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Sonogashira cross-coupling reactions of aryl chlorides with alkynes catalysed by a tetraphosphine–palladium catalyst

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Abstract—A range of aryl chlorides undergoes cross-couplings with alkynes in good yields in the presence of $[PdCl(C_3H_5)]_2$/*cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane as catalyst. A variety of aryl chlorides such as chloroacetophenone, chlorobenzonitrile, chloronitrobenzene, chloroanisole or chlorotoluene have been used successfully. The reaction also tolerates several alkynes such as phenylacetylene, dec-1-yne, ethynylcyclohexene or alk-1-ynols. Furthermore, this catalyst can be used at low loading with some substrates.

The cross-coupling reactions between aryl halides and alkynes are among the most widely used palladium-catalysed methodologies in organic synthesis.[1–3] In recent years, the efficiency of several palladium catalysts such as palladacycles for the reaction of aryl iodides and bromides with alkynes has been described.[4–12] On the other hand, the reaction in the presence of aryl chlorides has attracted less attention.[13–26] A few ligands have been successfully employed for the reaction with these substrates. The first one was triphenylphosphine, however, the catalyst formed by association of this ligand with palladium complexes is not very efficient in terms of the ratio substrate/catalyst and 2–6% catalyst had to be used.[13–16] Recently, more efficient palladium catalysts have also been successfully employed for the cross-coupling reactions with aryl chlorides.[17–26] For example, Buchmeiser et al. described that a polymeric bis-pyrimidine–palladium complex is an efficient catalyst for the reaction of chlorobenzene with phenylacetylene.[17] In the monophosphine ligand series, interesting results have been reported recently by Plenio et al. They described that $P(t\text{-}Bu)_3$ associated to palladium is a good ligand for the reaction of 4-chloroanisole with phenylacetylene.[20] Astruc and co-workers have reported that turnover numbers (TONs) of 4–30 could be obtained for the coupling of aryl chlorides in the presence of a bis-*tert*-butylphosphine ligand.[21] A palladium–carbene catalyst has also been used successfully.[23,24] Good results have been described recently by Eberhard et al. with a phosphinito–palladium complex in the presence of $ZnCl_2$ as co-catalyst.[25] Finally, Gelman and Buchwald obtained good results for the coupling of electron rich and electron poor aryl chlorides in the presence of $P(Cy)_2Ar$ as ligand.[26] However, to our knowledge, the efficiency of tetraphosphine ligands for the cross-coupling of aryl chlorides with alkynes has not been reported.

In order to find stable and efficient palladium catalysts, we have prepared the tetrapodal phosphine ligand, *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane or Tedicyp (Fig. 1)[27] in which the four diphenylphosphinoalkyl groups are stereospecifically bound to the same face of the cyclopentane ring. We have already reported the results obtained in allylic substitution,[27] in Heck reaction,[28] in Suzuki cross-coupling[29] and in Sonogashira[30–32] reaction using Tedicyp as ligand. For example, a TON of 2,800,000

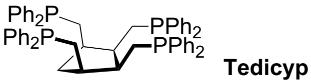

Figure 1.

Keywords: Palladium; Tetraphosphine; Catalysis; Cross-coupling; Aryl chlorides; Alkynes.

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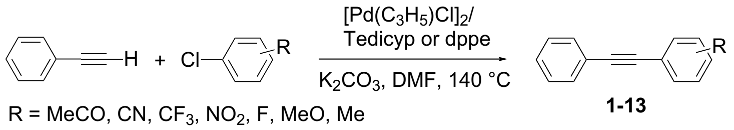
for the coupling of 3,5-bis(trifluoromethyl)bromobenzene with phenylacetylene had been obtained.[30] We have also recently reported the cross-coupling of alkynes with a range of sterically congested aryl bromides[31] and the coupling of alk-1-ynols with aryl bromides.[32] In this letter, we wish to report on the efficiency of this ligand for the reaction of aryl chlorides with terminal alkynes such as phenylacetylene, dec-1-yne or alk-1-ynols.

For this study, based on our previous results,[30–32] DMF was chosen as the solvent and potassium carbonate as the base. The reactions were generally performed at 140 °C under argon in the presence of a ratio 1/2 of $[Pd(C_3H_5)Cl]_2$/Tedicyp as catalyst. A few reactions were performed with 5% copper(I) iodide as co-catalyst.

First, we tried to couple phenylacetylene with a range of aryl chlorides. We observed that it is indeed possible to efficiently cross-couple this alkyne with aryl chlorides, under conditions similar to those employed for the corresponding aryl bromides (Scheme 1, Table 1).

The coupling of 4-chloroacetophenone in the presence of 0.1% catalyst led to the expected adduct **1** in 82% yield (turnover number: TON 820). A lower conversion of 30% was obtained using similar conditions with copper(I) iodide as co-catalyst (Table 1, entries 1–3). Similar results were obtained with 3-chlorobenzonitrile or 4-chloroanisole (Table 1, entries 6–8 and 18–20); the TONs obtained in the presence of CuI were lower than for the reactions performed without CuI. The presence of copper iodide often led to the formation of side products such as the dimerisation of phenylacetylene. The use of $ZnCl_2$ as co-catalyst also led to disappointing results (Table 1, entry 5), so we performed the reactions with the other aryl chlorides without addition of co-catalysts. The $[Pd(C_3H_5)Cl]_2$/Tedicyp catalyst system is tolerant of electronic variation in the aryl halide



Scheme 1.

Table 1. Cross-coupling reactions of aryl chlorides with phenylacetylene (Scheme 1)[33]

Entry	ArCl	Ratio substrate/catalyst	Ligand	Product number	Yield (%)[a]
1	4-MeCO–C_6H_4Cl	100	Tedicyp	**1**	30[b,c]
2	4-MeCO–C_6H_4Cl	1000	Tedicyp	**1**	82
3	4-MeCO–C_6H_4Cl	10,000	Tedicyp	**1**	15[b]
4	4-CN–C_6H_4Cl	100	Dppe	**2**	40[b]
5	4-CN–C_6H_4Cl	1000	Tedicyp	**2**	40[b,d]
6	4-CN–C_6H_4Cl	1000	Tedicyp	**2**	60[b,c]
7	4-CN–C_6H_4Cl	10,000	Tedicyp	**2**	93
8	4-CN–C_6H_4Cl	100,000	Tedicyp	**2**	16[b]
9	4-CF_3–C_6H_4Cl	1000	Tedicyp	**3**	91
10	4-CF_3–C_6H_4Cl	10,000	Tedicyp	**3**	20[b]
11	4-NO_2–C_6H_4Cl	1000	Tedicyp	**4**	92
12	3-CN–C_6H_4Cl	50	Tedicyp	**5**	70[b,c]
13	3-CN–C_6H_4Cl	100	Dppe	**5**	38[b]
14	3-CN–C_6H_4Cl	100	Tedicyp	**5**	95
15	3-CN–C_6H_4Cl	1000	Tedicyp	**5**	50[b]
16	4-F–C_6H_4Cl	250	Tedicyp	**6**	87
17	4-MeO–C_6H_4Cl	100	Dppe	**7**	30[b]
18	4-MeO–C_6H_4Cl	100	Tedicyp	**7**	0[b,c]
19	4-MeO–C_6H_4Cl	100	Tedicyp	**7**	96
20	4-MeO–C_6H_4Cl	500	Tedicyp	**7**	31[b]
21	2-CF_3–C_6H_4Cl	1000	Tedicyp	**8**	92
22	2-CF_3–C_6H_4Cl	10,000	Tedicyp	**8**	45[b]
23	2-CN–C_6H_4Cl	100	Tedicyp	**9**	98
24	2-CN–C_6H_4Cl	1000	Tedicyp	**9**	10[b]
25	2-Me–C_6H_4Cl	25	Tedicyp	**10**	60
26	2-NO_2-4-CF_3–C_6H_3Cl	1000	Tedicyp	**11**	95[b,c]
27	2-NO_2-4-CF_3–C_6H_3Cl	1000	Tedicyp	**11**	100[b]
28	2-NO_2-4-CF_3–C_6H_3Cl	10,000	Tedicyp	**11**	91[e]
29	3-NO_2-4-NO_2–C_6H_3Cl	100	Tedicyp	**12**	93
30	2-CN-4-NO_2–C_6H_3Cl	500	Tedicyp	**13**	87

[a] Conditions: catalyst see Ref. 27, aryl chloride (1 equiv), phenylacetylene (2 equiv), K_2CO_3 (2 equiv), DMF, 140 °C, 20 h.

[b] GC and NMR yield.

[c] Reaction performed with 0.05 equiv of CuI.

[d] Reaction performed with 0.05 equiv of $ZnCl_2$.

[e] Reaction temperature 100 °C.

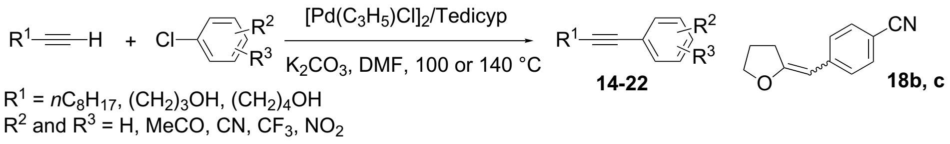
component. Phenylacetylene reacts cleanly at 140 °C with electron-poor and electron-rich aryl chlorides. With electron-poor aryl chlorides such as 3- or 4-chlorobenzonitrile, 2- or 4-trifluoromethylchlorobenzene or 4-chloronitrobenzene TONs of 500–16,000 have been obtained (Table 1, entries 7–11, 14, 15, 21 and 22). On the other hand, with the electron-rich aryl chlorides: 4-chloroanisole or 2-chlorotoluene lower TONs of 155 and 15 were obtained, respectively (Table 1, entries 19, 20 and 25). 2-Chlorobenzonitrile and the disubstituted electron-poor aryl chlorides such as 4-trifluoromethyl-2-nitrochlorobenzene or 2-chloro-5-nitrobenzonitrile also led to the corresponding coupling products **9** and **11**–**13** in good yields and TONs of 93–9100 (Table 1, entries 23, 24 and 26–30). These result seems to indicate that the lower reaction rates observed with some of these electron-poor aryl chlorides more likely comes from partial poisoning of the catalyst rather than from electronic factors.

We also compared the rates of the reactions in the presence of the diphosphine ligand dppe and with our tetraphosphine. Using similar conditions, the reactions led to the coupling products in TONs of 30–40 with dppe as ligand (Table 1, entries 4, 13 and 17) and in TONs of 96–16,000 in the presence of Tedicyp ligand (Table 1, entries 8, 15 and 20).

Having demonstrated that aryl chlorides can be efficiently cross-coupled with phenylacetylene, we investigated the scope of this coupling reaction using four other alkynes: dec-1-yne, 1-ethynylcyclohexene, pent-4-yn-1-ol and hex-5-yn-1-ol (Scheme 2, Table 2).

First, we studied the reactivity of three aryl chlorides with dec-1-yne. The results in Table 2 show that with dec-1-yne better results were obtained in the absence of CuI as a co-catalyst. The coupling of 4-chloroacetophenone or 3- and 4-chlorobenzonitrile led to the coupling adducts **14**–**16** in TONs of 89–390 in the absence of CuI, and in TONs of 30–61 in the presence of CuI (Table 2, entries 1–9). The reaction of 1-ethynylcyclohexene with 4-chlorobenzonitrile gave the corresponding enyne **17** in good yield, but with this alkyne, 4% catalyst had to be used. Pent-4-yn-1-ol and hex-5-yn-1-ol gave the expected arylalkynols **18a** and **19**–**22** (Table 2, entries 11–16). The reaction of pent-1-yn-5-ol with 4-chlorobenzonitrile also led to the formation of the cyclisation products **18b** and **18c** when 1% catalyst was used. We had already observed the formation of such cyclisation products for the reaction of aryl bromides with phenylacetylene.[32] These cyclisations products were not detected for the other reactions with alky-1-nols.

In summary, we have established that the Tedicyp–palladium system is not limited to the coupling reactions of aryl bromides with alkynes; aryl chlorides are also efficiently coupled. The complex seems to possess a fine balance of steric and electronic properties, which allow fast catalytic processes with activated aryl chlorides. With this catalyst, the cross-coupling reaction of phenylacetylene can be performed with as little as 0.01% catalyst



Scheme 2.

Table 2. Cross-coupling reactions of aryl chlorides with various alkynes (Scheme 2)[33]

Entry	ArCl	Alkyne	Substrate/catalyst	Product number	Yield (%)[a]
1	4-MeCO–C_6H_4Cl	Dec-1-yne	50	**14**	60[b,c]
2	4-MeCO–C_6H_4Cl	Dec-1-yne	100	**14**	93
3	4-MeCO–C_6H_4Cl	Dec-1-yne	1000	**14**	39[b]
4	4-CN–C_6H_4Cl	Dec-1-yne	100	**15**	61[b,c]
5	4-CN–C_6H_4Cl	Dec-1-yne	100	**15**	93
6	4-CN–C_6H_4Cl	Dec-1-yne	1000	**15**	62[b]
7	3-CN–C_6H_4Cl	Dec-1-yne	100	**16**	48[b,c]
8	3-CN–C_6H_4Cl	Dec-1-yne	100	**16**	89
9	3-CN–C_6H_4Cl	Dec-1-yne	1000	**16**	12[b]
10	4-CN–C_6H_4Cl	1-Ethynylcyclohexene	25	**17**	80
11	4-CN–C_6H_4Cl	Pent-4-yn-1-ol	100	**18a**–**c**	95[d,e]
12	4-CN–C_6H_4Cl	Pent-4-yn-1-ol	1000	**18a**	28[b,d]
13	2-NO_2–4-CF_3–C_6H_3Cl	Pent-4-yn-1-ol	100	**19**	94[d]
14	4-MeCO–C_6H_4Cl	Hex-5-yn-1-ol	100	**20**	45[d]
15	4-CN–C_6H_4Cl	Hex-5-yn-1-ol	100	**21**	**93**[d]
16	2-NO_2–4-CF_3–C_6H_3Cl	Hex-5-yn-1-ol	100	**22**	80[d]

[a] Conditions: catalyst see Ref. 27, aryl chloride (1 equiv), alkyne (2 equiv), K_2CO_3 (2 equiv), DMF, 140 °C, 20 h.

[b] GC and NMR yield.

[c] Reaction performed with 0.05 equiv of CuI.

[d] Reaction temperature 100 °C.

[e] Mixture of 4-(5-hydroxy-1-pentyn-1-yl)benzonitrile **18a**, (*E*)-4-(tetrahydrofuran-2-ylidenemethyl)-benzonitrile **18b** and (*Z*)-4-(tetrahydrofuran-2-ylidenemethyl)benzonitrile **18c** obtained in a ratio 46:40:14.

without addition of co-catalysts. Lower TONs were obtained for the coupling of dec-1-yne, pent-4-yn-1-ol or hex-5-yn-1-ol. These reactions gave better results in absence of copper iodide. The presence of copper iodide often led to the formation of side products such as the dimerisation of the alkynes. As expected, the electronic properties of the aryl chloride have an important effect on the reaction rates. Electron-poor aryl chlorides are more reactive than electron-rich aryl chlorides but even the electron-rich 4-chloroanisole led to the desired coupling product in good yield. We believe that this system compares favourably with other catalyst systems that have been reported for this process.

Acknowledgements

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33. *General procedure*: The reaction of the aryl chloride (10 mmol), K_2CO_3 (2.76 g, 20 mmol) and the alkyne (20 mmol) at 100 or 140 °C (see tables) during 20 h in DMF (10 mL) in the presence of the Tedicyp–palladium complex under argon affords the corresponding coupling product after addition of water, extraction with dichloromethane or ether, separation, drying ($MgSO_4$), evaporation and filtration on silica gel.