COMMUNICATION

OBC
www.rsc.org/obc

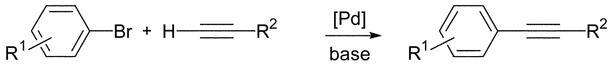
Palladium-tetraphosphine complex: an efficient catalyst for the coupling of aryl halides with alkynes

Marie Feuerstein, Florian Berthiol, Henri Doucet * and Maurice Santelli *
Laboratoire de Synthèse Organique associé au CNRS, Faculté des Sciences de Saint Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France.
E-mail: henri.doucet@univ.u-3mrs.fr; m.santelli@univ.u-3mrs.fr; Fax: 04 91 98 38 65; Tel: 04 91 28 84 16

Received 6th June 2003, Accepted 6th June 2003
First published as an Advance Article on the web 11th June 2003

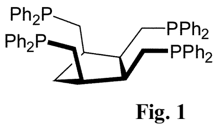
The *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane–[PdCl(η^3–C_3H_5)]$_2$ system catalyses the coupling of aryl halides with alkynes with very high ratios of substrates–catalyst in good yields; a turnover number of 2 600 000 can be obtained for the reaction of 4-trifluoromethylbromobenzene with phenylacetylene in the presence of this catalyst.

The coupling reaction of terminal alkynes with aryl halides provides an efficient method for the preparation of arylalkynes (Scheme 1). The classical method used to perform this reaction is to employ a palladium catalyst in the presence of a catalytic amount of copper iodide.[1,2] These palladium complexes are generally associated with the triphenylphosphine ligand.[3] Even if the catalyst formed by association of this ligand with palladium complexes is quite efficient in terms of yield of adduct, the efficiency in terms of ratio of substrate–catalyst is generally low, and 1–10% of the catalyst must be used. Recently a few more efficient catalysts have been successfully used for this reaction. For example, Herrmann *et al.* have reported that the palladacycle [Pd(*o*-tol)(OAc)]$_2$ is efficient for the reaction of 4-bromoacetophenone with phenylacetylene.[4a] An oxime palladacycle in the presence of tetrabutylammonium acetate also led to coupling products with high turnover numbers (TONs).[4b] Two of the most active catalytic systems uses palladium associated to bulky monodentate phosphine ligands.[5] Carbene ligands also lead to the formation of palladium catalysts which are more efficient than those of triphenylphosphine for this reaction.[6] Finally, a very efficient catalyst for this reaction has been prepared with a bis-pyrimidine ligand. With this ligand a TON of 22 300 has been obtained for the reaction of iodobenzene with phenylacetylene.[7] If carbenes, pyrimidines or monophosphine ligands have been successfully used for this reaction, to our knowledge, the efficiency of tetraphosphine ligands has not yet been demonstrated.



Scheme 1

The nature of phosphine ligands on complexes has an important influence on the rate of catalysed reactions. In order to find more efficient palladium catalysts we have prepared a new tetrapodal[8] phosphine ligand, *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane or Tedicyp **1**[9a] (Fig. 1) in which the four diphenylphosphino groups are stereospecifically bound to the same face of the cyclopentane ring. The presence of four phosphines close to the metal centre seems to increase the stability of the catalyst. A very high efficiency has been observed for allylic substitution,[9a,9b] and for Suzuki cross-coupling using tedicyp as the ligand.[9c] We have also reported recently the first results obtained for Heck reactions.[9d] In this paper, we wish to report on the efficiency of this ligand for the reaction of aryl halides with terminal alkynes.



Tedicyp **1**

Fig. 1

In the literature, many reaction conditions have been employed, so our first objective was to determine the most suitable reaction conditions with our tetraphosphine ligand. We observed that the reaction of 4-bromoacetophenone with phenyl acetylene in the presence of triethylamine and the catalytic system [PdCl(η^3–C_3H_5)]$_2$–tedicyp in DMF at room temperature does not proceed (Table 1, entry 1). The reaction performed at 50 and 80 °C using similar conditions led to the coupling product in reasonable yields, however in all cases an important amount of the dimer of phenylacetylene was observed (entries 2–4). The reaction performed at 140 °C with piperidine as base led to higher reaction rates, but the dimer of phenylacetylene was still observed (entries 6 and 7). A much cleaner and faster reaction was observed using K_2CO_3 as base (entry 8). With this base, only traces of dimerisation product were observed.

Next we tried to evaluate the importance of the presence of phosphine ligands on the complex using these conditions. So we performed the reaction with [PdCl(η^3–C_3H_5)]$_2$ as catalyst in the absence of ligand. We observed that 4-bromoanisole with phenylacetylene in the presence of 0.1% catalyst was recovered unreacted (Table 1, entry 9). Then, we studied the difference of efficiency between mono, di and polydentate ligands bearing diphenylphosphino groups for this reaction. For this we compared the rate of the reaction in the presence of monophosphines, a diphosphine and with our tetraphosphine. The reaction performed in the presence of 0.1% catalyst, led to the addition product in 5 and 3% conversion when PPh_3 and P(*o*-Tol)$_3$ were used as ligands (Table 1, entries 10 and 11) and 50% conversion with dppb (entry 12). With the tetradentate ligand Tedicyp conversions of 100% and 38% in the presence of 0.1 and 0.01% catalyst were obtained (entries 13 and 14).

Then, we tried to evaluate the scope and limitations of the Tedicyp–palladium complex for this reaction. A survey of catalytic coupling of aryl halides with alkynes is provided in Table 2. A wide variety of functional groups on the aryl bromide are tolerated. In the presence of activating groups high reaction rates are observed. For example, the coupling of 4-fluorobromobenzene, 4-trifluoromethylbromobenzene, 4-bromoacetophenone, 4-bromobenzophenone, 4-bromobenzonitrile and 4-bromobenzaldehyde with phenylacetylene in the presence of 0.0001% of the Tedicyp–palladium complex (ratio substrate–catalyst: 1 000 000) led to the coupling products in 70–100% yields (Table 2, entries 3, 5, 13, 15, 18 and 19). A turnover number of 2 800 000 has been obtained for the

DOI: 10.1039/b306428j

Table 1 Palladium-catalysed reaction of aryl bromides with phenylacetylene: influence of the reaction conditions and of the ligand[a]

Entry	Aryl bromide	Base	Ligand	Temp./°C	Ratio of substrate–catalyst	Conv. (%)
1	4-Bromoacetophenone	NEt_3	**1**	20	1000	0[b]
2		Piperidine	**1**	50	100	79[b]
3		NEt_3	**1**	50	100	60[b]
4		NEt_3	**1**	80	1000	33[b]
5		NEt_3	**1**	140	1000	16[b]
6		Piperidine	**1**	140	1000	88[b]
7		Piperidine	**1**	140	10 000	58[b]
8		K_2CO_3	**1**	140	100 000	100
9	4-Bromoanisole	K_2CO_3	No ligand	140	1000	0
10		K_2CO_3	PPh_3	140	1000	5[c]
11		K_2CO_3	P(*o*-tol)$_3$	140	1000	3[c]
12		K_2CO_3	dppb	140	1000	50[d]
13		K_2CO_3	**1**	140	1000	100
14		K_2CO_3	**1**	140	10 000	38

[a] Conditions: catalyst: $[Pd(C_3H_5)Cl]_2$–**1**: 1 : 2 see ref. 9a, aryl halide 1 eq., phenylacetylene 2 eq., K_2CO_3 2 eq., CuI 0.05 eq., DMF, 20 h, conversion determined by GC and NMR. [b] The formation of a large amount of the dimer of phenylacetylene was observed (GC ratio dimer–product > 1 : 2). [c] $[Pd(\eta^3–C_3H_5)Cl]_2$–PAr_3 1 : 8. [d] $[Pd(\eta^3–C_3H_5)Cl]_2$–dppb 1 : 4.

Table 2 Tedicyp-Pd catalysed reaction of aryl halides with alkynes[12,a]

Entry	Aryl bromide	Alkyne	Ratio of substrate–catalyst	Yield (%)
1	Bromobenzene	Phenyl-acetylene	1000	100[b]
2			10 000	82
3	4-Fluorobromobenzene		1 000 000	85
4			100 000	86[b]
5	4-Trifluoromethylbromobenzene		1 000 000	100[b]
6			10 000 000	26[b]
7			1 000 000	59[c]
8	3,5-Bis(trifluoromethyl)bromobenzene		1 000 000	92
9			1 000 000	93[c]
10			10 000 000	28[b]
11			10 000 000	25[b,c]
12	4-Bromoacetophenone		100 000	90
13			1 000 000	70
14			1 000 000	26[b,c]
15	4-Bromobenzophenone		1 000 000	84
16			1 000 000	66[c]
17	4-Bromonitrobenzene		100 000	78
18	4-Bromobenzonitrile		1 000 000	87
19	4-Bromobenzaldehyde		1 000 000	81
20	4-Bromo-*N*,*N*-dimethylaniline		10 000	50
21	Iodobenzene		1 000 000	88
22			10 000 000	38[b]
23	4-Chlorobenzonitrile		1000	85[c]
24	4-Chloronitrobenzene		1000	88[d]
25	4-Chloroacetophenone		1000	82[c]
26	3-Trifluoromethyl-4-nitrochlorobenzene		10 000	91[d]
27	2-Bromotoluene		100	89
28	1-Bromo-2,6-dimethylbenzene		100	69
29	2-Trifluoromethylbromo-benzene		100 000	89
30	3,5-Bis(trifluoromethyl)bromo-benzene	Dec-1-yne	100 000	92
31	4-Bromoacetophenone	Oct-1-yne	10 000	77[c]

[a] *Conditions:* catalyst $[Pd(\eta^3–C_3H_5)Cl]_2$–Tedicyp 1 : 2 see ref 9a, aryl halide 1 eq., alkyne 2 eq., K_2CO_3 2 eq., CuI 0.05 eq., DMF, argon, 20 h, 140 °C, isolated yield. [b] GC yield. [c] Reaction performed without CuI. [d] Reaction performed at 100 °C.

addition of 3,5-bis(trifluoromethyl)-bromobenzene to phenylacetylene (entry 10). Lower TONs were observed in the course of the coupling of bromobenzene or 4-bromo-*N*,*N*-dimethylaniline (entries 2 and 20). These results seems to indicate that, as expected, electron-poor aryl bromides can be reacted at higher TON than electron-rich aryl bromides.

Next we performed a few reactions in the presence of iodobenzene and with activated arylchlorides.[10] A very high TON can be obtained for the reaction of iodobenzene with phenylacetylene: 3 800 000 (entry 22). On the other hand, lower TONs were obtained with arylchlorides such as 4-chlorobenzonitrile or 4-chloroacetophenone (entries 23–26). We also tried to determine the influence of *ortho* substituents on the aryl bromide on the rate of the reaction. Slower reaction rates were observed in the presence of 2-bromotoluene and 1-bromo-2,6-dimethylbenzene (entries 27 and 28). With the activated 2-trifluoromethylbromobenzene, a higher TON was obtained (entry 29).

Finally, we performed the reaction with the aliphatic alkynes: oct-1-yne and dec-1-yne. With these alkynes TONs of 7700 and 92 000 were obtained in the presence of activated aryl bromides (entries 30 and 31).

All these reactions were performed with a catalytic amount of copper iodide (Sonogashira conditions).[1c] However, the reaction also proceeds without copper iodide (Heck conditions).[1a,11] For example, the reaction of 4-trifluoromethylbromobenzene or 4-bromobenzophenone with phenylacetylene led to the coupling adducts in the presence of 0.0001% catalyst in 59 and 66% yields respectively (entries 7 and 16).

In conclusion, the use of the tetradentate ligand Tedicyp associated with a palladium complex provides a convenient catalyst for the coupling of aryl halides to alkynes. This catalyst is much more efficient than the complex formed with a triphenylphosphine ligand. This efficiency probably comes from the presence of the four diphenylphosphinoalkyl groups stereospecifically bound to the same face of the cyclopentane ring which probably increases the coordination of the ligand to the metal and prevents precipitation of the catalyst. The reaction can be performed with as little as 0.0001% catalyst.

We thank the CNRS and the "Conseil Général des Bouches-du-Rhône, Fr" for financial support and M. F. is grateful to the Ministère de la Recherche et de la Technologie for a grant.

Notes and references

1 (*a*) H. A. Dieck and F. R. Heck, *J. Organomet. Chem.*, 1975, **93**, 259; (*b*) L. Cassar, *J. Organomet. Chem.*, 1975, **93**, 253; (*c*) K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **50**, 4467.

2 For reviews on the cross coupling of aryl halides with alkynes: (*a*) K. Sonogashira, *Metal-Catalyzed Cross-Coupling Reactions*, eds F. Diederich and P. J. Stang, Wiley-VCH, New York, 1998; (*b*) L. Brandsma, S. F. Vasilevsky and H. D. Verkruijsse, *Application of Transition Metal Catalysts in Organic Synthesis*, Springer-Verlag, Berlin, 1998; (*c*) K. Sonogashira, *J. Organomet. Chem.*, 2002, **653**, 46.

3 (*a*) N. Bumagin, L. Sukhomlinova, E. Luzikova, T. Tolstaya and I. Beletskaya, *Tetrahedron Lett.*, 1996, **37**, 897; (*b*) S. Thorand and N. Krause, *J. Org. Chem.*, 1998, **63**, 8551; (*c*) M. Erdélyi and A. Gogoll, *J. Org. Chem.*, 2000, **66**, 4165; (*d*) W.-M. Dai, D.-S. Guo and L.-P. Sun, *Tetrahedron Lett.*, 2001, **42**, 5275; (*e*) A. Mori, T. Shimada, T. Kondo and A. Sekiguchi, *Synlett*, 2001, 649.

4 (*a*) W. A. Herrmann, V. Böhm and C.-P. Reisinger, *J. Organomet. Chem.*, 1999, **576**, 23; (*b*) D. Alonso, C. Najera and C. Pacheco, *Tetrahedron Lett.*, 2002, **43**, 9365.

5 (*a*) K. Nakamura, H. Okubo and M. Yamaguchi, *Synlett*, 1999, 549; (*b*) T. Hundertmark, A. Littke, S. Buchwald and G. Fu, *Org. Lett.*, 2000, **2**, 1729.

6 (*a*) W. Herrmann, C.-P. Reisinger and M. Spiegler, *J. Organomet. Chem.*, 1998, **557**, 93; (*b*) D. McGuinness and K. Cavell, *Organometallics*, 2000, **19**, 741; (*c*) C. Yang and S. Nolan, *Organometallics*, 2002, **21**, 1020; (*d*) R. Batey, M. Shen and A. Lough, *Org. Lett.*, 2002, **4**, 1411.

7 M. Buchmeiser, T. Schareina, R. Kempe and K. Wurst, *J. Organomet. Chem.*, 2001, **634**, 39.

8 For a review on the synthesis of polypodal diphenylphosphine ligands, see: D. Laurenti and M. Santelli, *Org. Prep. Proced. Int.*, 1999, **31**, 245.

9 (*a*) D. Laurenti, M. Feuerstein, G. Pèpe, H. Doucet and M. Santelli, *J. Org. Chem.*, 2001, **66**, 1633; (*b*) M. Feuerstein, D. Laurenti, H. Doucet and M. Santelli, *Chem. Commun.*, 2001, 43; (*c*) M. Feuerstein, D. Laurenti, C. Bougeant, H. Doucet and M. Santelli, *Chem. Commun.*, 2001, 325; (*d*) M. Feuerstein, H. Doucet and M. Santelli, *J. Org. Chem.*, 2001, **66**, 5923.

10 M. Alami, B. Crousse and F. Ferri, *J. Organomet. Chem.*, 2001, **624**, 114.

11 (*a*) M. Alami, F. Ferri and G. Linstrumelle, *Tetrahedron Lett.*, 1993, **34**, 6403; (*b*) J.-F. Nguefack, V. Bollit and D. Sinou, *Tetrahedron Lett.*, 1996, **37**, 5527; (*c*) V. Böhm and W. Herrmann, *Eur. J. Org. Chem.*, 2000, 3679.

12 As a typical experiment, the reaction of 4-bromoacetophenone (19.9 g, 0.1 mol), phenylacetylene (20.4 g, 0.2 mol), K_2CO_3 (27.6 g, 0.2 mol) and CuI (0.95 g, 0.005 mol) at 140 °C during 20 h in dry DMF (100 mL) in the presence of *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane–$[PdCl(\eta^3{-}C_3H_5)]_2$ complex (0.10 mg, 1 10^{-7} mol) under argon affords the corresponding biaryl adduct after evaporation and filtration on silica gel in 70% (15.4 g) isolated yield.