ELSEVIER

Palladium and rhodium-catalyzed intramolecular [2+2+2] cycloisomerizations in molten tetrabutylammonium bromide

Iván González,[a,b] Sandrine Bouquillon,[b] Anna Roglans[a,*] and Jacques Muzart[b,*]

[a]*Department of Chemistry, Universitat de Girona, Campus de Montilivi, s/n, 17071, Girona, Spain*
[b]*Unité Mixte de Recherche 6519 'Réactions Sélectives et Applications', Boîte n° 44, CNRS-Université de Reims Champagne-Ardenne, BP 1039, 51687 Reims Cedex 2, France*

Abstract—The cycloisomerization reaction of triacetylenic macrocycles **1** was carried out in molten *n*-Bu$_4$NBr using either the Wilkinson's catalyst RhCl(PPh$_3$)$_3$, or PdCl$_2$ leading to good yields of the corresponding cycloisomerized compounds. It was possible to recycle the catalytic system. When PdCl$_2$/TBAB was used, palladium nanoparticles were identified by means of transmission electron microscopy (TEM) and energy dispersive X-ray spectroscopy (EDX).
© 2007 Elsevier Ltd. All rights reserved.

The [2+2+2] cyclotrimerization of alkynes catalyzed by transition-metal-based systems to give benzene derivatives is a field of considerable interest in organic synthesis as three new carbon-carbon bonds are formed in only one step and as polysubstituted benzene derivatives they are important building blocks for the synthesis of biological compounds and polymers.[1] In recent years, Roglans

et al.[2] have been involved in the [2+2+2] cycloisomerization processes of cyclic triynes of type **1** and enediynes of type **2** promoted by transition-metal catalysts to afford the corresponding cycloisomerized compounds **3** and **4**, respectively (Eqs. 1 and 2). Among the readily available and familiar cyclotrimerization systems examined, the Wilkinson complex, RhCl(PPh$_3$)$_3$, was found to be a

$$(1)$$
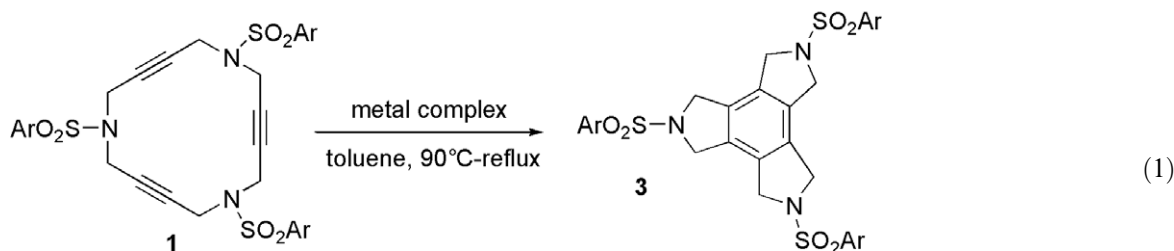
metal complex = 0.05 equiv. RhCl(PPh$_3$)$_3$, yields: 88–96%
metal complex = 1.1 equiv. Pd(PPh$_3$)$_4$, yields: 45–65%

$$(2)$$
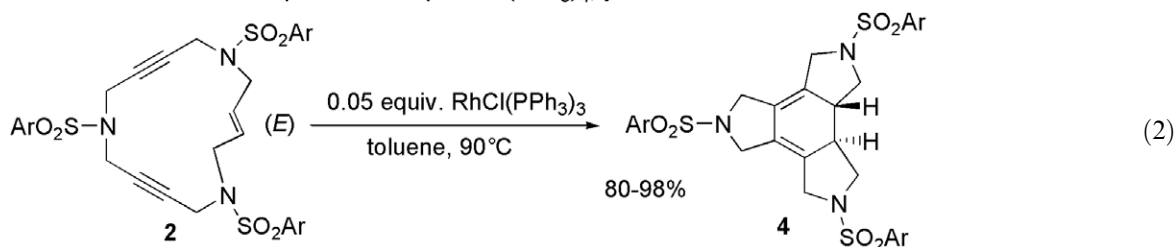
* Corresponding authors. Tel.: +34 972 418275; fax: +34 972 418150 (A.R.); tel.: +33 3 2691 3237; fax: +33 3 2691 3166 (J.M.); e-mail addresses: anna.roglans@udg.edu; jacques.muzart@univreims.fr

good catalyst while Pd(PPh₃)₄ was much less efficient and stoichiometric amounts were required.

One important aspect of all processes involving transition-metal based catalysts is the recovery and the reuse of the catalyst to fully exploit their potential. Among the various approaches to address this issue, the use of ionic liquids or molten salts as good immobilizing agents for transition-metal catalysts has emerged as one of the most important alternatives.[3] The ability of the molten salts to immobilize catalysts favors their recovery at the end of the process. In addition, the substitution of organic solvents for these non-conventional media is environmentally and economically desirable. With regards to the transition metal-catalyzed cycloisomerization reactions, only one study, to the best of our knowledge, reports the use of molten salts in alkyne cyclotrimerization reactions and the dimerization process proved to be predominant.[4]

Here, we present the use of molten tetra-*n*-butylammonium bromide as an efficient solvent for the [2+2+2] cycloisomerization of unsaturated azamacrocycles catalyzed by rhodium and palladium complexes. In the case of the use of palladium salts, palladium nanoparticles have been identified and are probably the real catalytic species.

Initial experimentation using ionic liquids such as [BMIM]BF₄ and [BMIM]PF₆, and the Wilkinson complex (0.05 equiv) as the catalyst did not lead to the cycloisomerization of **1a** (Ar = 2,4,6-triisopropylphenyl). In contrast, this reaction occurred in molten tetra-*n*-butylammonium bromide. The best way to isolate the cyclotrimerized compound in a good yield was found to be the addition of water to the crude mixture in order to precipitate **3a** (Ar = 2,4,6-triisopropylphenyl), followed by its purification by column chromatography (method

A). This procedure afforded 80% of **3a** (Table 1, entry 1). The above aqueous phase was evaporated, and the resulting catalyst/*n*-Bu₄NBr mixture was dried under vacuum but its reuse led to considerably reduced yields (entries 2 and 3). With an increase in the initial amount of catalyst to 10 mol %, the result of the first run (entry 4) was similar to that with 5 mol % but the recycling was more efficient (compare entries 2 and 5). This increase in yields with the initial amount of catalyst indicates that some catalyst is lost during the work ups. One of the problems of this reaction is the poor solubility of **3a** in the common organic solvents. For this reason, we checked the cycloisomerization reaction of enediyne azamacrocycle **2a** (Ar = 2,4,6-triisopropylphenyl) as we have previously demonstrated its high solubility in these organic solvents.[2b] A different extraction method was used (method B): (i) ethyl acetate was added to the reaction mixture, (ii) after stirring at room temperature for 10 min, the liquid phase was decanted and the organic solvent distilled off, (iii) the residue thus obtained was purified by column chromatography. This procedure led to the isolation of the cycloisomerized compound **4a** (Ar = 2,4,6-triisopropylphenyl) in 57% yield (entry 6). Unexpectedly, the yield increased to 73% for the recycling run (entry 7). This increase in yield could be due to incomplete extraction of **4a** in the first run, and to the modification of the catalytic system during this run by, for example, the exchange of ligand: diene, **4a** replacing PPh₃.

Next we turn our attention to palladium catalysts. We have previously demonstrated[2] that equimolar amounts of Pd(PPh₃)₄ were required to cyclize triacetylenic azamacrocycles **1** in fair yields. In addition, Muzart et al. have reported the use of catalytic amounts of PdCl₂ in molten *n*-Bu₄NBr as a recyclable system for the oxidation of benzylic alcohols,[5] for the Mizoroki-Heck reaction[6] and for the isomerization[7] of allylic alcohols.

Table 1. Cycloisomerization of unsaturated azamacrocycles **1a** and **2a** (Ar = 2,4,6-triisopropylphenyl) in molten tetra-*n*-butylammonium bromide[a]

Entry	SM	Catalyst (mol %)	Reaction time (h)	Extraction method	Yield (%)
1	**1a**	RhCl(PPh₃)₃ (5)	7	A	**3** (80)
2	**1a**	Recycling	24	A	**3** (39)
3	**1a**	Recycling	24	A	**3** (24)
4	**1a**	RhCl(PPh₃)₃ (10)	3	A	**3** (82)
5	**1a**	Recycling	24	A	**3** (61)
6	**2a**	RhCl(PPh₃)₃ (5)	24	B	**4** (57)
7	**2a**	Recycling	24	B	**4** (73)
8	**1a**	PdCl₂ (10)	24	A	**3** (72)
9	**1a**	Recycling	24	A	**3** (40)
10	**1a**	PdCl₂ (10)	24	B	**3** (36)
11	**1a**	Recycling	24	B	**3** (66)
12	**1a**	PdCl₂ (10)	24	C	**3** (86)
13	**1a**	PdCl₂ (10)	48	C	**3** (86)
14	**1a**	Recycling	24	C	**3** (36)
15	**1a**	PdCl₂ (10)	24	D	**3** (60)
16	**1a**	Recycling	24	D	**3** (25)
17[b]	**1a**	PdCl₂ (10)	24 + 48	C	**3** (73)
18	**1a**	Pd(OAc)₂ (10)	24	C	**3** (74)
19	**1a**	Recycling	24	C	**3** (35)
20[c]	**1a**	PdCl₂ (10)	24		**3** (0)

[a] Reaction carried out at 130 °C using 0.05 mmol of **1a** or **2a** (SM) and 1.0 g of *n*-Bu₄NBr.
[b] A second batch of **1a** (0.05 mmol) was added after a reaction time of 24 h.
[c] Reaction carried out in refluxing toluene instead of *n*-Bu₄NBr.

More recently, this group has demonstrated that palladium nanoparticles, prepared from a mixture of molten n-Bu$_4$NBr, n-Bu$_3$N and PdCl$_2$, are catalytically active for the chemoselective hydrogenation of carbon-carbon double bonds.[8] Therefore, we decided to test the catalytic system PdCl$_2$/n-Bu$_4$NBr in the cycloisomerization of **1a** using PdCl$_2$ (0.1 equiv) at 130 °C for 24 h, and different extraction methods since the isolated yield and the activity of the recovered catalytic system seem to be highly dependent on the workup. Method A led to a good yield (entry 8) but did not preserve the activity of the catalyst (entry 9). With method B, **3a** was isolated in a lower yield in the first run (entry 10) but the catalyst activity is more preserved (entry 11). Two other extraction methods have been used. Method C consisted in

dissolving the crude mixture in CH$_2$Cl$_2$ and washing it with water. While **3a** remains in the organic phase, both catalyst and n-Bu$_4$NBr are extracted in the aqueous phase and recovered after the evaporation of the water. This procedure led to good results for the first run but did not improve the recycling experiment (entries 12–14). The use of a 1:1 mixture of CH$_2$Cl$_2$ and EtOAc instead of CH$_2$Cl$_2$ (method D) was much less efficient (entries 15 and 16). The above results show that the PdCl$_2$/n-Bu$_4$NBr system is recyclable. This led us to perform a reaction where a second batch of **1a** was added after one day of reaction (entry 17). Under these particular conditions, **3a** was isolated in 73% yield. Switching from PdCl$_2$ to Pd(OAc)$_2$ as the catalyst led to the effective cycloisomerization of **1a** (entry 18) but it was not
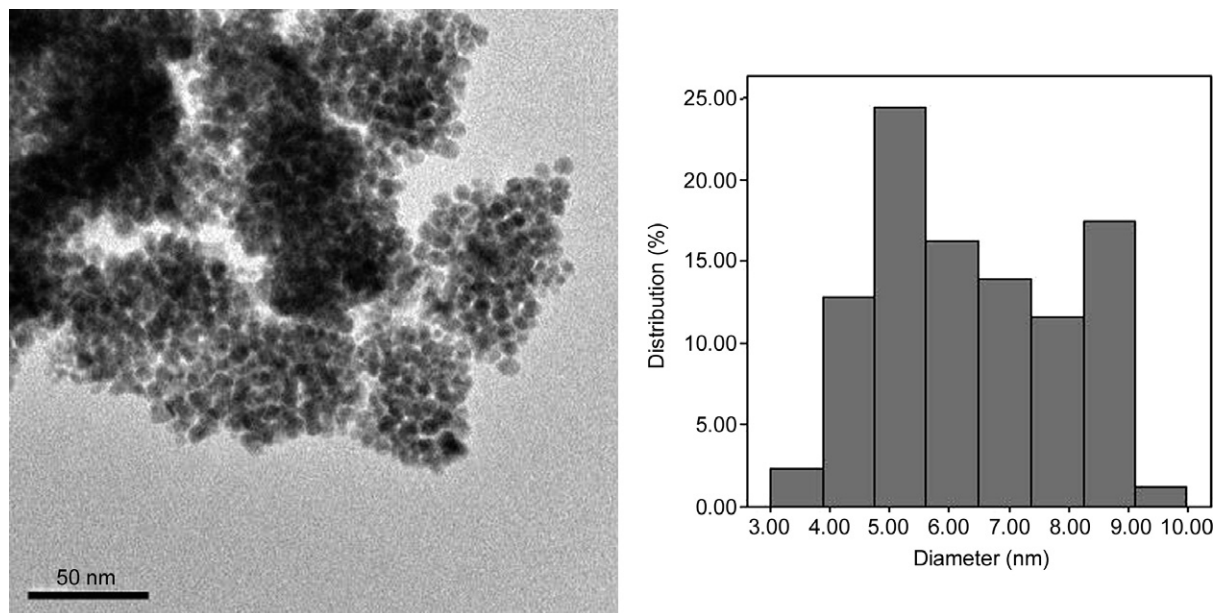

Figure 1. TEM image and particle size histogram of Pd-nanoparticles before catalysis.
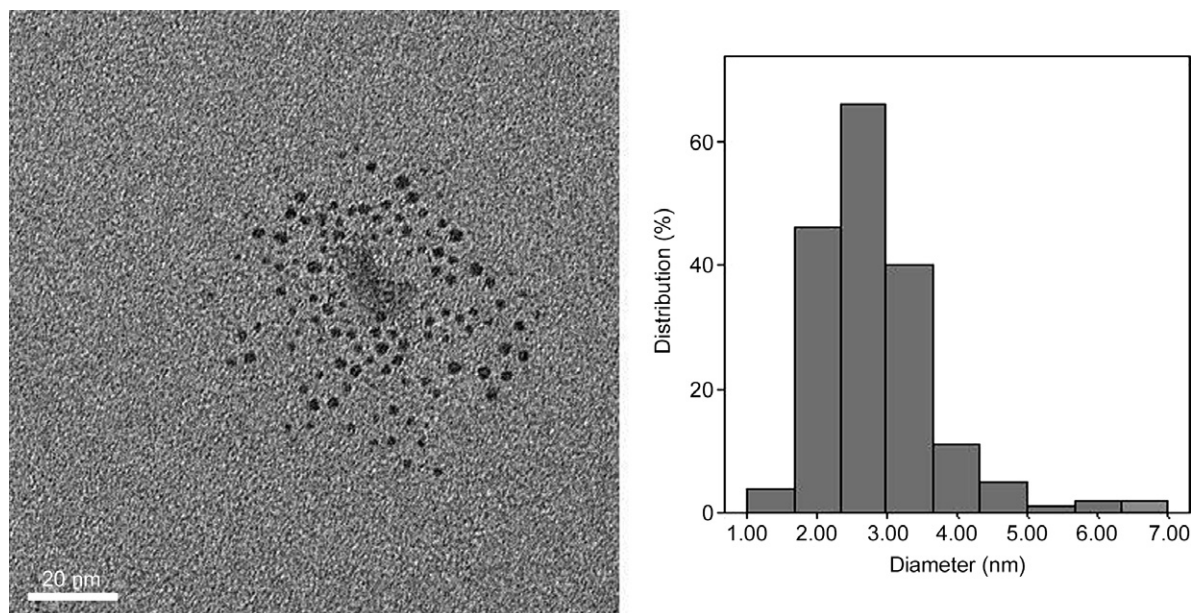

Figure 2. TEM image and particle size histogram of Pd-nanoparticles after catalysis.

suitable for recycling experiments (entry 19). Having noted the absence of cycloisomerization of **1a** when $PdCl_2$ was used with toluene as solvent (entry 20), we examined the $PdCl_2$/*n*-Bu$_4$NBr system by transmission electron microscopy (TEM) and energy dispersive X-ray spectroscopy (EDX).

After mixing 0.005 mmol of $PdCl_2$ and 1 g of molten salt at 130 °C for 15 min, an aliquot was withdrawn and analyzed by TEM and EDX. The observed nanoparticles presented near-spherical shapes and were gathered as aggregates (Fig. 1). The diameter of nanoparticles was determined as 6.4 ± 1.5 nm. Then, 0.050 mmol of **1a** was added to the initial mixture. After stirring at 130 °C for 24 h and extraction using method C, the recovered catalytic system was analyzed by TEM and EDX (Fig. 2). More separated, smaller and more irregular nanoparticles were now observed. The average diameter of 177 particles was found to be 2.8 ± 0.8 nm.

Taking into account the experiment in the absence of *n*-Bu$_4$NBr (entry 20), and the results of TEM analysis, we can hypothesize that palladium nanoparticles stabilized with *n*-Bu$_4$NBr are the active catalytic species leading to the cycloisomerization of **1a**. The process using molten *n*-Bu$_4$NBr as a medium is an improvement with respect to the cycloisomerization process in conventional organic solvents[2] in that it is catalytic in palladium, gives higher yields, and presents recycling possibilities.

In conclusion, molten *n*-Bu$_4$NBr is a good medium for rhodium and palladium-catalyzed cycloisomerization reactions of triacetylenic azamacrocycles. When $PdCl_2$ is the starting catalyst, TEM analysis has shown the formation of nanoparticles, which, presumably, are the active catalytic species. Work is currently in progress to apply this process to other substrates.

Acknowledgments

References and notes

1. For monographs and reviews on cyclotrimerization reactions see: (a) Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 1129–1162; (b) Grotjahn, D. B. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Hegedus, L., Eds.; Pergamon Press: Oxford, 1995; Vol. 12, pp 741–770; (c) Vollhardt, K. P. C. *Acc. Chem. Res.* **1977**, *10*, 1–8; (d) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081–1119; (e) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49–92; (f) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901–2915; (g) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741–4767; (h) Yamamoto, Y. *Curr. Org. Chem.* **2005**, *9*, 503–519; (i) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307–2327.
2. (a) Pla-Quintana, A.; Roglans, A.; Torrent, A.; Moreno-Mañas, M.; Benet-Buchholz, J. *Organometallics* **2004**, *23*, 2762–2767; (b) Torrent, A.; González, I.; Pla-Quintana, A.; Roglans, A.; Moreno-Mañas, M.; Parella, T.; Benet-Buchholz, J. *J. Org. Chem.* **2005**, *70*, 2033–2041.
3. (a) Sundermeyer, W. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 222–238; (b) Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2083; (c) Olivier, H. *J. Mol. Catal. A: Chem.* **1999**, *146*, 285–289; (d) Holbrey, J. D.; Seddon, K. R. *Clean Prod. Processes* **1999**, *1*, 223–236; (e) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772–3789; (f) Sheldon, R. *Chem. Commun.* **2001**, 2399–2407; (g) Olivier-Bourbigou, H.; Magna, L. *J. Mol. Catal. A: Chem.* **2002**, *182–183*, 419–437; (h) Zhao, D.; Wu, M.; Kou, Y.; Min, E. *Catal. Today* **2002**, *74*, 157–189; (i) Dupont, J.; Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667–3692; (j) Welton, T. *Coord. Chem. Rev.* **2004**, *248*, 2459–2477; (k) Muzart, J. *Adv. Synth. Catal.* **2006**, *348*, 275–295; (l) Calò, V.; Nacci, A.; Monopoli, A. *Eur. J. Org. Chem.* **2006**, 3791–3802; (m) Pârvulescu, V. I.; Hardacre, C. *Chem. Rev.* **2007**, *107*, 2615–2665.
4. Conte, V.; Elakkari, E.; Floris, B.; Mirruzzo, V.; Tagliatesta, P. *Chem. Commun.* **2005**, 1587–1588.
5. Ganchegui, B.; Bouquillon, S.; Hénin, F.; Muzart, J. *Tetrahedron Lett.* **2002**, *43*, 6641–6644.
6. Bouquillon, S.; Ganchegui, B.; Estrine, B.; Hénin, F.; Muzart, J. *J. Organomet. Chem.* **2001**, *634*, 153–156.
7. Ganchegui, B.; Bouquillon, S.; Hénin, F.; Muzart, J. *J. Mol. Catal. A: Chem.* **2004**, *214*, 65–69.
8. Le Bras, J.; Mukherjee, D. K.; González, S.; Tristany, M.; Ganchegui, B.; Moreno-Mañas, M.; Pleixats, R.; Hénin, F.; Muzart, J. *New J. Chem.* **2004**, *28*, 1550–1553.