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# Mild hydroarylation of alkynes with chelating dicarbene palladium(II) complex catalysts☆

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ABSTRACT

Chelating dicarbene palladium(II) complexes have been found to catalyse the hydroarylation of alkynes with excellent conversions and selectivities at low catalyst loading (0.1 mol.%). Products of formal *trans* hydroarylation of the triple bond are formed in high yields. Optimisation of the reaction parameters (nature of the solvent system, concentration of the reagents, reaction temperature) allows to further increase the selectivity of the reaction under mild reaction conditions.



## 1. Introduction

The development of C–H activation/functionalisation reactions into useful synthetic tools represents a formidable challenge in at least two respects, namely (i) the high average strength and low polarisability of a C–H bond, and (ii) the presence in the same molecule of many C–H bonds characterised by only slight differences in energy. Consequently, it is difficult to develop catalytic systems that are sufficiently active for practical use, and to control at the same time their selectivity in order to functionalise only a predetermined C–H bond in a target substrate. Nevertheless, research in this field has developed considerably in the course of the last 10–15 years [1,2], also as a result of some ground breaking discoveries mostly made at the beginning of the new century [3–8].

Among the different synthetic strategies proposed to functionalise C–H bonds, aromatic C–H bond functionalisation reactions can represent green and economical alternatives to more classical coupling reactions involving, e.g., aryl halides, such as Heck and cross-coupling reactions [9]. Several examples of such reactions have been reported in the recent literature [10–17]. They are based on: (i) chelate-assisted oxidative addition of the C–H bond to metal centres in low oxidation state [3,16–18], (ii) arene metallation by electrophilic metal centres which attack the aromatic ring *via* electrophilic aromatic substitution or *via* σ-bond metathesis [11,12,19], and finally (iii) Friedel–Crafts-type reactions promoted by metal centres that upon coordination activate electrophilically organic molecules toward attack at the aromatic ring [20,21].

Simple palladium(II) compounds such as $Pd(OAc)_2$ in a trifluoroacetic acid environment are for example known to promote the coupling reaction of arenes with alkynes [22–24]. In this case, products of formal *trans* hydroarylation of the triple bond are formed. The reaction is characterised by a high and quite unusual regio- and stereo-selectivity: in fact, it is remarkable that the thermodynamically less favoured *cis*-arylalkenes are the major products. There is at present some controversy about the reaction mechanism that fits best with these experimental findings. In fact, the initial (and purely speculative) mechanistic proposal made by Fujiwara and co-workers, invoking electrophilic arene metallation as the key reaction step with $Pd(OAc)_2$ as catalyst (left cycle in Scheme 1) [23] has been recently questioned by the valuable experimental work carried out by Tunge and Foresee as well as by the theoretical calculations of Soriano and Marco-Contelles, both favouring a Friedel–Crafts-type alkenylation (right cycle in Scheme 1) [25,26].

From the technological point of view, this reaction is arguably one of the most promising C–C coupling reactions *via* C–H activation/functionalisation, since it involves cheap, commercially available reagents and it requires neither directing groups on the arene nor oxidizing agents to regenerate the catalyst. However, its possible industrial utilization cannot leave apart a thorough optimisation of the catalyst and of the reaction conditions. In

☆ Reactivity of chelating dicarbene metal complex catalysts, III; for Part II, see [A. Biffis, C. Tubaro, G. Buscemi, M. Basato, Adv. Synth. Catal. 350 (2008) 189.].

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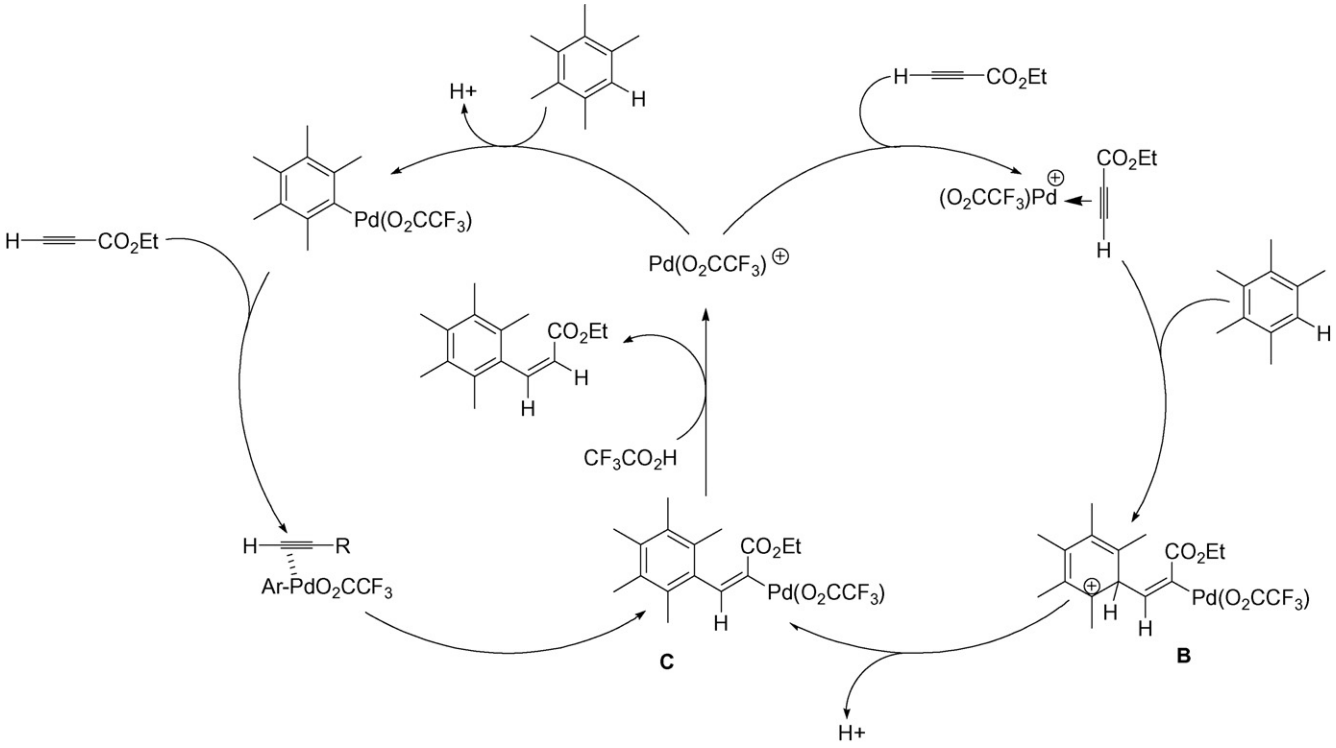



**Scheme 1.** Possible mechanistic pathways of the Fujiwara reaction; the actual catalytically active species $Pd(O_2CCF_3)^+$ is supposedly generated in situ from $Pd(OAc)_2$ and $CF_3COOH$.

particular, the original Fujiwara reaction protocol implies the use of 1–5 mol.% palladium, which heavily affects the cost of the process. Other metal centres such as platinum(II) [27–29], gold(I) and gold(III) [30,31] have been successfully employed as alternative catalyst, but their efficiency appears to be lower than that of palladium(II). Furthermore, use of less-noble, electrophilic metal centres has been also reported; however, their applicability appears to be currently limited to arylacetylenes [32–34].

A viable solution could be the use of palladium(II) complexes with suitable ligands, which should increase the stability of the catalyst under reaction conditions without negatively affecting its reactivity. *N*-Heterocyclic carbene ligands [35–39] appear particularly suited to this purpose, in that it is known that their palladium(II) complexes possess a high thermal and hydrolytic stability, even under strongly acidic conditions [40,41]. Indeed, very recently our group [42] as well as others [43] have reported on palladium(II) complexes with chelating dicarbene ligands or monocarbene ligands, respectively, that are active in the Fujiwara reaction in the absence of other promoters, and exhibit a superior performance in comparison to that of simple $Pd(OAc)_2$. In this contribution, we pursue further our work on chelating dicarbene palladium(II) complexes and investigate on the most suitable conditions for carrying out the hydroarylation reaction.

## 2. Experimental

### 2.1. General remarks

All manipulations were carried out using standard Schlenk techniques under an atmosphere of argon. The reagents were purchased by Aldrich as high-purity products and generally used as received. Complexes (**1**) [44], (**2**) [45,46], (**3**) [47], (**4**) [48], (**5**) [48], (**6**) [49], (**7**) [42], (**8**) [50] were prepared by literature procedures. All solvents were used as received as technical grade solvents. NMR spectra were recorded on a Bruker Avance 300 MHz (300.1 MHz for $^1H$ and 75.5 for $^{13}C$).

#### 2.1.1. General procedure for the catalytic tests

General procedure for the catalytic tests reported in Tables 1 and 2. The arene (5.3 mmol) and the palladium(II) complex (0.0265 or 0.00265 mmol) were placed in a 50 mL round bottomed flask, previously evacuated and filled with argon. Trifluoroacetic acid (4 mL) and 1,2-dichloroethane (1 mL) were then added and the resulting solution was stirred at room temperature for 5 min. Finally the alkyne (2.65 mmol) was added and the reaction mixture was heated at 80 °C and further stirred for 20 h (or 5 h for the tests reported in Table 2). Portions of the solution (0.2 mL) were drawn off from the reaction mixture and analysed by $^1H$ NMR or GC–MS. For the catalytic tests reported in Figs. 2 and 4 the molar amounts of the various reagents were slightly changed as indicated in the figure captions.

**Table 1**
Conversion (%) for the reaction of pentamethylbenzene and ethyl propiolate catalysed by different dicarbene palladium(II) complexes (1 mol.% catalyst, reaction time 20 h)

| Complex | Conversion (%)[a] | Yield (%)[b] | | |
|---|---|---|---|---|
| | | **a** | **b** | **c** |
| **1** | 98 | 49(33) | 10(6) | – |
| **2** | 98 | 54(28) | 9(3) | 2 |
| **3** | 96 | 45(17) | 7(3) | 12 |
| **4** | 100 | 84(9) | 6(1) | – |
| **6** | 100 | 73(15) | 5(1) | 3 |
| **8** | 92 | 84 | 8 | – |

Reaction conditions: see Section 2.
[a] Conversion and yields determined by GC–MS and/or $^1H$ NMR.
[b] In parentheses the yield in the hydrolysed product.

**Table 2**
Conversion (%) for the reaction of pentamethylbenzene and ethyl propiolate catalysed by different dicarbene palladium(II) complexes (0.1 mol.% catalyst, reaction time 5 h)

| Complex | Conversion (%)[a] | Yield (%)[b] | | |
|---|---|---|---|---|
| | | **a** | **b** | **c** |
| **1** | 78 | 68(6) | 2(2) | – |
| **2** | 88 | 79(7) | 2 | – |
| **3** | 91 | 76(8) | 3 | 2 |
| **5** | 96 | 86(8) | 2 | – |
| **7** | 87 | 75(6) | 2 | 2 |
| $Pd(OAc)_2$ | 44 | 36(1) | 1(1) | 3 |

Reaction conditions: see Section 2.
[a] Conversion and yields determined by GC–MS and/or $^1$H NMR.
[b] In parentheses the yield in the hydrolysed product.

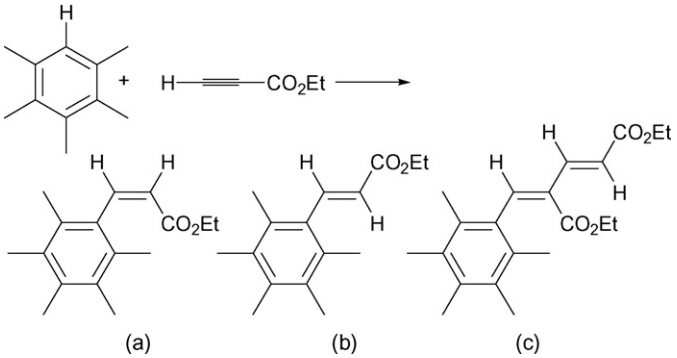
## 3. Results and discussion

We have started our work by investigating the catalytic behaviour of a library of dicarbene palladium(II) compounds, prepared from the corresponding diimidazolium salts and $Pd(OAc)_2$ using well-established literature methods (Fig. 1) [42,44–50]. As a standard test reaction we chose the reaction between pentamethylbenzene and ethyl propiolate (Scheme 2).

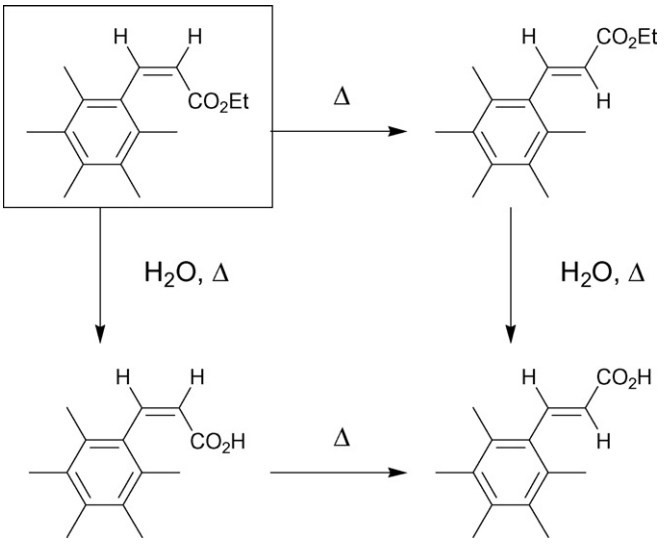
The complexes were found to exhibit low reactivity under the reaction conditions usually employed by Fujiwara et al. using $Pd(OAc)_2$ as catalyst (1 equiv. alkyne, 2 equiv. arene, 0.01 equiv. catalyst, solvent $CF_3COOH$:$CH_2Cl_2$ 4:1, room temperature, 20 h). However, by increasing the reaction temperature to 80 °C and by replacing dichloromethane with 1,2-dichloroethane all the complexes gave very high conversions and selectivities (Table 1) to the Z product **a**, other main products being the *E* isomer **b** and the product of double alkyne insertion **c** (Scheme 2).

Further optimisation of the reaction time and of the amount of catalyst was carried out mainly with complexes carrying bromides as anionic ligands, since bromide was expected to be more easily displaced than iodide [51]. This expectation was also supported by the results of Strassner and co-workers with related platinum(II) complexes, whose reactivity in the methane C–H activation reaction was markedly enhanced on going from iodide to bromide complexes [41]. Indeed, the optimisation of the catalytic performance with these complexes made it apparent that the reaction could be run in just 5 h with only 0.1 mol.% catalyst (Table 2).

Use of excess arene was not necessary in order to achieve good results, although the reaction rate was somewhat slower: 68% conversion with 94% selectivity for the Z product were obtained after 7 h using catalyst (**7**) with only 1 equiv. of pentamethylbenzene. On the other hand, we noticed that longer reaction times caused an increase in the amounts of by-products generated from




**Scheme 2.** Main products of the hydroarylation reaction between pentamethylbenzene and ethyl propiolate.




**Scheme 3.** Evolution reactions (isomerisation and hydrolysis) of the main hydroarylation product under catalytic conditions.

the main reaction product *via* hydrolysis of the ester function and thermally induced *cis*/*trans* isomerisation (Scheme 3; compare also the amounts of hydrolysed products reported in Tables 1 and 2). Therefore, we set out to further improve the reaction conditions in order to minimise the amount of by-products.

### 3.1. Optimisation of the solvent

We initially attempted to optimise the nature of the solvent system employed in the reaction, i.e., a two-component system

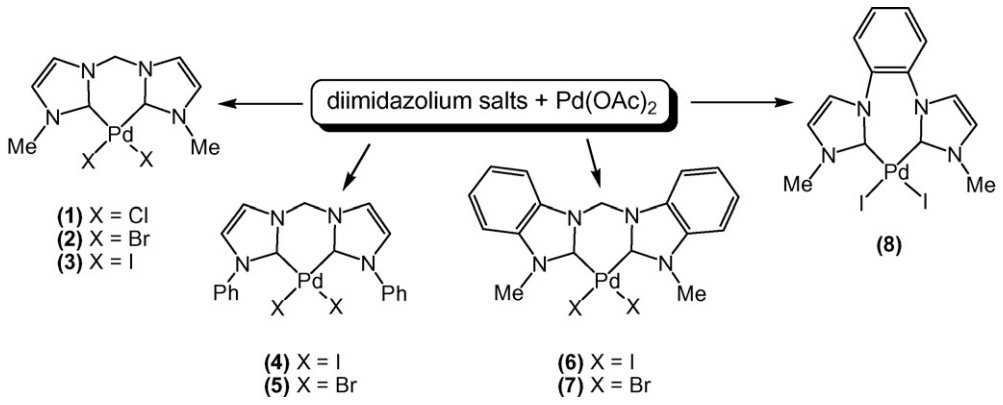



**Fig. 1.** Palladium(II) dicarbene complexes employed as catalysts in this study.

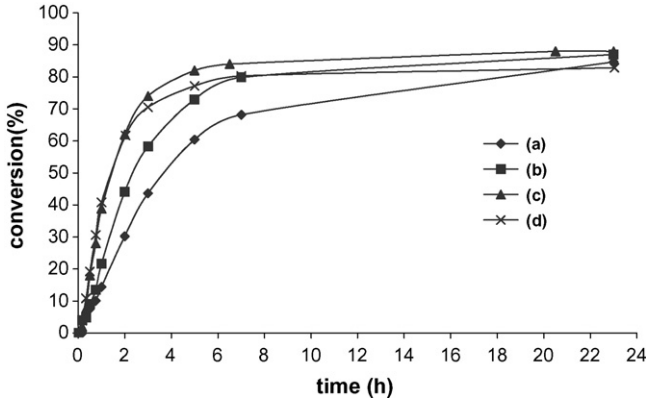



**Fig. 2.** Conversion (%) vs. time diagram for the reaction of pentamethylbenzene and ethyl propiolate catalysed by 0.1 mol.% complex (**7**) at different concentrations of the organic reagents: (a) arene and alkyne 2.65 mmol (0.5 M), TFA/substrates molar ratio = 20/1; (b) arene and alkyne 4.28 mmol (0.8 M), TFA/substrates molar ratio = 12/1; (c) arene and alkyne 7.94 mmol (1.4 M), TFA/substrates molar ratio = 7/1; and (d) arene and alkyne 13.25 mmol (2.1 M), TFA/substrates molar ratio = 4/1.

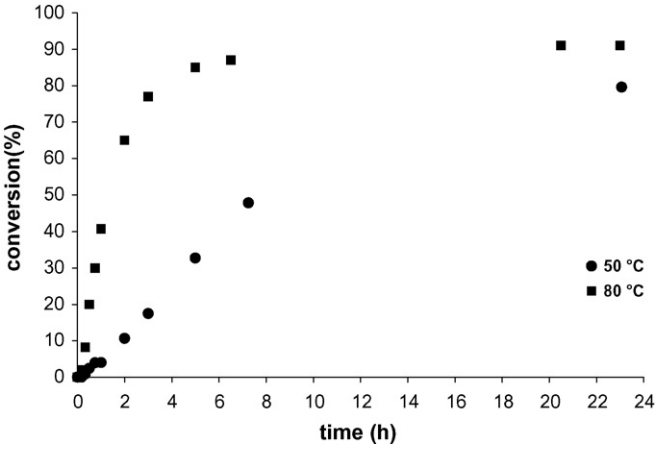



**Fig. 4.** Conversion (%) vs. time diagram for the reaction of pentamethylbenzene and ethyl propiolate catalysed by 0.1 mol.% complex (**7**) at different temperatures. Reaction conditions: arene and alkyne 7.9 mmol (1.4 M), TFA/DCE = 4/1.

made out of trifluoroacetic acid and an organic solvent, which is added in order to favour the dissolution of the reagents and of the catalyst in trifluoroacetic acid, yielding a homogeneous system. We tried to use alternative organic solvents to replace the initially employed 1,2-dichloroethane, but due to the scarse solubility of the catalyst in nonpolar solvents, the choice was restricted to relatively polar ones. Unfortunately, we did not observe any improvement: for example, coordinating solvents such as DMSO lowered the conversion under our standard reaction conditions (arene 1 equiv., 4.28 mmol; alkyne 1 equiv., 4.28 mmol; catalyst (**7**) 0.001 equiv., 0.00428 mmol; 80 °C, 5 h) from 73 to 23%. On the other hand, an excess of trifluoroacetic acid was fundamental, as in Fujiwara's case. Using as solvent $CF_3COOH$:1,2-dichloroethane 1:4 the conversion was halved, while the selectivity remained high (94%).

### 3.2. Optimisation of the reagent concentration

Subsequently, another investigation was performed in order to evaluate the effect of the concentration of the reagents on the performance of the catalytic system. The ratio between the concentrations of the arene, alkyne and catalyst (**7**) was kept constant at 1:1:1000 and the absolute concentration of the organic reagents was varied between 0.5 and 2 M. The resulting conversion curves are reported in Fig. 2.

It is apparent from the reported curves that the conversion at prolonged reaction times (23 h) is the same irrespective of the concentrations employed. On the other hand, at shorter reaction times the conversion at a given time increases with increasing concentration, but it appears to reach a limiting rate for concentrations greater than 1.4 M. Presumably, above such concentration it is the concentration of the trifluoroacetic acid

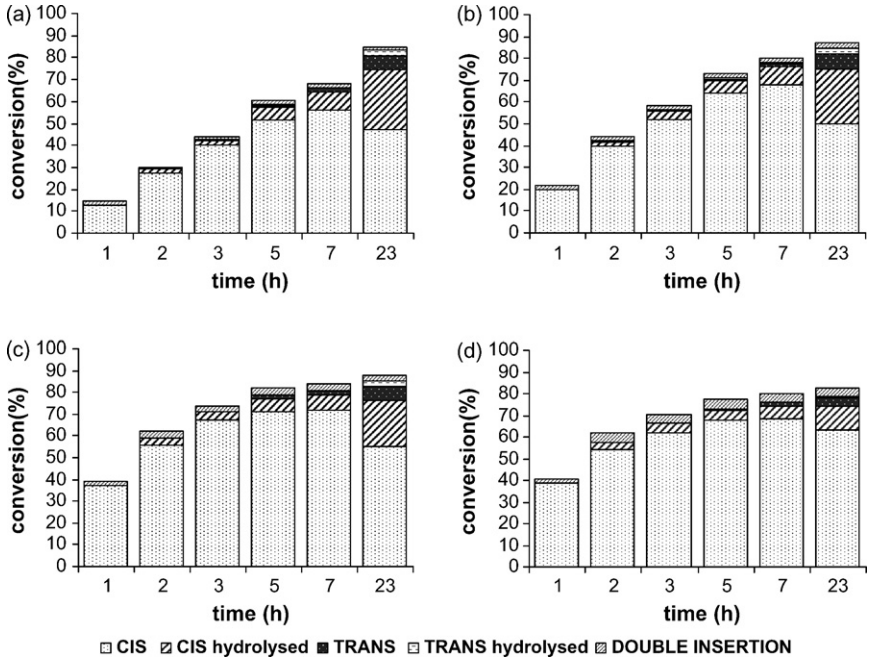



**Fig. 3.** Products distribution in the reaction of pentamethylbenzene and ethyl propiolate catalysed by 0.1 mol.% complex (**7**) at different times and concentrations of the organic reagents: (a) arene and alkyne 2.65 mmol (0.5 M), TFA/substrates molar ratio = 20/1; (b) arene and alkyne 4.28 mmol (0.8 M), TFA/substrates molar ratio = 12/1; (c) arene and alkyne 7.94 mmol (1.4 M), TFA/substrates molar ratio = 7/1; and (d) arene and alkyne 13.25 mmol (2.1 M), TFA/substrates molar ratio = 4/1.

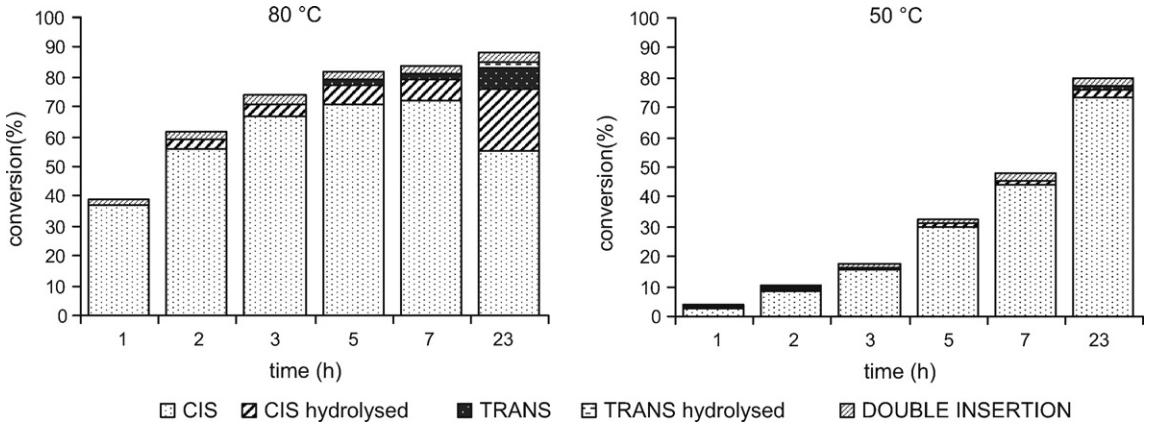



**Fig. 5.** Products distribution for the reaction of pentamethylbenzene and ethyl propiolate catalysed by 0.1 mol.% complex (**7**) at different temperatures. Reaction conditions: arene and alkyne 7.9 mmol (1.4 M), TFA/DCE = 4/1.

that becomes limiting for the reaction rate; work is currently in progress in order to understand the role of trifluoroacetic acid in greater detail. Most importantly, looking at the composition of the product mixture at different concentration and reaction times, it is apparent that the overall selectivity of the reaction increases, the incidence of hydrolysis/isomerisation products becoming lower at higher reagent concentration (Fig. 3).

### 3.3. Optimisation of the reaction temperature

Using the optimised reagent concentrations determined above, we then evaluated the effect of the reaction temperature on the catalytic performance. Given that room temperature is too low to enable the catalytic cycle to proceed at a significant rate (see above), we made a comparison between reactions carried out at 50 and at 80 °C. In Fig. 4 the conversion profiles obtained at the two temperatures with catalyst (**7**) have been reported. As expected, the reaction rate at 50 °C is significantly lower than at 80 °C, but it still allows to reach high conversion in reasonable reaction times.

Most notably, the overall selectivity of the catalytic system is much better at 50 °C than at 80 °C (Fig. 5). In fact, both the incidence of hydrolysis and of isomerisation of the reaction product are markedly reduced.

## 4. Conclusions

In the course of the work presented herein, we have been able to optimise the selectivity of a model alkyne hydroarylation reaction catalysed by chelating dicarbene palladium(II) complex catalysts. Using a high concentration of reagents (greater than 1.4 M) and a decreased reaction temperature (50 °C) the reaction can be carried out with stoichiometric reagents and 0.1 mol.% catalyst in reasonable reaction times, with only very limited degradation of the main reaction product (the *cis*-arylalkene) through hydrolysis and isomerisation reactions.

We are currently aiming at developing novel dicarbene palladium(II) complex catalysts that display good catalytic activity under even milder reaction conditions, in order to further improve the selectivity of the system and its range of applicability.

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