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Sonogashira cross-coupling reactions with heteroaryl halides in the presence of a tetraphosphine–palladium catalyst

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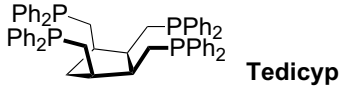
Abstract—Heteroaryl halides undergoes cross-couplings with alkynes in good yields in the presence of $[PdCl(C_3H_5)]_2$/*cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane as catalyst. A variety of heteroaryl halides such as pyridines, quinolines, a pyrimidine, an indole, a thiophene, or a thiazole have been used successfully. The reaction also tolerates several alkynes such as phenylacetylene and a range of alk-1-ynols. Furthermore, this catalyst can be used at low loading with some substrates.

The cross-coupling palladium-catalysed reactions between aryl halides and alkynes are among the most widely used methodologies in organic synthesis.[1–3] In recent years, the efficiency of several palladium catalysts for these reactions has been described.[4–11] On the other hand, the reaction of heteroaryl halides has attracted less attention, and suffers generally from high catalyst loadings. A few ligands have been successfully employed for the reaction with these substrates.[12–29] 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 3–10% catalyst had to be used.[12–22] Recently, new palladium catalysts have also been successfully employed for the alkynylation reactions with heteroaryl halides.[23–29] In the monophosphine ligand series, interesting results have been recently reported.[23–25] Soheili et al. described that P(*t*-Bu)$_3$ associated to [(allyl)PdCl]$_2$ is a good ligand for the reaction of 3-bromopyridine or 3-bromothiophene with phenylacetylene, without CuI, at room temperature.[23] Buchwald obtained high yields using 1% of a catalyst derived from $PdCl_2(CH_3CN)_2$ and a bulky and electron-rich *ortho*-biphenylphosphane ligand.[24] With the imidazolium carbene ligand good results were obtained for the coupling of 2-iodothiophene using 3% of palladium catalyst.[26,27] Finally, one of the best catalyst reported is a palladium (II) complex containing a ferrocene-based phosphinimine-phosphine ligand which gave good yields using 2-iodo- or 2-bromothiophene.[28] Despite these recent advances, there still remained a need for a general protocol; moreover, the efficiency of tetraphosphine ligands for the alkynylation of heteroaryl halides 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)[30] 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,[30] in Heck reaction,[31] in Suzuki cross-coupling[32] and in Sonogashira reaction[33–36] using Tedicyp as ligand. For example, we obtained a turnover number (TON) of 2,800,000 for the coupling of 3,5-bis(trifluoromethyl)bromobenzene with phenyl-acetylene.[33] We have also recently reported the coupling of alkynes with a range of aryl chlorides with as little as 0.01% catalyst.[35] Here, we wish to report on the efficiency of



Tedicyp

Figure 1.

Keywords: Palladium; Catalysis; Heteroaryl halide; Alkyne; Sonogashira reaction; Tetraphosphine.
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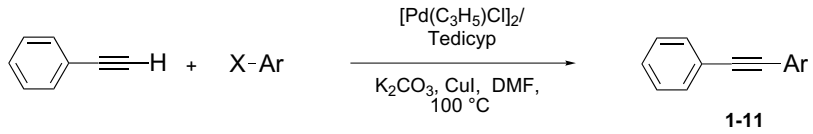


Scheme 1.

Tedicyp ligand for the reaction of heteroaryl halides with terminal alkynes such as phenylacetylene or alk-1-ynols.

For this study, based on our previous results,[33–36] DMF was chosen as the solvent and potassium carbonate as the base. The reactions were generally performed at 100 °C under argon in the presence of a ratio 1/2 of $[Pd(C_3H_5)Cl]_2$/Tedicyp as catalyst and 5% copper (I) iodide as co-catalyst.

First, we tried to couple phenylacetylene with a range of heteroaryl halides (Scheme 1, Table 1). We studied the influence of the position of the bromo-substituent on pyridines on the reaction rate. Due to the electronegativity of the nitrogen atom, the α and the γ positions of halo pyridines should be most susceptible to do the oxidative addition to palladium (0). In fact, we observed similar reactions rates for the 2-, 3- and 4-bromopyridines for a ratio S/C = 10,000 (Table 1, entries 1, 3 and 7). These results seem to indicate that the oxidative addition of bromopyridines to palladium is not the rate-limiting step of the reaction with this catalyst. We have also investigated the influence of the nature of the halogen on the reactivity of pyridines. As expected, the oxidative addition of 2- and 4-chloropyridines to Pd(0) is faster than for 3-chloropyridine (Table 1, entries 2, 4–5, 8). In fact, it was not possible to cross-couple 3-chloropyridine with phenylacetylene under conditions similar to those employed for 3-bromopyridine (Table 1, entry 4), but a conversion of 90% was obtained using 1% catalyst without addition of CuI at 130 °C (Table 1, entry 5). Then, we studied the reactivity of haloquinolines. We observed that the reactivity is similar to halopyridines. 2-Chloroquinoline, 3-bromoquinoline and 4-bromoisoquinoline led to the coupling products **4**, **5** and **6** using 0.01% catalyst (Table 1, entries 9–12). Next, we studied the influence of the position of the halogen on thiophenes and we observed that 3-bromothiophene gave a lower TON: 780 (Table 1, entry 19) than 2-bromothiophene: 5600 (Table 1, entry 18).

Table 1. Cross-coupling reactions of heteroaryl halides with phenylacetylene (Scheme 1)[37]

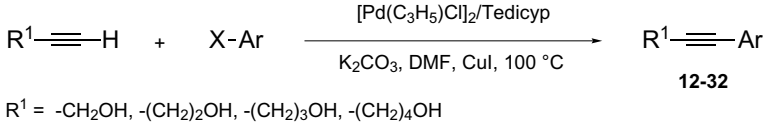
Entry	ArX	Ratio substrate/catalyst	Product number	Yield (%)[a]
1	2-Bromopyridine	10,000	**1**	80
2	2-Chloropyridine	1000	**1**	90
3	3-Bromopyridine	10,000	**2**	75[b]
4	3-Chloropyridine	100	**2**	0[c]
5	3-Chloropyridine	100	**2**	90[d]
6	4-Bromopyridine[e]	1000	**3**	97
7	4-Bromopyridine[e]	10,000	**3**	50[c]
8	4-Chloropyridine[e]	1000	**3**	75
9	2-Chloroquinoline	1000	**4**	97
10	2-Chloroquinoline	10,000	**4**	60[c]
11	3-Bromoquinoline	10,000	**5**	79
12	4-Bromoisoquinoline	10,000	**6**	60
13	5-Bromoindole	10,000	**7**	60
14	5-Bromopyrimidine	1000	**8**	100[c]
15	5-Bromopyrimidine	10,000	**8**	80
16	2-Bromothiazole	10,000	**9**	76
17	2-Bromothiophene	1000	**10**	95[b]
18	2-Bromothiophene	10,000	**10**	56[c]
19	3-Bromothiophene	1000	**11**	78[b]

[a] Conditions: catalyst see Ref. 30, heteroaryl halide (1 equiv), phenylacetylene (2 equiv), K_2CO_3 (2 equiv), CuI (0.05 equiv), DMF, 100 °C, 20 h.
[b] The reaction performed under similar conditions using $[Pd(C_3H_5)Cl]_2$ without Tedicyp ligand does not proceed.
[c] GC and NMR yield.
[d] Reaction performed without CuI at 130 °C.
[e] 4-Bromo- or 4-chloropyridine hydrochlorides were used directly with 3 equiv of K_2CO_3.

As expected, the reactions of bromothiophenes (π-electron excessive heterocycles) with phenylacetylene are more sensitive to the halogen position than bromopyridines (π-electron deficient heterocycles). With bromothiophenes the oxidative addition step is probably rate-limiting.

Bromo-substituted indole, pyrimidine and thiazole which have the potential to bind to palladium through nitrogen or sulfur are also suitable substrates for Sonogashira reactions. TONs between 6000 and 8000 were obtained for the couplings of 5-bromoindole, 5-bromopyrimidine and 2-bromothiazole with phenylacetylene (Table 1, entries 13–16).

Having demonstrated that heteroaryl halides can be efficiently cross-coupled with phenylacetylene, we investigated the scope of this reaction using four alk-1-ynols (Scheme 2, Table 2).



Scheme 2.

Table 2. Cross-coupling reactions of heteroaryl halides with various alk-1-ynols (Scheme 2)[37]

Entry	ArX	Alkyne	Ratio substrate/catalyst	Product number	Yield (%)[a]
1	2-Bromopyridine	Propargyl alcohol	5000	**12**	90
2	2-Chloropyridine	Propargyl alcohol	100	**12**	97
3	3-Iodopyridine	Propargyl alcohol	100,000	**13**	80
4	3-Bromopyridine	Propargyl alcohol	100	**13**	90
5	3-Chloropyridine	Propargyl alcohol	100	**13**	30
6	4-Bromopyridine[c]	Propargyl alcohol	1000	**14**	60
7	4-Chloropyridine[c]	Propargyl alcohol	100	**14**	86
8	2-Chloroquinoline	Propargyl alcohol	100	**15**	80
9	2-Chloroquinoline	Propargyl alcohol	1000	**15**	49[b]
10	2-Bromothiazole	Propargyl alcohol	100	**16**	85
11	2-Bromothiophene	Propargyl alcohol	100	**17**	65
12	3-Bromothiophene	Propargyl alcohol	100	**18**	55
13	2-Bromopyridine	But-3-yn-1-ol	1000	**19**	90
14	2-Bromopyridine	But-3-yn-1-ol	10,000	**19**	20[b]
15	3-Iodopyridine	But-3-yn-1-ol	1,000,000	**20**	90
16	3-Bromopyridine	But-3-yn-1-ol	1000	**20**	80
17	4-Chloropyridine[c]	But-3-yn-1-ol	1000	**21**	72
18	3-Bromoquinoline	But-3-yn-1-ol	100	**22**	98
19	2-Chloroquinoline	But-3-yn-1-ol	1000	**23**	90
20	5-Bromoindole	But-3-yn-1-ol	100	**24**	99
21	5-Bromopyrimidine	But-3-yn-1-ol	1000	**25**	75
22	2-Bromothiazole	But-3-yn-1-ol	1000	**26**	60
23	2-Bromothiophene	But-3-yn-1-ol	1000	**27**	52
24	3-Bromothiophene	But-3-yn-1-ol	100	**28**	95
25	3-Bromopyridine	Pent-4-yn-1-ol	1000	**29**	92
26	4-Bromoisoquinoline	Pent-4-yn-1-ol	100	**30**	97
27	4-Bromoisoquinoline	Pent-4-yn-1-ol	1000	**30**	50[b]
28	2-Iodothiophene	Pent-4-yn-1-ol	10,000	**31**	58
29	2-Bromothiophene	Pent-4-yn-1-ol	1000	**31**	70[b]
30	4-Bromoisoquinoline	Hex-5-yn-1-ol	10,000	**32**	15

[a] Conditions: catalyst see Ref. 30, heteroaryl halide (1 equiv), alkyne (2 equiv), K_2CO_3 (2 equiv), CuI (0.05 equiv), DMF, 100 °C, 20 h.
[b] GC and NMR yield.
[c] 4-Bromo- or 4-chloropyridines hydrochloride were used directly with 3 equiv of K_2CO_3.

First, we studied the reactivity of propargyl alcohol with some heteroaryl halides. The results described in Table 2 shown that lower reactions rates were obtained using this alk-1-ynol than with phenylacetylene (Table 2, entries 1–12). Only 2-bromopyridine (Table 2, entry 1), 4-bromopyridine (entry 6) and 2-chloroquinoline (entry 9) were coupled efficiently using 0.1% catalyst. The best result was obtained with 3-iodopyridine with a TON of 80,000 (Table 2, entry 3). The other heteroaryl halides required the presence of 1% catalyst in order to obtain the desired products in good yields. The reactions with but-3-yn-1-ol gave better results than with propargylic alcohol. With the most reactive heteroaryl halides the coupling products were obtained in good yields using 0.1% catalyst (Table 2, entries 16–17, 19, 21–23). The highest TON was obtained for the reaction of 3-iodopyridine: 900,000 (Table 2, entry 15). Much slower reactions rates were observed with 3-bromoquinoline, 5-bromoindole and 3-bromothiophene (Table 2, entries 18, 20, 24). Finally, we studied the reactivity of pent-4-yn-1-ol and hex-5-yn-1-ol (Table 2, entries 25–30). These reactions can be performed with the same amount of catalyst than with but-3-yn-1-ol. A TON of 1500 was obtained for the coupling of 4-bromoisoquinoline with hex-5-yn-1-ol (Table 2, entry 30).

In conclusion, Tedicyp–palladium complex provides a convenient catalyst for the cross-coupling of a variety of heteroaromatics with several alkynes. Despite the presence of heteroatoms, including N and S, that might be expected to significantly affect the course of the Pd-catalysed reaction of heteroaryl halides, a wide variety of heteroaryl substrates have been successfully alkynylated. The position and the nature of the halide on the heteroaromatic has an important effect on the reactions rates. The reactions can be performed with as little as 0.01% with the most reactive heteroaryl bromides. We believe that this system compares favourably with other catalyst systems that have been reported for this process.

Acknowledgements

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37. General procedure: The reaction of the heteroaryl halide (10 mmol), K_2CO_3 (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol) and the alkyne (20 mmol) at 100 or 130 °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.