Mononuclear Ruthenium Catalysts for the Direct Propargylation of Heterocycles with Propargyl Alcohols

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Dedicated to Professor Richard R. Schrock on the occasion of his 60th birthday.

Supporting Information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

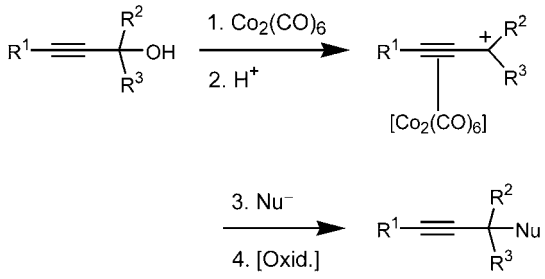
Abstract: A new family of *mononuclear ruthenium catalysts* for the catalytic direct propargylation by propargylic alcohols of heterocycles is presented. The catalyst activity can be improved by tuning the ligand's influence and electronic properties at the metal centre. Whereas [(*p*-cymene)RuCl(PR_3)][OTf] ($PR_3 = PCy_3$, PPh_3) complexes catalyse the propargylation of furan or 2-methylfuran by the alkynol $HC\equiv CCH(OH)Ph$ in moderate yield, mononuclear [(*p*-cymene)RuCl(CO)(PR_3)][OTf] complexes are more active to achieve the same reaction. Low temperature NMR experiments performed on the stoichiometric reaction of the parent [(*p*-cymene)RuCl(PR_3)][$B(Ar_F)_4$] and the alkynol show the unexpected *in situ* formation, *via* allenylidene and hydroxycarbene intermediates, of the carbonyl complexes [(*p*-cymene)RuCl(CO)(PR_3)][$B(Ar_F)_4$] [$Ar_F = 3,5\text{-}(CF_3)_2C_6H_3$] that appear to be the best catalyst precursors.

Keywords: allenylidene; furan; hydroxycarbene; propargyl alcohol; propargylation; ruthenium arene complexes

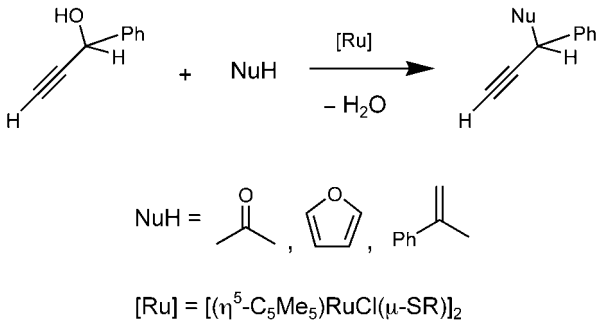
The application of metal complexes in catalysis has undergone a tremendous development, due to efforts to transform stoichiometric activation processes into catalytic ones.[1] The direct propargylation of substrates by propargylic alcohols, easily prepared from ketones and aldehydes, represents a straightforward method for the synthesis of functional products bearing the reactive and versatile alkyne group. The first efficient approach is the Nicholas reaction, in which a stoichiometric amount of carbonyl cobalt complex is employed as a protecting group for the C-C triple bond, and stabilizing reactive propargyl cations (Scheme 1).[2]

Allenylidene metal complexes $M{=}C{=}C{=}CR_2$, readily available from propargyl alcohols,[3] have become an important class of compounds with a rich stoichiometric reactivity.[4] Allenylidene formation may be envisioned as an alternative activation process to perform propargylic substitution, although few examples of catalytic reactions *via* allenylidene intermediates have been reported so far.[5]

Nishibayashi et al.[6] have provided a sound contribution to this field by reporting the selective propargylic substitution of alkynols catalyzed by thiolate-bridged diruthenium complexes. In spite of the fact that this reaction is often limited to secondary alcohols, it provides a versatile method to carry out catalytic propargylic substitutions with a large number of heteroatom (O, N) and carbon-centered nucleophiles (Scheme 2).[6]



Scheme 1.



Scheme 2.

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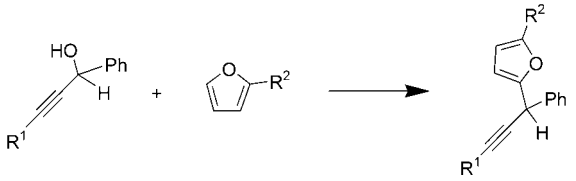
Table 1. Ruthenium-catalysed propargylation of furans by propargyl alcohols.



Entry	Complex	R^1	Equivalents[a]	R^2	Time[b]	Conversion	Yield[c]
1	[(*p*-cymene)$RuCl_2(PPh_3)$]	H	20	H	15 h	25%	<5%
2	[(*p*-cymene)$RuCl(PPh_3)$][OTf]	H	20	H	15 h	100%	<10%
3	[(*p*- cymene)$RuCl(PPh_3)$][OTf]/H_2O	H	10	H	15 h	100%	25%
4	[(*p*-cymene)$RuCl(PPh_3)$][OTf]/H_2O	H	1	Me	15 h	100%	30%
5	[(*p*-cymene)$RuCl(PPh_3)(CO)$][OTf]	H	10	H	2 h	100%	25%
6	[(*p*-cymene)$RuCl(PPh_3)(CO)$][OTf]	H	1	Me	2 h	100%	30%
7	[(*p*-cymene)$RuCl(PPh_3)(CO)$][OTf]	*n*-Bu	1	Me	2 h	100%	45%

[a] Number of furan equivalents with respect to propargyl alcohol.
[b] Reaction conditions: 1,2-dichloroethane, 60 °C, 5% catalyst loading.
[c] Isolated yield.

Some evidence points to the participation of allenylidene species in this catalytic reaction that seems to require a binuclear ruthenium complex bearing sulfur bridges as catalyst. The development of alternative and particularly more readily available ruthenium complexes than the sulfur bridged binuclear catalyst would be of remarkable interest in order to achieve a better understanding of the process and consequently to improve the efficiency and practical potential of this reaction. Surprisingly, a variety of mononuclear ruthenium complexes that usually afford stable allenylidene intermediates,[7] did not show any catalytic activity[6] for this reaction.

In this paper, we report the birth of the first mononuclear ruthenium precatalyst for the catalytic propargylic subtitution of heterocycles by propargylic alcohols, based on readily available [(arene)$RuCl_2(L)$] complexes. By means of low temperature NMR and characterization of intermediates, the catalyst precursors were identified. It is shown that the catalyst activity can be improved by tuning the electronic properties at the metal center.

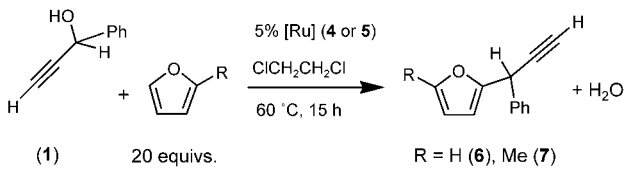
Besides cyclopentadienyl-ruthenium complexes,[3] semi-sandwich arene-ruthenium compounds of the type [(arene)$RuCl_2(PR_3)$] are among the first reported complexes able to activate propargylic alcohols to give allenylidene species.[8] Moreover, the allenylidene derivative [(*p*-cymene)$RuCl(PCy_3)(=C=C=CPh_2)$][OTf] has recently shown to be a highly active precatalyst for olefin metathesis.[9] Therefore, [(*p*-cymene)$RuCl_2(PR_3)$] complexes have first been evaluated as mononuclear catalyst precursors to perform the catalytic propargylation of nucleophiles.

The reaction of the alkynol HC≡CCH(OH)Ph (**1**) with a large excess (20 equivalents) of furan or 2-methylfuran was first attempted with the neutral complexes [(*p*-cymene)$RuCl_2(PR_3)$] [PR_3 = PCy_3 (**2**), PPh_3 (**3**)]. Only a low conversion took place, but the formation of the expected propargylated products was detected in traces (Table 1, entry 1).

In order to enhance the interaction between the alkynol and the ruthenium complex, [(*p*-cymene)$RuCl(PR_3)$][OTf] [PR_3 = PCy_3 (**4**), PPh_3 (**5**)] complexes were prepared by simple chloride abstraction with AgOTf in polar solvents. The prototypic reaction of alkynol **1** and an excess of furan, or 2-methylfuran, in the presence of a 5 mol % of **4** or **5**, led to a complete conversion of the propargyl alcohol, giving rise to the propargylated heterocycles HC≡CCHPh(Nu) [Nu = 2-furanyl (**6**), 5-methyl-2-furanyl (**7**)] in low yield (Table 1, entry 2), besides polymeric materials.

As the reaction released one equivalent of water, the influence of additional water was evaluated. It is noteworthy that addition of small amounts of water to the reaction mixture increased the yield up to 25–30% (Table 1, entries 3 and 4) and, more importantly, it allowed the reduction of the excess of furan to 10 equivalents and in the case of 2-methylfuran to just one equivalent.

This observation could have been interpreted in terms of a better stabilization of the unsaturated ruthenium complexes **4** and **5** by coordination of water. Indeed, the water adduct [(*p*-cymene)$RuCl(PCy_3)(H_2O)$][OTf] was readily prepared by addition of water during the



Scheme 3.

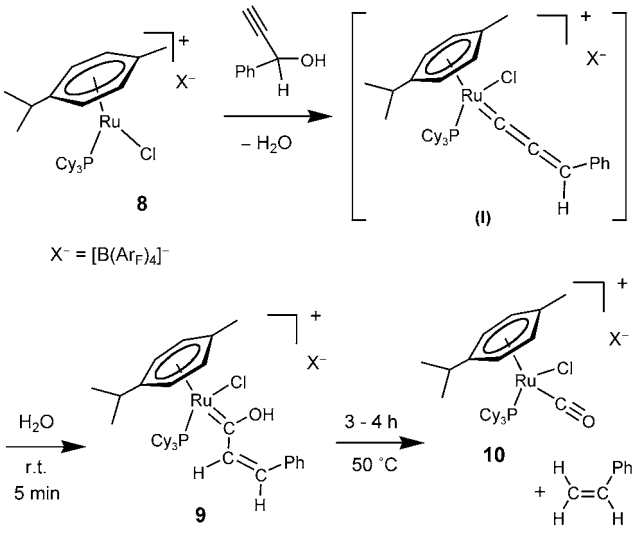
chloride abstraction from **2** and it also catalysed the reaction.

Stoichiometric low temperature NMR experiments provided a more accurate explanation. The unsaturated complex [(*p*-cymene)RuCl(PCy$_3$)][B(Ar$_F$)$_4$] (**8**) [Ar$_F$ = 3,5-(CF$_3$)$_2$C$_6$H$_3$][10] was treated with one equivalent of the alkynol **1** in CD_2Cl_2 and immediately cooled to −60 °C. Two species were detected by $^{31}P\{^1H\}$ NMR, showing singlets at δ = 39.0 and 58.1 ppm. When the temperature was raised to 0 °C, the first one (δ = 39.0 ppm) increased while the other completely disappeared (δ = 58.1 ppm).

The remaining species (δ = 39.0 ppm) could be identified by NMR as the alkenyl-hydroxycarbene complex [(*p*-cymene)RuCl(P-Cy$_3$){=C(OH)CH=CHPh}][B(Ar$_F$)$_4$] (**9**) (Scheme 4). The main spectroscopic data consist in signals at δ = 14.18 ppm and 287.5 ppm in the ^1H and $^{13}C\{^1H\}$ NMR spectra, respectively, which were analysed by COSY, HMBC and HMQC bidimensional experiments.[11] A comparison with related hydroxy and methoxycarbene complexes is also in good agreement with our data: [(η^5-C$_5$H$_5$)Ru(CO)(P-*i*-Pr$_3$){=C(OH)CH=CPh$_2$}][BF$_4$] (δ = 12.80 ppm, 298.7 ppm)[12] and [(η^6-C$_6$Me$_6$)RuCl-(PMe$_3$){=C(OMe)CH=CHPh}][PF$_6$] (δ = 302.6 ppm).[8]

The addition of water to a CD_2Cl_2 solution of **8** and the alkynol **1** in a NMR tube at −60 °C gave directly complex **9** as the only observed reaction product. Complex **9** was quite stable in solution at room temperature as a [B(Ar$_F$)$_4$]$^-$ salt, but it slowly disappeared over 50 °C, giving rise to a stable complex identified as [(*p*-cymene)-RuCl(PCy$_3$)(CO)][B(Ar$_F$)$_4$] (**10**) and to the release of free styrene, detected by NMR and GC-mass spectroscopy (Scheme 4).

The formation of complex **9** can be explained *via* the initial formation of an allenylidene complex **I** (signal at δ = 58.1 ppm in the $^{31}P\{^1H\}$ NMR spectrum), followed



Scheme 4.

by the addition of the released water to the electrophilic allenylidene α carbon atom, as depicted in Scheme 4. This is consistent with the faster hydroxycarbene formation observed in the presence of additional water, and with the addition of methanol to analogous arene-ruthenium allenylidene complexes, giving methoxycarbene complexes.[8]

Analogous experiments were carried out with the complex [(*p*-cymene)RuCl(PPh$_3$)][B(Ar$_F$)$_4$] (**11**), giving also the hydroxycarbene intermediate [(*p*-cymene)-RuCl(PPh$_3$){=C(OH)CH=CHPh}][B(Ar$_F$)$_4$] (**12**), and [(*p*-cymene)RuCl(PPh$_3$)(CO)][B(Ar$_F$)$_4$] (**13**) as the final product.

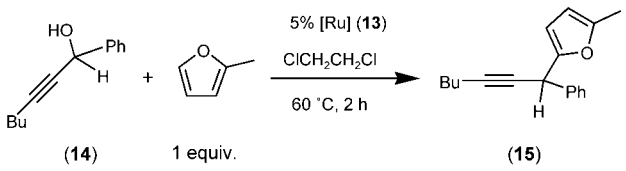
Hydroxycarbene species are reactive intermediates that have been seldom detected or isolated, although they are involved in stoichiometric and catalytic processes.[13] The selective allenylidene Cα-Cβ bond cleavage by water to carbonyl complexes with alkene release,[14] is a stoichiometric transformation similar to that reported here, and closely related to new catalytic transformations of propargyl alcohols such as hydration[15] or decarbonylation.[5d]

Mixed phosphine-carbonyl arene-ruthenium complexes have already been reported by Werner et al.,[16] and complexes **10** and **13** can be more readily prepared from the parent complexes **4** and **5** on addition of carbon monoxide. Surprisingly, the saturated complexes **10** and **13** also catalyse the propargylation of furan and 2-methylfuran by alkynol **1** and require a remarkable shorter reaction time. Under similar conditions (1,2-dichloroethane, 60 °C) the catalytic reaction was complete in 2 h. This observation explains why the addition of water improved the outcome of the reaction, favoring the formation of hydroxycarbene and subsequently of the carbonyl complex, which is actually the catalyst precursor.

The catalyst of choice appears to be the stable [(*p*-cymene)RuCl(CO)(PPh$_3$)][OTf] (**13**), which can be prepared with high yield in a three-steps synthesis from readily available reagents. A catalyst loading of 5% of **13** affords propargylated furan and 2-methylfuran in moderate yields (25 and 30%, respectively), when the catalytic mixture in 1,2-dichloroethane is heated for 2 h at 60 °C (Table 1, entries 5 and 6). Although an excess of the volatile furan is required (10 equivs.), only one equivalent of 2-methylfuran is necessary.

In order to test the propargylic substitution on internal alkynols and to question the possible existence of an allenylidene intermediate, the propargylic alcohol *n*-BuC≡CCH(OH)Ph (**14**) was reacted with one equivalent of 2-methylfuran at 60 °C in dichloroethane for 2 h in the presence of a 5 mol % of complex **13**, affording the corresponding propargylated product *n*-BuC≡CCHPh(Nu) [Nu = 5-methyl-2-furanyl (**15**)] in 45% yield (Table 1, entry 7 and Scheme 5).

The propargylic substitution of furan and 2-methylfuran with propargylic alcohols bearing both terminal or substituted alkynes, catalysed by complexes **10** and **13**,



Scheme 5.

cannot involve the formation of the allenylidene species Ru=C=C=CHR, which is specific for terminal alkynols HC≡CCH(OH)R. The operating mechanism still remains unclear since the release of one ligand seems to be mandatory to allow alkyne coordination. As a working hypothesis, precatalysts **10** and **13** can release the *p*-cymene during the initial catalytic step, to generate a coordinatively unsaturated, thus very reactive electrophilic species "[RuCl(CO)(PR_3)(solvent)$^+$]". This is supported by the observation (GC-MS) of free *p*-cymene besides the catalysis product. Since allenylidene involvement has been discarded, it seems more plausible that an activation process, analogous to that of the Nicholas reaction (Scheme 1),[2] takes place involving temporarily coordination of the triple bond, assistance to OH elimination and stabilization of the resulting propargyl cation.

In spite of the moderate yields obtained in the direct propargylation with respect to the Nishibayashi catalyst,[6e, f] this study reveals for the first time that a family of readily available mononuclear ruthenium precursors is able to catalyse such a reaction. This is attractive in view of the long list of tested mononuclear ruthenium complexes that failed as catalysts,[6] probably due to their electron-rich character and the non-lability of the ligands. The success in using more electrophilic complexes may arise from a good compromise between the ligands lability and the electronic properties of the resulting ruthenium species. Ongoing work intends to extend this reaction to other nucleophiles and to improve the yield by decreasing the side-reactions responsible of the formation of polymeric materials.

Experimental Section

General Remarks

All catalytic reactions were carried out under an inert atmosphere in Schlenk tubes. Chemicals were obtained commercially and used as supplied. Complexes [(*p*-cymene)$RuCl_2(PR_3)$] [PR_3=PPh_3 (**2**), PCy_3 (**3**)],[16] [(*p*-cymene)RuCl(PR_3)][OTf] [PR_3=PCy_3 (**4**), PPh_3 (**5**)],[17] were prepared according to the reported methods. [(*p*-cymene)RuCl(PR_3)][$B(Ar_F)_4$] [PR_3=PCy_3 (**8**), PPh_3 (**11**)] were obtained similarly to **4** and **5** but using $Na[B(Ar_F)_4]$[18] instead of silver salts as chloride abstractor. The complexes [(*p*-cymene)RuCl(CO)(PR_3)][OTf] [PR_3=PCy_3 (**10**), PPh_3 (**13**)] were obtained as described by Werner et al.,[16] but using AgOTf as chloride abstractor. NMR spectra were recorded on Bruker AM 3000 WB and DPX 200 spectrometers in deuterated solvents. IR spectra were recorded on a Bruker IFS28 spectrometer. Solvents were distilled before use from the appropriate drying agents. A Büchi GKR-51 oven was used for distillation.

Catalysis Products

122 μL of 1-phenyl-2-propyn-1-ol (1 mmol) were added to a 1,2-dichloroethane (2 mL) solution of the corresponding heterocycle (10 mmol of furan, 1 mmol of 2-methylfuran) and 0.05 mmol of the corresponding ruthenium catalyst. After 2 h at 60 °C, the solvent was removed under vacuum and the residue extracted with 2 × 5 mL of Et_2O. Purification of the product was carried out by distillation under reduced pressure, giving a pale yellow oil. NMR, IR and analysis data for 2-(1-phenyl-2-propynyl)furan (**6**), 2-methyl-(1-phenyl-2-propynyl)furan (**7**) and 2-methyl-(1-phenyl-2-heptynyl)furan (**15**) match well with those previously reported.[6] Although the catalytic tests were carried out under an inert atmosphere, none of the catalysts are specially sensitive to air or humidity.

Variable Temperature NMR Experiments

6.0 μL (0.049 mmol) of alkynol **1** were added to a CD_2Cl_2 solution of 64 mg (0.046 mmol) of **8**, or 65 mg (0.046 mmol) of **11**, in an NMR tube under inert atmosphere and cooled in an acetone/liquid N_2 bath. After mixing the reagents, the tube was immediately inserted into the NMR probe, previously cooled at −60 °C. ^1H, $^{31}P\{^1H\}$ NMR and bidimensional experiments (COSY, HMQC, HMBC) were recorded at different temperatures. Analogous experiments were carried out in the presence of 10 μL of H_2O, which was added just before the alkynol. Likewise, experiments with the triflate salts 4 and 5 confirmed the previous results, as inferred from ^1H and $^{31}P\{^1H\}$ NMR comparison.

Supporting Information Available

Characterization data (IR, ^1H, $^{31}P\{^1H\}$, $^{13}C\{^1H\}$ and bidimensional NMR) for compounds **9**, **10**, **12** and **13** are contained in the Supporting Information file.

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