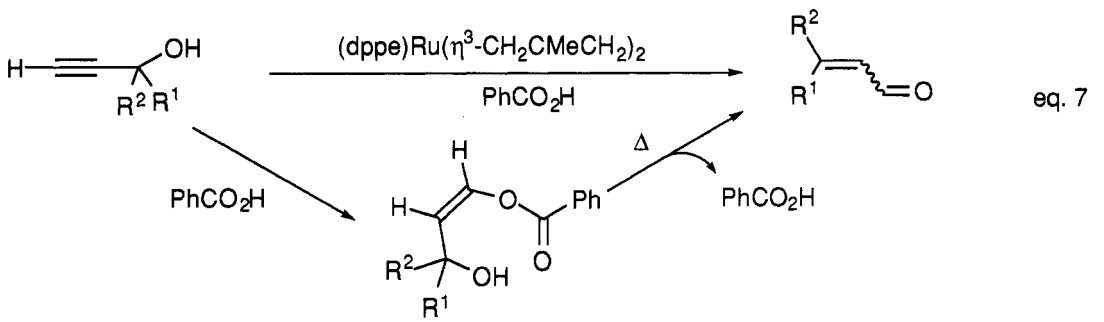
Catalyst F_2 also appeared to be by far the most efficient for the activation of a variety of 3-methoxyprop-1-ynes and the corresponding (*Z*)-alkenyl esters were obtained with excellent regio- and stereoselectivities (ref. 20).
When a similar reaction was applied to unprotected propargylic alcohol derivatives the reaction took a quite different way and led us to discover a new isomerisation reaction of prop-2-yn-1-ols.

1.3 Isomerisation of prop-2-yn-1-ols into α,β-unsaturated aldehydes *via* anti-Markovnikov addition

The activation of prop-2-yn-1-ols towards carboxylic acids promoted by catalyst (**B**) [Ru(O_2CH)(CO)$_2$(PPh_3)]$_2$ allows the direct access to β-oxopropyl esters corresponding to the Markovnikov addition to the C≡C bond followed by transesterification (ref. 21, 22).

An attempt to add benzoic acid to the C≡C bond of prop-2-yn-1-ols in the *anti*-Markovnikov way with the help of the catalyst F_2 led us *apparently* to a different reaction. The heating of but-3-yn-2-ol with one equivalent of benzoic acid in the presence of 5 mol% of (dppe)Ru(methally)$_2$ F_2 without a solvent led to a

complete conversion of the acetylenic alcohol in 3 hours and, *after distillation*, the α,β-unsaturated aldehyde, corresponding to the formal isomerisation of the alkynol, was obtained (eq. 7, ref. 23). When the reaction was performed at 50 °C for 3 hours, the alcohol was selectively transformed into the ester corresponding to the *anti*-Markovnikov addition of the benzoate to the C≡C bond. Thus the catalyst $\mathbf{F_2}$, but not the catalyst $\mathbf{F_4}$ in this case, again controlled the *anti*-Markovnikov addition. The heating of the benzoate in the presence or the absence of catalyst $\mathbf{F_2}$ led to the elimination of benzoic acid and the formation of the corresponding α, β-unsaturated aldehyde (eq. 7).



eq. 7

Our study of the anti-Markovnikov addition of carboxylic acids to a variety of alkynes and promoted by catalyst precursors of the type **F** $(Ph_2P(CH_2)_nPPh_2)Ru(\eta^3\text{-}CH_2C(Me)CH_2)_2$ shows two classes of alkynes

I - those for which the reaction is promoted by the catalyst $\mathbf{F_4}$ (n= 4) *e.g.* $^nBuC{\equiv}CH$, $PhC{\equiv}CH$, $HC{\equiv}C\text{-}CMe{=}CH_2$, $HC{\equiv}C\text{-}CH{=}CH\text{-}OMe$

II - those for which the reaction is promoted by the catalyst $\mathbf{F_2}$ (n= 2) *e.g.* $HC{\equiv}C\text{-}SiMe_3$, $HC{\equiv}C\text{-}CR_2(OMe)$ and $HC{\equiv}C\text{-}CR_2(OH)$ that have a bulky group directly attached to the C≡CH bond.

It is likely that the activated species allowing the addition of the carboxylate to the terminal carbon of the C≡C bond is a ruthenium vinylidene species. The main difference between the $(Ph_2PCH_2CH_2CH_2CH_2PPh_2)Ru$ ($\mathbf{F_4}$) and the $(Ph_2PCH_2CH_2PPh_2)Ru$ ($\mathbf{F_2}$) moieties is that the former one is more bulky and disfavours the approach of bulky substrates. Indeed the P-M-P angle is larger in $\mathbf{F_4}$ than in $\mathbf{F_2}$, thus in $\mathbf{F_4}$ the (PPh_2) phenyl groups are expected to sterically hinder the ruthenium site. From $\mathbf{F_4}$, if a vinylidene is formed with the bulky alkynes of class II, the external approach of the carboxylate to the carbon C_1 is likely to be more difficult than to that of a similar moiety formed from $\mathbf{F_2}$. We thus make the hypothesis that the sterical hindrance around the ruthenium site controls the regioselectivity of the addition at carbon C_1.

It is noteworthy that if (diphosphine)Ru(methallyl)$_2$ precursors allow the anti-Markovnikov addition to a variety of alkynes, a slight modification of the chelating ligand associated with the nature of the alkyne allows to reach high regioselectivity.

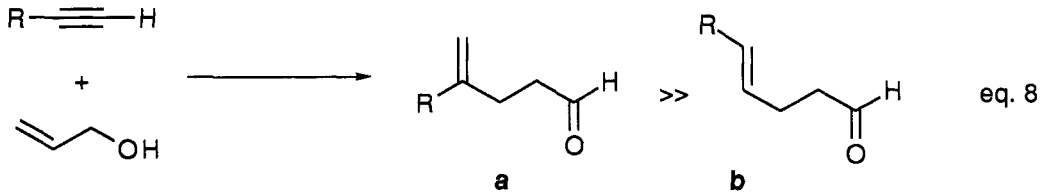
2. Regioselective formation of carbon-carbon bonds by coupling C≡C and C=C bonds

2.1 Catalytic synthesis of γ,δ-unsaturated aldehydes

Trost has shown that the coupling of terminal alkynes with allyl alcohol derivatives could selectively lead to unsaturated ketones. This reaction which is catalysed by $RuCl(PPh_3)_2(C_5H_5)\text{-}NH_4PF_6$ has been shown to proceed *via* a ruthenium vinylidene moiety (ref. 24). By contrast Mitsudo has shown that the related but bulkier $RuCl(cod)(C_5Me_5)$ complex could promote the coupling of alkynes with olefins to produce cyclobutene derivatives (ref.25).

We have shown that the same catalyst precursor $RuCl(cod)(C_5Me_5)$ (**G**) is able to catalyse the coupling of alkynes with allyl alcohol but to produce γ,δ-unsaturated aldehydes (eq. 8, ref. 26). The branched isomer

(**a**), corresponding to the C-C coupling of the substituted C≡C bond carbon, is the major isomer. The reaction can be performed in water (allyl alcohol-water 1/8), but the best regioselectivity **a/b** = 4/1 was obtained in reactions performed without solvent, in neat allyl alcohol (ref. 26). This high regioselectivity in the branched isomer is noteworthy as in previous mixed coupling of C≡C / C=C bonds, with the less bulky and electron-rich complex RuCl(cod)(C_5H_5) the major isomer was the linear one (ref. 27).

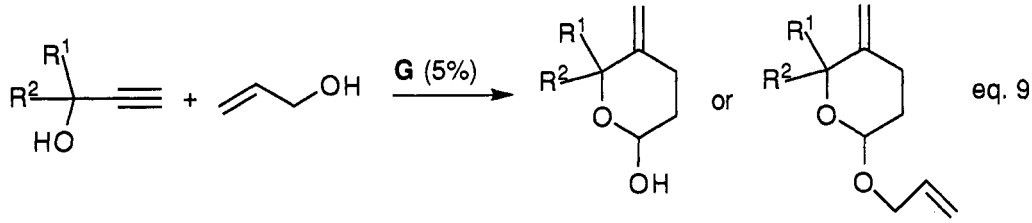


eq. 8

This reaction is not specific of terminal alkynes as symmetrically substituted alkynes lead to only one aldehyde in 90-95 % yield (ref. 26). Therefore a vinylidene-ruthenium intermediate cannot be involved and an oxidative coupling of both C≡C and C=C bond should be considered.

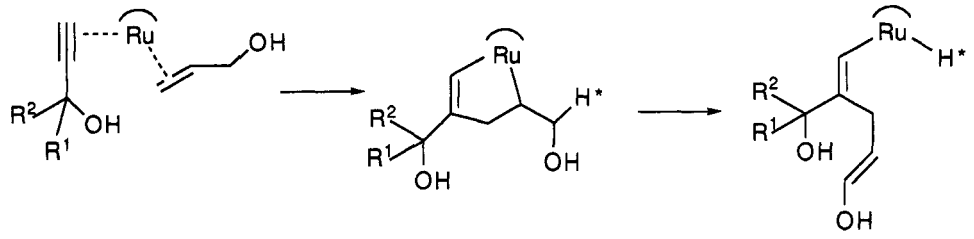
2.2 Catalytic synthesis of 5-methylenetetrahydropyrans

The previous C-C coupling reaction promoted by RuCl(cod)(C_5Me_5) **G** (5 mol %) from prop-2-yn-1-ols and allyl alcohol led to tetrahydropyran derivatives. At 25 °C, only the hemiacetal was formed whereas at 80 °C only the mixed acetal was obtained (eq. 9, ref. 28). The propargylic alcohols favour the formation of the branched isomers observed as the sole reaction products.



eq. 9

To explain both the formation of γ,δ-unsaturated aldehydes and that of 5-methylenetetrahydropyran derivatives a mechanism could be proposed. It is based on the oxidative coupling of both C≡C and C=C bonds, β-elimination of an exocyclic hydrogen atom and formation of the γ,δ-unsaturated aldehyde (eq. 10), which can lead to the cyclisation with the hydroxy group, if present in the δ position.



eq. 10

The above two reactions show examples of regioselective C-C bond formation from two unsaturated substrates to produce, with atom economy, high value chemicals.

Conclusion

A variety of easy to make and to handle ruthenium complexes have been used to promote the activation of terminal alkynes and the regioselective formation of C-O and C-C bonds, with *electrophilic* and *electron-rich* ruthenium(II) complexes. Thus, these ruthenium precursors provide **smart catalysts** because by only slight modifications of the ancillary ligand around the ruthenium site the activity of the catalyst can be created and the regioselectivity of the coupling highly modified.

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