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Ruthenium mediated carbon–carbon and carbon–nitrogen bond formation: parameters governing the reactivity of the metal centre

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Summary — A series of *C,N*-cyclometallated *N,N*-dimethylbenzylamine derivatives, [{*C,N*-benzylamine}RuCl(η^6-arene)] (η^6-arene = benzene or *para*-cymene), have been reacted with various alkynes in order to define the electronic and steric parameters governing the overall heterocyclisation reaction. As a general trend the electronic perturbations introduced by the substituents on the cycloruthenated substrate have a rather strong influence onto the reactivity of the Ru-center whereas the ancillary η^6-arene ligands show a less pronounced effect. The alkynes, ie, their substituents, were found to dramatically alter the course of the reaction. When the insertion of the alkyne into the Ru–C bond led to a compound displaying an ester group onto the metallated vinyl C-atom the reaction stopped at this organometallic intermediate whereas for aryl or alkyl substituents the insertion step was instantaneously followed by the C–N bond formation giving an isoquinolinium unit. These latter observations lead us to propose a reductive elimination pathway for the formation of the C–N bond.

ruthenium / alkyne / insertion / cycloaddition / heterocycle / cyclometallation

Résumé — Synthèses de liaisons carbone–carbone et carbone–azote induites par le ruthénium: étude du rôle des ligands sur la réactivité du centre métallique. Cet article traite de l'étude des différents paramètres stériques et électroniques mis en jeu lors de la réaction d'une série de composés cyclométallés [{*C,N*-benzylamine}RuCl(η^6-arène)] (η^6-arène = benzène ou *para*-cymène), avec divers acétyléniques pour conduire à des hétérocycles azotés. D'une manière générale les modifications électroniques introduites au niveau du ligand métallé ont une influence très marquée sur la réactivité du centre métallique alors que la nature du ligand ancillaire arène a peu d'effet. Les substituants des acétyléniques par contre ont un effet déterminant sur le cours de la réaction. Lorsque la réaction d'addition d'un alcyne conduit à un composé ayant une fonction ester sur le carbone lié au ruthénium la réaction s'arrête à ce stade. Lorsque c'est un groupe alkyle ou aryle qui se trouve sur le carbone ruthénié la réaction conduit alors sélectivement à la formation d'un composé hétérocyclique de type isoquinolinium. Cette observation nous a conduit à proposer un mécanisme pour la réaction d'élimination réductrice responsable de la formation de la liaison C–N.

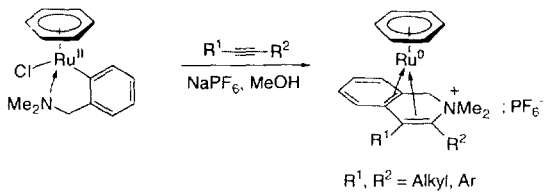
ruthénium / alkyne / insertion / cycloaddition / hétérocycle / cyclométallation

Introduction

In the field of metal-induced organic synthesis, cyclometallated complexes of transition metals are widely encountered [1]. A very appealing feature of these compounds resides in the ability of the metal center to activate both atoms of the substrate which are directly bound to the metal (ie, one C and one heteroatom), and to involve them in a novel type of cycloaddition reaction leading to heterocyclic products. This heterocyclisation was indeed observed through reaction of cyclopalladated species with internal alkynes. The products are thus obtained via a carbon–carbon and a carbon–heteroatom bond formation. Whereas the synthesis of the former bond can be rationalized by a formal insertion of the alkyne into the Pd–C bond, the latter step has not been rationalized yet. Indeed this type of C–N or C–S bond formation is not common in organic synthesis [2] and moreover it occurs with tertiary amines (sp^3 or sp^2 and pyridinic N atoms) [3] or thioether functions [4]. It appears that this reaction scheme is quite general since it takes place with various internal alkynes and compounds containing a large variety of metallocyclic units. It is therefore important to gain deeper insight into the mechanism by which the heterocycles are formed. The present paper is dealing with product selectivity and reactivity studies contributing to an understanding of this area.

Recently we reported on a very efficient Ru-mediated formation of *N*-heterocycles (ie, isoquinoline derivatives) by reaction of cyclometallated *N,N*-dimethylbenzylamines with alkynes [5]:

* Correspondence and reprints



This reaction was thought to proceed by insertion of the alkyne unit into the Ru–C bond followed by a C–N reductive coupling step. This assumption has been recently confirmed by a mechanistic study [6]. It has been shown that the first step of the process was the insertion of the alkyne into the Ru–C bond, this reaction being mechanistically very similar to the insertion of an alkyne into the Pd–C bond of related cyclopalladated complexes. This study has moreover shown that the rate of the insertion is mainly governed by electronic effects of the substituents at the cycloruthenated units, those bearing electron releasing groups being the more reactive ones. In contrast the nature of the substituents on the alkynes seem to have only a marginal effect on the reaction rate.

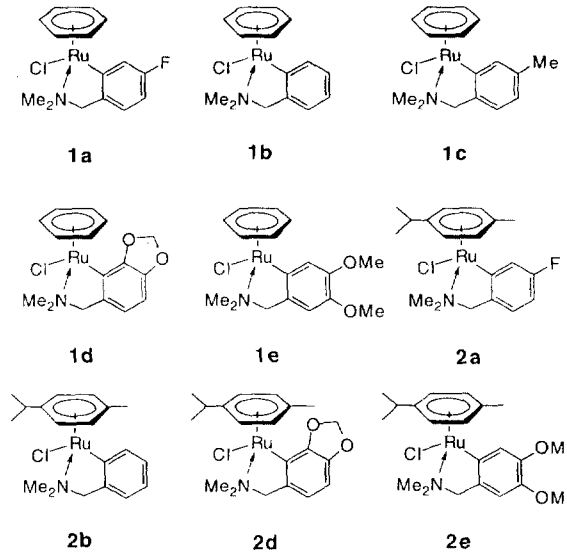
With this in mind we have embarked on a study aimed at defining the scope and limits of this heterocyclisation reaction and to gain more insight into the mechanism of the formation of the C–N bond. We have thus performed a more systematic study of the reactivity of a series of cycloruthenated benzylamine derivatives with various internal alkynes. This paper reports on the relative influence of (i) the metallated benzylamine substrate, (ii) the ancillary η^6-arene and (iii) the alkyne reagent on the cycloaddition process. In order to study their effects on the reaction rate and product distribution we have choosen electronic and steric perturbations via various substituents on each of these three components and followed the development of the reactions by ^{1}H NMR spectroscopy.

Results

In our first report, the reaction of *C,N*-cycloruthenated compounds with alkynes was described to be fast in MeOH in the presence of $NaPF_6$, to afford the isoquinoline heterocycle η^4-coordinated to the Ru(0) moiety (see the equation above) [5]. However, $NaPF_6$ as activating reagent is not essential for the reaction to take place. Under stoichiometric conditions in MeOH, complete reaction can occur in a range of minutes to hours, allowing us to compare the effects of the perturbations introduced by the substituents at the ligands by means of conversion rate to product versus time.

A series of *C,N*-cycloruthenated *N,N*-dimethylbenzylamine derivatives, [{*C,N*-benzylamine}RuCl(η^6-arene)], were prepared with electron-donating and electron-withdrawing substituents on the metallated aryl moiety, and either benzene, **1a–e**, or *para*-cymene, **2a,b,d,e**, as ancillary η^6-arene ligand (see scheme 1) [7].

These complexes were reacted with internal alkynes containing electron-releasing groups, ie, Et≡Et, **A**, and Ph≡Me, **B**, and electron-withdrawing groups, ie, Ph≡CO_2Et, **C** and MeO_2C≡CO_2Me, **D** (see scheme 2).



Scheme 1

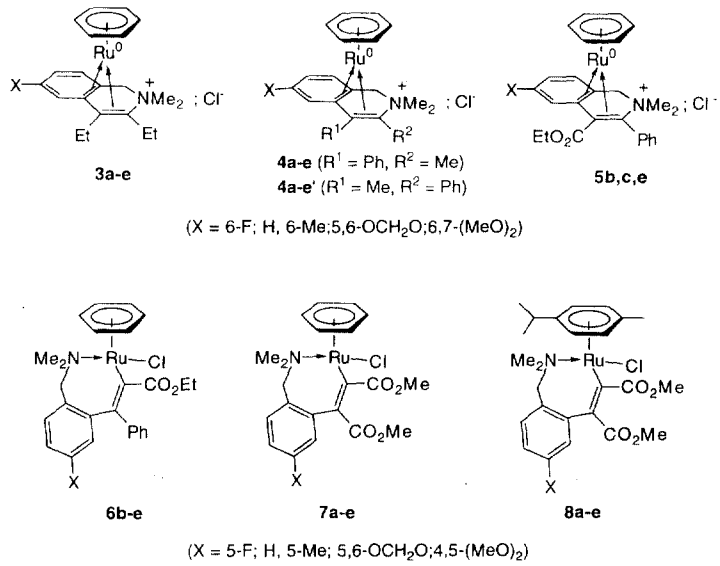
Moreover the use of non-symmetrically substituted alkynes, **B** and **C**, may shed light on the regioselectivity of the insertion reation.

All reactions have been performed in standard conditions: [Ru compound]$_0$ = [alkyne]$_0$ = 0.1 mol L^{-1} in MeOH at 25 °C under a nitrogen atmosphere. After 15 min, 30 min, 60 min and 120 min, aliquots of the reaction mixture were taken, evaporated to dryness and redissolved in $CDCl_3$ for ^{1}H NMR measurement. The relative amount of starting material and Ru-products present in each samples were obtained by integration. The results are shown in table I as conversion (%) vs time. The compounds **3–5** obtained here, though rather stable in solution, proved to be very difficult to handle in the solid state and their purification was not possible so that we could not get good combustion analyses for none of them. This behaviour is likely to be due to the presence of the Cl^- counter anion as we have shown in our previous study that the PF_6^- analogues could be fully characterised including by a crystal structure determination.

For one of these compounds, ie, **3e**, we have substituted the Cl anion by BF_4^- and we have indeed obtained good analytical results for this derivative (**3e**($\mathbf{BF_4}$), see experimental section). The other reaction products obtained in this study, **6–8** did also display an analogous behaviour, since except for **7d**, they all decomposed whilst we attempted their isolation in the solid state. We have thus mainly characterised the products by their ^{1}H NMR spectra and for some of them by conductivity measurements.

The alkyne

The data gathered in this study show that for a given cycloruthenated compound the alkyne has a rather small effect on the insertion rate. The developments of the reactions of **1b** with each of the alkynes, **A** through **D**, are presented in figure 1. No significant difference appeared between the reactions performed with the electron rich or electron poor alkynes. As a general feature though, the electron poor alkynes **C** and **D** reacted



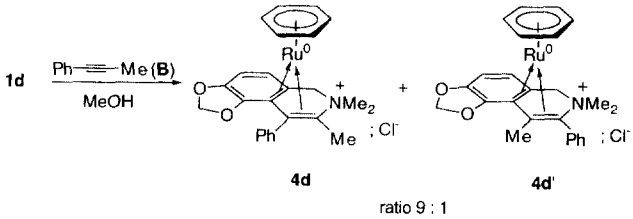
Scheme 2

Table I. Conversion (%) versus time of compounds **1a–e**, **2a,b** and **2d,e** followed by ^{1}H NMR.

Entry	*Complex*	*Alkyne*[a]	*Product*[d]	*Conversion (%) versus time (min)*[b,c]				*Ratio*[c]
				t = 15	*t = 30*	*t = 60*	*t = 120*	
1	**1a**	**A**	**3a**	6.8	12.2	20.6	38.0	
2	**1a**	**B**	**4a, 4a′**	7.3	15.6	27.7	60.5	1/1
3	**1a**	**D**	**7a**	13	27	36	61	
4	**1b**	**A**	**3b**	21.7	36	55	77	
5	**1b**	**B**	**4b, 4b′**	29.7	40.7	58.6	81.2	5/7
6	**1b**	**C**	**5b, 6b**	18.6	34.3	48.5	70.8	1/4
7	**1b**	**D**	**7b**	21.8	37.9	59.4	83.4	
8	**1c**	**A**	**3c**	100	–	–	–	–
9	**1c**	**B**	**4c, 4c′**	100	–	–	–	2/3
10	**1c**	**C**	**6c**	100	–	–	–	
11	**1c**	**D**	**7c**	100	–	–	–	
12	**1d**	**A**	**3d**	31	50	75	100	
13	**1d**	**B**	**4d, 4d′**	27	44	100	–	9/1
14	**1d**	**C**	**6d**	63	100	–	–	
15	**1d**	**D**	**7d**	54	84	100	–	
16	**1e**	**A**	**3e**	100	–	–	–	
17	**1e**	**B**	**4e, 4e′**	100	–	–	–	1/1
18	**1e**	**C**	**6e**	100	–	–	–	
19	**1e**	**D**	**7e**	100	–	–	–	
20	**2a**	**D**	**8a**	–	–	–	10	
21	**2b**	**D**	**8b**	18	32	49	59	
22	**2d**	**D**	**8d**	18	36	51	58	
23	**2e**	**D**	**8d**	100	–	–	–	

[a] **A** = Et≡Et, **B** = Ph≡Me, **C** = Ph≡CO_2Et and **D** = MeO_2C≡CO_2Me; [b] reaction performed in MeOH, c = 0.1 mol L^{-1}, at room temperature; [c] % conversion and ratio were deduced from ^{1}H NMR signal integrations of the reaction products and cycloruthenated reagent; [d] products identified on the assignment of the ^{1}H NMR chemical shifts.

slightly faster with the organoruthenium compounds. In the case of the non-symmetrical substituted alkynes two regioisomers were usually observed and it is very likely that their ratio depends mainly on steric factors. When the steric demand of both substituents of the incoming alkyne are similar, like Me and Ph in **B** [8], the regioselectivity is poor and the two regioisomers, **4** and **4′** (see scheme 2) were found in a ratio close to 1:1 (see table I). In contrast when the two substituents are sterically more different as in Ph≡CO_2Et, the selectivity increases and the major compound, **6**, displays the Ph group on the carbon atom adjacent to the previously ruthenated aryl unit. The presence of a group *ortho* to Ru in the metallated aryl unit, as in compound **1d**, dramatically increases the regioselectivity, and even for alkyne **B**, a selectivity close to 90% was observed:



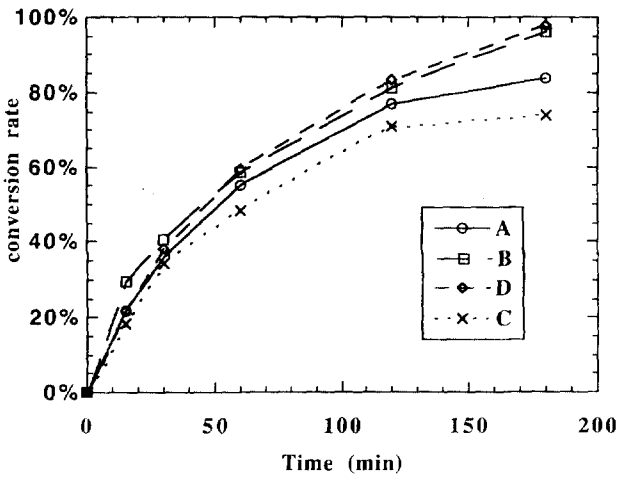
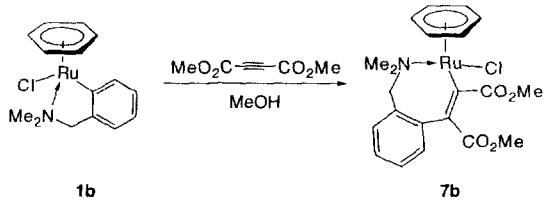


Fig 1. Graphical view of the conversion (%) versus time of **1b** with alkynes **A** to **D**.

Based on its ^{1}H NMR spectrum the major product, **4d**, corresponds to the isoquinolinium isomer in which the Me group is adjacent to the N atom.

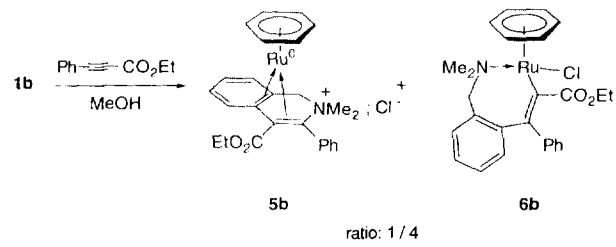
A dramatic difference in the reaction course was found for alkynes **C** and **D** bearing at least one electron withdrawing group. For example the product of the reaction of **D** with **1b**, **7b**, was found to have peculiar properties compared to the cycloaddition products **3b** and **4b**. It was poorly soluble in MeOH, rather stable towards air oxidation and it did not afford the organic heterocycle in the presence of Cu(II) salt as observed previously with the Ru(0) compounds [5]. The ^{1}H NMR data of **7b** showed a set of resonances corresponding to a product obtained through a 1:1 addition stoichiometry. However, markedly different chemical shifts as compared to those observed for $[\{\eta^4$-isoquinolinium$\}$Ru$(\eta^6$-$C_6H_6)]^+$ compounds were found. For **7b** the signals corresponding to η^6-C_6H_6, CH_2 and NMe_2 fragments display resonances upfield of those found in **3b** (see table II). Moreover, a conductivity measurement performed in acetone showed that **7b** is non-ionic in solution as compared to the conductivity measured for a typical cationic product. This information strongly suggests that **7b** is the organoruthenium (II) compound resulting from the insertion of alkyne **D** into the Ru–C bond of **1b**:



1b **7b**

Thus with **D**, C–N bond formation does not take place. The same result was obtained for all the cycloruthenated benzylamine derivatives when reacted with the alkyne **D**. In no case the formation of an heterocycle has been observed.

The asymmetric alkyne, **C**, led to the formation of two compounds. For instance, the reaction of **C** with **1b** gave two products, **5b** and **6b**, in ca 1:4 ratio. Based on ^{1}H NMR and conductivity data these compounds were indentified as the $[\{\eta^4$-isoquinolinium$\}$Ru(0)], **5b**, and the Ru(II) insertion products, **6b**, respectively:



5b **6b**

ratio: 1 / 4

These compounds result from the two possible regioisomers of the insertion of **C** into the Ru–C bond. For **5b** the alkyne was inserted in such a way that it is the C atom substituted with the CO_2Et group which is involved in the C–C bond formation with the aryl moiety. This insertion step leading to a transient Ru(II) intermediate was followed by a C–N reductive coupling step to give **5b**.

For **6b** the insertion led to the formation of the new C–Ru bond with the C atom being substituted by the ester substituent and the reaction stopped at this stage as was observed for alkyne **D**. These results gathered with **C** and **D** suggest that the presence on the metallated C atom of an electron-withdrawing group like an ester deactivates the metal center towards the C, N reductive elimination step.

The benzylamine substrate

In agreement with the previous mechanistic studies based upon analyses of electronic spectra [6] we have good evidence that the electronic perturbation of the benzylamine substrate by various substituents has an important effect on the reactivity of the metal center. This was confirmed here by the conversion rates observed for the substituted compounds **1a,c–e** compared to the non-substituted reference compound **1b** (see table I and fig 1).

A graphical view of the rates of conversion vs time for the addition reactions of **1a–e** with **A** is given in figure 2. Compound **1a**, substituted by an electron-withdrawing group, showed a conversion into **3a** of ca 40% after 120 min whereas **1c** or **1d**, substituted by electron releasing groups, were already totally converted in less than 15 min into **3c** and **3d**, respectively. The conversion rate of the unsubstituted compound **1b** into **3b** was found to be intermediate between **1a** and **1e**. The derivative **1d**, although substituted by electron releasing groups, has a somewhat slower conversion rate as compared to that of **1c** or **1e**. Here the presence of a substituent *ortho* to the metal could account for this difference as steric hindrance between the incoming alkyne and the organoruthenium moiety is likely to occur during the addition process and thus slows down the reaction rate.

The observed kinetics are clearly related to the electronic effects due to the metallated arylamine unit. An electron rich cycloruthenated aryl moiety as for **1c** and **1d**, increases the reactivity of the metal center.

Table II. ^{1}H NMR data ($CDCl_3$, δ in ppm and J in Hz).

Product	*^{1}H chemical shifts*				
	Aromatics	*η^6-arene*	*CH_2N*	*NMe_2*	*Other groups*
3a	7.33 (dd, ^{1}H, $^3J_{HH}$ = 8, $^4J_{FH}$ = 6); 6.97(dd, 1H, $^3J_{FH}$ = 11, $^4J_{HH}$ = 2); 6.53 (ddd, 1H, $^3J_{FH}$ = 10)	5.18 (s, 6H)	4.05, 3.25 (2d, $^2J_{HH}$ = 13)	3.17, 2.76 (2s)	2.85, 2.45 (2m, 4H, CH_2CH$_3$); 1.39, 1.24 (2t, 6H, CH$_2$CH_3, $^3J_{HH}$ = 7)
4a	7.58–6.96 (broad m)	5.38	4.41, 3.54 (2d, $^2J_{HH}$ = 15)	3.37, 2.64	1.69 (s, 3H, Me)
4a′	7.58–6.96 (broad m)	5.22	4.36, 3.54 (2d, $^2J_{HH}$ = 14)	3.29, 2.71	2.40 (s, 3H, Me)
7a	7.30, 7.18, 7.02 (3m, 3H)	5.02	3.49, 2.84 (2d, $^2J_{HH}$ = 12)	3.15, 2.44	3.72 and 3.69 (2s, CO_2Me)
3b	7.48, 7.17, 6.71 (3m, 4H)	5.09	4.18, 3.63 (2d, $^2J_{HH}$ = 13.8)	3.38, 2.89	3.45, 2.85 and 2.40 (3m, 4H, CH_2CH$_3$); 1.43 and 1.25 (2t, 6H, CH$_2$CH_3, $^3J_{HH}$ = 7.5, 7.4)
4b	7.60–6.60 (m, 8H)	5.30	4.33, 3.55 (2d, $^2J_{HH}$ = 14)	3.47, 2.81	1.70 (s, 3H, Me)
4b′	7.60–6.60 (m, 8H)	5.11	4.33, 3.63 (2d, $^2J_{HH}$ = 13.8)	3.46, 2.78	2.46 (s, 3H, Me)
5b	7.40–7.15 (m, 9H)	5.26	[a]	2.60	3.95 (m, 2H, CH_2CH$_3$); 1.19 (t, 3H, CH$_2$CH_3, $^3J_{HH}$ = 7.1)
6b	7.40–7.15 (m, 9H)	5.02	3.75, 2.78 (2d, $^2J_{HH}$ = 11)	3.22, 2.48	3.92 (m, 2H, CH_2CH$_3$); 0.85 (t, 3H, CH$_2$CH_3, $^3J_{HH}$ = 7)
7b	7.58 (d, 1H, $^3J_{HH}$ = 7.6); 7.41 (dt, 1H, $^3J_{HH}$ = 7.6, 1.6); 7.30 (dt, 1H, J_{HH} = 7.5, 1.6), 7.23 (d, 1H)	4.97	3.55, 2.75 (2d, $^2J_{HH}$ = 12)	3.18, 2.44	3.74 and 3.70 (2s, 6H, OMe)
3c	7.18 (s); 7.06 (d, $^3J_{HH}$ = 9); 6.49 (dd, $^4J_{HH}$ = 1.6)	5.09	3.82, 3.15 (2d, $^2J_{HH}$ = 14)	3.12, 2.63	2.20 (s, 3H, Me); 2.70, 2.37 (2m, 4H, CH_2CH$_3$); 1.41, 1.24 (2t, 6H, CH$_2$CH_3, $^3J_{HH}$ = 7.5)
4c	7.50 (broad s); 7.33 (m); 7.21 (m)	5.25	4.22, 3.24 (2 broad d)	3.27, 2.46	2.52 and 1.84 (2s, 6H, Me)
4c′	7.50 (broad s); 7.33 (m); 7.21 (m)	5.08	4.22, 3.24 (2 broad d)	3.39, 2.36	2.46, 2.02 (2s, 6H, Me)
5c	not observed				
6c	7.19–7.14 (m, 5H) 7.10, 6.99 (2d, $^3J_{HH}$ = 8), 7.00 (s, 1H, H6)	5.00	3.67, 2.74 (2d, $^2J_{HH}$ = 11)	3.18, 2.52	3.88 (m, 2H, CH_2CH$_3$); 2.25 (s, 3H, Me); 0.68 (t, 3H, CH$_2$CH_3, $^3J_{HH}$ = 7)
7c	7.35 (s, 1H), 7.11, 7.08 (2d, 2H, $^3J_{HH}$ = 8)	4.95	3.88, 3.57 (2d, $^2J_{HH}$ = 11)	3.15, 2.47	3.71, 3.68 (2s, CO_2Me), 2.40 (s, Me)
3d	6.87 (d); 6.58 (d, 2H, $^3J_{HH}$ = 9)	5.16	4.10, 3.28 (2d, $^2J_{HH}$ = 13)	3.20, 2.79	6.05, 5.83 (2d, OCH$_2$O, $^2J_{HH}$ = 1.5); 3.14, 2.30 (2m, 4H, CH_2CH$_3$); 1.40, 1.23 (2t, 6H, CH$_2$CH_3, $^3J_{HH}$ = 7)
4d	7.37 (m); 6.99, 6.64 (d, 1H, $^3J_{HH}$ = 9)	5.37	4.16, 3.19 (2d, $^2J_{HH}$ = 14)	3.25, 2.94	5.84, 5.54 (d, OCH$_2$O, $^2J_{HH}$ = 1.4); 1.62 (s, Me)
5d	not observed				
6d	7.17–7.05 (m, 5H), 6.75, 6.71 (2d, 2H, $^3J_{HH}$ = 8)	5.04	3.61, 2.67 (2d, $^2J_{HH}$ = 12)	3.12, 2.41	5.88, 5.64 (2d, OCH$_2$O, $^2J_{HH}$ = 1) 3.92, 3.75 (2m, CH_2CH$_3$), 0.72 (t, CH$_3$, $^3J_{HH}$ = 7)
7d	6.78, 6.73 (2d, 2H, $^3J_{HH}$ = 8)	5.03	3.44, 2.66 (2d, $^2J_{HH}$ = 12)	3.12, 2.39	6.08, 5.98 (2d, OCH$_2$O, $^2J_{HH}$ = 1.2); 3.68 (s, 6H, CO_2Me)
3e	6.48, 6.34 (2s, 2H)	5.09	3.99, 3.24 (2d, $^2J_{HH}$ = 13)	3.10, 2.72	3.82, 3.75 (2s, OMe); 2.91, 2.72, 2.43, 2.22 (4m, 4H, CH$_2$); 1.37, 1.19 (2t, 6H, CH$_2$CH_3, $^3J_{HH}$ = 7)
4e	7.60–7.13 (m, 5H); 6.83, 6.08 (2s, 2H)	5.25	3.19, 2.62 (2 broad d)	3.41, 2.46	3.80 (s, 6H, OMe); 1.99 (s, 3H, CH$_3$)
4e′	7.60–7.13 (m, 5H); 6.84, 6.54 (2s, 2H)	5.10	3.19, 2.62 (2 broad d)	3.57, 2.51	3.80 (s, 6H, OMe); 2.51 (s, 3H, CH$_3$)
5e	not observed				
6e	7.18–7.07 (m, 5H), 6.69, 6.52 (2s)	5.05	3.64, 2.70 (2d, $^2J_{HH}$ = 12)	3.19, 2.52	3.84 (m, CH_2CH$_3$) 3.81 (s, 2CH$_3$), 0.67 (t, CH$_2$CH_3, $^3J_{HH}$ = 7)
7e	7.33, 7.06 (2s, 2H)	5.02	3.45, 2.65 (2d, $^2J_{HH}$ = 12)	3.17, 2.41	3.92, 3.91 (2s, OMe); 3.71, 3.69 (2s, CO_2Me)
8a	7.18 (m, 2H); 6.96 (dt, 1H, J_{HH} = 12 and 1.5)	3.31, 4.81, 4.88 (3d, 3H, $^3J_{HH}$ = 5.8); 2.87 (sept, 1H, $^3J_{HH}$ = 5); 2.02 (s, 3H); 1.31, 1.17 (2d, 6H)	3.45, 2.70 (2d, $^2J_{HH}$ = 12)	3.00, 2.48	3.71 and 3.69 (2s, 6H, CO_2Me)
8b	7.47 (d, 1H, $^2J_{HH}$ = 7.8); 7.32 (dt, 1H, J_{HH} = 1.3 and 7), 7.21 (m, 2H)	5.25, 4.73, 4.55 and 3.45 (4d, 4H, $^3J_{HH}$ = 6); 2.80 (m, 1H); 1.96 (s, 3H), 1.27, 1.10 (2d, 6H, $^3J_{HH}$ = 7)	3.42, 2.69 (2d, $^2J_{HH}$ = 12)	3.00, 2.42	3.64 (s, CO_2Me)

Table II. (continued)

Product	^1H *chemical shifts* *aromatics*	η^6-*arene*	CH_2N	NMe_2	*Other groups*
8d	6.76 and 6.71 (2d, 2H, $^3J_{HH} = 8$)	5.24 and 4.91 (2 broad s, 2H); 3.80 (m, 2H); 2.90 (m, 1H); 2.04 (s, 3H). 1.30 and 1.19 (2d, 6H, $^3J_{HH} = 8$)	3.43, 2.67 (2d, $^2J_{HH} = 12$)	2.98, 2.48	6.07 and 6.98 (2s, 2H OCH_2O); 3.70 (s, 6H, OMe)
8e	6.91 and 6.65 (2s, 1H)	5.16, 4.83, 4.72, 3.69 (4d, $^3J_{HH} = 5.5$); 2.83 (m, 1H); 1.98 (s, 3H); 1.24, 1.13 (2d, 6H, $^3J_{HH} = 7$)	3.38, 2.61 (2d, $^2J_{HH} = 12$)	2.96, 2.45	3.78 (s, 6H, CO_2Me); 3.65, 3.61 (2s, 6H, OMe)

[a] Signals superimposed on the resonances of the second isomer of the reaction.

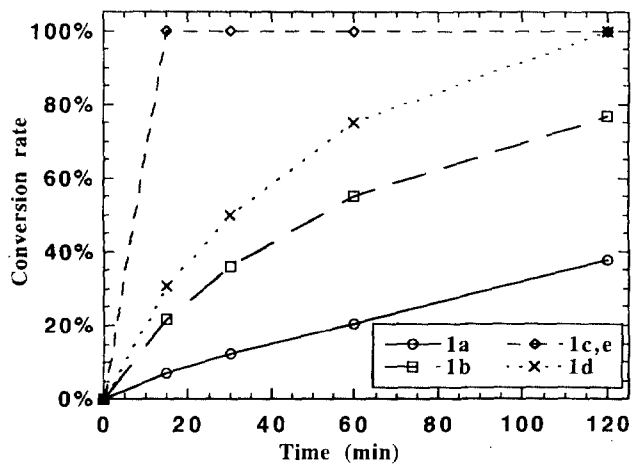


Fig 2. Graphical view of the conversion (%) versus time of **1a–e** with alkyne **A**.

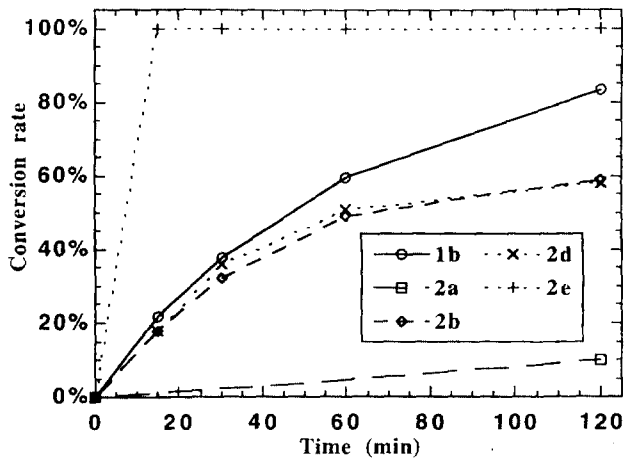


Fig 3. Graphical view of the conversion (%) versus time of **2a,b,d,e** with alkyne **D** compared to **1b**.

ie, the addition rate is increased, whereas the opposite trend is found for the substrate substituted by an electron-withdrawing group. These electronic considerations might also have an influence on the stability of the products formed by the reaction. Indeed in the reactions performed with **1c**, the evolution of the products rapidly took place leading to some decomposition of the Ru(0) product, this being not the case with the less reactive *C,N*-cycloruthenated compounds.

The η^6-arene

The effect of the η^6-arene ancillary ligand on the reactivity of the [{benzylamine}RuCl(η^6-arene)] compounds has been investigated by comparing the η^6-benzene derivatives, **1a–e**, and their η^6-*para*-cymene analogues, **2a,b,d,e** (table I and fig 3).

The reaction rates of the *para*-cymene compounds towards alkynes appeared somewhat slower than for the benzene derivatives but followed the same trend, ie, the substrates substituted by electron releasing groups react much faster than those containing an electron withdrawing group. For example, in the reaction with alkyne **D** a conversion of ca 60% for **2b** was found after 120 min compared to ca 80% for **1b**. For the very reactive substrate as in **1e** and **2a** no noticeable difference was observed as for both compounds total transformation was obtained within 15 min. For **1d** and **2d** containing a sterically more congested C–Ru bond the difference of reaction rate was much more pronounced. A complete transformation of **1d** in **7d** was found in 30 min whereas the conversion of **2d** only amounted ca 60% after 120 min.

Discussion

The work described in this report was undertaken in order to gain some information about the influence of the metal-surrounding on the reactivity of the Ru–C σ-bond and the subsequent C–N bond formation step. The present results show that the three components, ie, the cyclometallated benzylamine substrate, the η^6-arene ligand, and the incoming alkyne have an influence on the cycloaddition reaction. This is expressed by the observed reaction rates as well as by the obtained reaction products. The nature of the effects – electronic or/and steric – and their localisation on each of the components (see above) determinate their relative importance.

The substrate

This study has indeed confirmed that the major effects on the relative rates of the various reaction studied is due to the electronic contributions brought about by

the cycloruthenated ligands. This is likely to be related to the ease of dissociation of the Ru–Cl bond, this being more readily achieved with the more electron rich cycloruthenated substrates [6].

Steric interferences of the substrate on the insertion have to be considered when a substituent is present on the C atom *ortho* to Ru. It is likely that any substituent in this position might hinder the formation of the C–C bond thus affecting significantly the rate of the insertion reaction. As anticipated, these steric interferences appeared to occur for compounds **1d** and **2d**. Despite an electron-donating group, (2,3-OCH_2O–), which clearly should have enhanced the conversion rate, a rather slow reaction was observed as compared to **1c** or **1e** and **2e**, respectively. However, the steric perturbation for compounds **1d** and **2d** remains weak compared to the electronic activation as they still react at least as fast as the unsubstituted derivatives, **1b** and **2b**, respectively.

The η^6-arene ligand

Similarly to what was observed for the benzylamine substrates the electronic effect of the η^6-*para*-cymene ligand should have resulted in an acceleration of the reaction rate as it might be considered as a more electron releasing ligand because of the methyl and isopropyl substituents [9]. However the overall effect of changing the η^6-benzene unit for the η^6-*para*-cymene is a slight decrease in the rate of the reaction observed. This can be interpreted as the result of increased steric hindrance at the ruthenium which would decrease the rate of the coordination of the alkyne to the metal unit. This effect might be in line with the steric interference of the η^6-arene substituents for which we have evidence from the synthesis of a series of *C,N*-cycloruthenated benzylamines [7]. The Ru(0) sandwich compounds obtained from the *para*-cymene derivatives which have been reacted with either alkynes **A** or **B** were so unstable that they decomposed while being formed. This is the reason why no such compounds have been described here. This high instability can be related to the electronic releasing properties of the *para*-cymene which increases the electronic density at the Ru centre and thus increases the rate of its oxidation.

The alkyne

The type of the alkyne used in this study has a dramatic effect upon the nature of the product formed. Whereas with 3-hexyne, **A**, and 1-phenylpropyne, **B**, the expected heterocyclisation has taken place affording **3** and **4**, with dimethyl acetylenedicarboxylate, **D**, the reaction stopped at the stage of the insertion of the alkyne into the Ru–C bond leading to the novel 7-membered cycloruthenated derivatives **7** and **8**. Earlier kinetic studies have indeed pointed to a peculiar behaviour of this latter electron poor alkyne as compared to that of other reagents used [6] but no evidence for the type of compound formed could be found.

Finally the non-symmetrical alkyne **C** led to a combination of both type of products (**5** and **6**) depending on the regioselectivity of the alkyne insertion into the Ru–C bond. This latter result shows that whilst the insertion into the Ru–C bond has taken place, the nature of the substituent on the vinyl carbon atom σ-bonded to Ru has a determining effect upon the occurence of the C–N coupling step to form the heterocyclic unit. Indeed the presence on this C atom of a strongly electron withdrawing group such as an ester unit totally inhibited the C to N coupling reaction. Interestingly, in the other regioisomer this coupling takes place. This result sheds light upon the likely pathway followed in the C–N bond formation step that we, and others, have found to occur with these cyclometallic compounds. We can consider either a nucleophilic addition of the decoordinated nitrogen atom onto the metallated vinyl group, or the reverse pathway through which the C atom could perform a formal nucleophilic addition on the N atom, the latter grouping being made electrophilic while coordinated to the metal center. According to the results obtained in the present study we tend to favour the second hypothesis. Indeed this somewhat provocative suggestion should take place in a concerted manner, this leading in the end to a reaction analogous to a reductive elimination reaction. The first hypothesis may be ruled out as we should have had observed an easy formation of the C–N bond in the case where the vinyl C atom is substituted by a CO_2Et group, and thus made more electrophilic. The same remark obviously applies for the reaction observed with the dimethyl acetylenedicarboxylate, **D**, leading to the compounds **7** and **8** as the vinyl C atoms should be here also much activated towards nucleophilic addition of the N atom. Analyzing related reactions obtained in our group for Pd analogues it appeared that the C to N addition pathway we have favoured in this study is somewhat able to rationalize most of the reactions observed. These organo-Pd derivatives were shown to demetalate under smooth conditions leading selectively to carbo- or heterocyclic compounds except when an ester group was present on the metallated C atom [10].

Conclusion

This study allows us to better understand and control the reactivity of the cycloruthenated complexes which should be useful in planned heterocycle syntheses. Thus we know that electron releasing groups on both the cyclometallated and ancillary ligands will speed up the C–C bond formation. We have also a deeper insight into the mechanism whereby the N–C bond is being formed by an overall reductive elimination process. It appears thus that the N–C coupling reaction will mainly depend upon the nature of the substituents of the alkynes, the presence of strongly electron withdrawing groups being less prone to induce the heterocyclisation.

Experimental section

General considerations

All reactions were performed by using standard Schlenk tube and vacuum line techniques. The solvents used were dried and distilled under N_2 prior to use. ^1H NMR and $^{13}C\{^1H\}$ spectra ($CDCl_3$, 298 K, δ in ppm, J in Hz, with the solvent signal as internal standard) were recorded at 300.13 MHz and 75.47 MHz respectively on Bruker AC 300 and ARX 300 spectrometers. Commercial compounds were

used as received. The cycloruthenated compounds **1a–e** and **2a,b,d,e** were prepared according to the published methods [5, 7]. The reaction products between these substrates and alkyne decomposed while trying to isolate them especially while trying to purify them by chromatography. We have thus not been able to obtain decent combustion analytical nor HRMS data except for the compounds reported below; therefore we have only characterized the various compounds by ^{1}H NMR. The conductivity measurements have been performed on a Philips PW9509 digital conductivitymeter from acetone solution of the complexes.

General procedure for ^{1}H NMR followed reactions

The appropriate cycloruthenated compound (0.5 mmol) was suspended into MeOH (5 mL), the alkyne (0.5 mmol) was added and the mixture stirred at room temperature. Samples for ^{1}H NMR were removed by syringe and immediately dried in vacuo. These samples were redissolved in $CDCl_3$ just before the ^{1}H NMR measurement.

- *Synthesis of $[(\eta^6\text{-}C_6H_6)Ru(C_6H_2\text{-}6,7\text{-}(OCH_3)_2\text{-}CH_2NMe_2CEt{=}CEt\text{-}3,4)]^+[BF_4]^-$,* ***3e(BF$_4$)***

$AgBF_4$ (0.12 g, 0.61 mmol) was added to a solution of $[(\eta^6\text{-}C_6H_6)Ru(C_6H_2\text{-}3,4\text{-}(OCH_3)_2CH_2NMe_2)Cl]$ (0.25 g, 0.61 mmol), **1e**, in MeOH (25 mL) at 20 °C. AgCl precipitated immediately and a deep red suspension was obtained. After 5 min of stirring at RT, hex-2-yne was added (0.07 mL, 0.62 mmol), the suspension was stirred for an additional hour (colour changed gradually to greenish- yellow) and then filtered over a Celite pad. The solution was concentrated under reduced pressure until a yellow solid began to precipitate. The suspension was kept at −18 °C for 12 h, resulting in the precipitation of a microcrystalline yellow solid (**3e(BF$_4$)**) which was filtered, washed with 5 mL of Et_2O and dried in vacuo (0.16 g, 47% yield).

Anal calc for $C_{23}H_{32}BF_4NO_2Ru$: C, 50.93; H, 5.94; N, 2.58. Found: C, 49.93; H, 5.87; N, 2.52.

^{1}H NMR data are identical to those of **3e** in table II.

$^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 152.18, 148.00, 112.12, 99.03, 94.52, 92.54, 77.90, 60.56 (C_6H_2 + $C_3{=}C_4$), 85.57 (C_6H_6), 75.31 (CH_2N), 56.03, 55.92 (2 OMe), 56.04, 51.81 (NMe_2), 29.26, 23.99 (–CH_2CH_3) and 15.99, 15.86 (–CH_2CH_3). Conductivity of **3e(BF$_4$)** (8.71×10^{-4} M): 130.9 ohm^{-1} cm^2 mol^{-1} (1:1 electrolyte) (for comparison: **1e** (neutral complex) (2.40×10^{-3} M): 0.42 ohm^{-1} cm^2 mol^{-1}; **3d(BF$_4$)** (8.26×10^{-4} M): 142.15 ohm^{-1} cm^2 mol^{-1}).

- *Synthesis of $[(\eta^6\text{-}C_6H_6)Ru(C(CO_2Me){=}C(CO_2Me)C_6H_2\text{-}2,3\text{-}(OCH_2O)CH_2NMe_2)Cl]$,* **7d**

To a suspension of $[(\eta^6\text{-}C_6H_6)Ru(C_6H_2\text{-}2,3\text{-}(OCH_2O)CH_2NMe_2)Cl]$, **1d**, (0.250 g, 0.64 mmol) in 15 mL of MeOH at room temperature, were added dimethyl acetylenedicarboxylate (DMAD, $MeO_2C{-}CC{-}CO_2Me$), (0.078 mL, 0.64 mmol). The suspension was stirred at RT during 6 h, then filtered. The yellow solid was washed with Et_2O (30 mL), dried in vacuo and identified spectroscopically as **7d** (0.255 g, 75% yield).

Anal calc for $C_{22}H_{24}ClNO_4Ru$: C, 52.54; H, 4.81; N, 2.78. Found: C, 52.01; H, 4.63; N, 2.34.

^{1}H NMR: see **7d** in table II.

Conductivity of **7d** (8.22×10^{-4} M): 0.39 ohm^{-1} cm^2 mol^{-1} (neutral complex) (for comparison: compound **1d** (neutral complex) (2.87×10^{-3} M): 0.55 ohm^{-1} cm^2 mol^{-1}; **7e** (7.98×10^{-4} M): 1.22 ohm^{-1} cm^2 mol^{-1}.

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