Sonogashira reaction of heteroaryl halides with alkynes catalysed by a palladium-tetraphosphine complex

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Abstract

cis,*cis*,*cis*-1,2,3,4-Tetrakis(diphenylphosphinomethyl)cyclopentane/(1/2)[PdCl(C$_3$H$_5$)]$_2$ system catalyses the Sonogashira reaction of heteroaryl halides with a range of alkynes with moderate to high substrate/catalyst ratios in good yields. A variety of heteroaryl halides such as pyridines, quinolines, a pyrimidine, an indole, thiophenes, or a thiazole have been used successfully. The reaction also tolerates several alkynes such as phenylacetylene and alk-1-ynols. The nature of the heteroaromatics and the substituent of the alkynes have both an important effect on the reaction rates. High reaction rates were generally observed with phenylacetylene. With this alkyne substrate/catalyst ratios up to 10,000 have been used successfully. An effect of the position of the alcohol function on the reaction rates was observed with alk-1-ynols. Higher substrate/catalyst ratios could be used with but-3-yn-1-ol, pent-4-yn-1-ol or hex-5-yn-1-ol than with propargyl alcohol. The nature and the position of the halide on the heteroaromatics have also an important effect on the reaction rates. As expected, higher reaction rates were obtained with heteroaryl iodides than with heteroaryl bromides or chlorides.
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Keywords: Tetraphosphine; Palladium; Sonogashira reaction; Alkynes; Heteroaryl halides

1. Introduction

The so-called Sonogashira cross-coupling palladium-catalysed reaction between aryl halides and alkynes is among the most widely used methodology in organic synthesis [1–4]. In recent years, the efficiency of several palladium catalysts for this reaction has been described [5–12]. The reaction of *heteroaryl* halides has attracted less attention than the coupling with *aryl* halides, and suffers generally from high catalysts loadings. A few ligands have been successfully employed for the reaction with these substrates [13–32]. The first one was triphenylphosphine, however, the catalyst formed by association of this ligand with palladium complexes is not very efficient in terms of substrate/catalyst ratio and 3–10% catalyst had to be used [13–25]. Recently, new palladium catalysts have been successfully employed for the alkynylation reactions with het-

eroaryl halides [26–32]. In the monophosphine ligand series, interesting results have been reported [26–28]. 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 [26]. Buchwald et al. obtained high yields of alkynylation adducts using 1% of a catalyst derived from PdCl$_2$(CH$_3$CN)$_2$ and a bulky electron-rich *ortho*-biphenylphosphane ligand [27]. 3-Bromopyridine reacts with phenylacetylene employing 2.5% Pd(OAc)$_2$ and an aminophosphine ligand [28]. With an imidazolium carbene ligand good results were obtained for the coupling of 2-iodothiophene using 3% of palladium catalyst [29,30]. One of the most efficient catalyst reported for this reaction is a palladium(II) complex containing a ferrocene-based phosphinimine-phosphine ligand which gave good yields of adducts using 2-iodo- or 2-bromothiophene as reactants [31]. A palladium-phosphinous acid catalysed Sonogashira cross-coupling reaction that proceeds in water under air atmosphere in the absence of organic co-solvents has been recently developed by Wolf et al. [32]. With this system the coupling of 3-bromo- or 3-chloropyridine with phenylacetylene gave the expected

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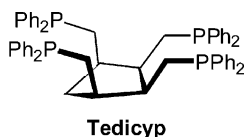m.santelli@univ.u-3mrs.fr (M. Santelli).

Tedicyp

Fig. 1.

adduct employing 10 mol.% catalyst. Finally, the reaction of 3-iodopyridine with alkynes proceeds in absence of ligand and CuI using 1% PdCl$_2$ as catalyst [33]. Despite these recent advances, there still remains a need for a general protocol employing low catalyst loadings for the coupling of heteroaryl halides with terminal alkynes.

In order to find a stable and efficient palladium catalyst, we have prepared the tetrapodal phosphine ligand, *cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl) cyclopentane or Tedicyp (Fig. 1) [34] 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 [34], in Heck reaction [35], in Suzuki cross-coupling [36] and in Sonogashira reaction [37] 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 phenylacetylene [37a]. We have also recently reported the coupling of alkynes with sterically congested aryl bromides [37b], with a range of aryl chlorides [37c], with alkynols [37d] or propargyl amines [37e]. We have also reported preliminary results using heteroaryl bromides and alkynes [38]. Here, we wish to describe our results involving heteroaryl bromides such as halopyridines, haloquinolines, a bromopyrimidine, a bromothiazole, a bromoindole and halothiophenes with terminal alkynes such as phenylacetylene or alk-1-ynols.

2. Experimental

2.1. General

All reactions were run under argon using vacuum lines in Schlenk tubes in oven-dried glassware. DMF was not distilled before use. Commercial alkynes, aryl halides and CuI were used without purification. The reactions were followed by GC and NMR for high boiling point substrates and by GC for low boiling point substrates. ^{1}H (300 MHz) and ^{13}C (75 MHz) spectra were recorded in CDCl$_3$ solutions. Chemical shift (δ) are reported in ppm relative to CDCl$_3$. Flash chromatographies were performed on silica gel (230–400 mesh).

2.2. Preparation of the Pd-Tedicyp catalyst [34]

An oven-dried 40-mL Schlenk tube equipped with a magnetic stirring bar, under argon atmosphere, was charged with [Pd(C$_3$H$_5$)Cl]$_2$ (4.2 mg, 11.6 μmol) and Tedicyp (20 mg, 23.2 μmol). 2.5 mL of anhydrous DMF were added, then the solution was stirred at room temperature for 10 min. The appropriate amount of catalyst (see tables) was transferred to the mixture of aryl halide, alkyne, CuI and base in DMF (see Section 2.3).

2.3. Catalytic procedure for Sonogashira reactions

As a typical experiment, the reaction of aryl halide (10 mmol), alkyne (20 mmol), CuI (0.5 mmol) and K$_2$CO$_3$ (20 mmol) at 100 °C during 20 h in DMF (10 mL) in the presence of *cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane/(1/2)[PdCl(C$_3$H$_5$)]$_2$ complex under argon affords the corresponding products after addition of water, extraction with dichloromethane, separation, drying (MgSO$_4$), evaporation and chromatography on silica gel.

2.4. Alkynylation products (Tables 1–4)

2-(Phenylethynyl)pyridine (**1**): (Table 1, entry 2) 2-Bromopyridine (0.95 mL, 10 mmol), phenylacetylene (2.20 mL, 20 mmol), K$_2$CO$_3$ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (1 μmol) at 100 °C gave **1** in 80% (1.43 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.55 (d, J = 4.9 Hz, 1H), 7.61–7.55 (m, 3H), 7.45 (d, J = 7.9 Hz, 1H), 7.30–7.28 (m, 3H), 7.15 (dd, J = 7.9 and 4.9 Hz, 1H).

3-(Phenylethynyl)pyridine (**2**): (Table 1, entry 6) 3-Bromopyridine (0.95 mL, 10 mmol), phenylacetylene (2.20 mL, 20 mmol), K$_2$CO$_3$ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (1 μmol) at 100 °C gave **2** in 75% (1.34 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.69 (s, 1H), 8.48 (d, J = 3.7 Hz, 1H), 7.69 (dt, J = 7.9 and 1.7 Hz, 1H), 7.44 (m, 2H), 7.30–7.28 (m, 3H), 7.23 (dd, J = 7.9 and 3.7 Hz, 1H).

4-(Phenylethynyl)pyridine (**3**): (Table 1, entry 9) 4-Bromopyridine hydrochloride (1.94 g, 10 mmol), phenylacetylene (2.20 mL, 20 mmol), K$_2$CO$_3$ (4.14 g, 30 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (10 μmol) at 100 °C gave **3** in 97% (1.74 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.58 (d, J = 4.9 Hz, 2H), 7.51 (m, 2H), 7.38–7.23 (m, 5H).

3-(Pyridin-2-yl)-2-propyn-1-ol (**4**): (Table 1, entry 13) 2-Bromopyridine (0.95 mL, 10 mmol), propargyl alcohol (1.12 g, 20 mmol), K$_2$CO$_3$ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (2 μmol) at 100 °C gave **4** in 90% (1.20 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.45 (d, J = 4.8 Hz, 1H), 7.58 (dd, J = 7.9 and 7.8 Hz, 1H), 7.35 (d, J = 7.9 Hz, 1H), 7.15 (dd, J = 7.8 and 4.8 Hz, 1H), 4.43 (s, 2H).

3-(Pyridin-3-yl)-2-propyn-1-ol (**5**): (Table 1, entry 16) 3-Iodopyridine (2.05 g, 10 mmol), propargyl alcohol (1.12 g, 20 mmol), K$_2$CO$_3$ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (0.1 μmol) at 100 °C gave **5** in 80% (1.07 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.71 (s, 1H), 8.47 (d, J = 4.9 Hz, 1H), 7.69 (d, J = 7.9 Hz, 1H), 7.20 (dd, J = 7.9 and 4.9 Hz, 1H), 4.40 (s, 2H).

3-(Pyridin-4-yl)-2-propyn-1-ol (**6**): (Table 1, entry 21) 4-Chloropyridine hydrochloride (1.50 g, 10 mmol), propargyl alcohol (1.12 g, 20 mmol), K$_2$CO$_3$ (4.14 g, 30 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (100 μmol) at 100 °C gave **6** in 86% (1.14 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.55 (d, J = 4.9 Hz, 2H), 7.27 (d, J = 4.9 Hz, 2H), 4.50 (s, 2H).

Table 1
Palladium-catalysed Sonogashira reactions with halopyridines (Scheme 1)

Entry	Aryl bromide	Alkyne	Substrate/catalyst ratio	Product	Yield (%)
1	2-Bromopyridine	Phenylacetylene	1000	**1**	100
2	2-Bromopyridine	Phenylacetylene	10000	**1**	(80)
3	2-Chloropyridine	Phenylacetylene	100	**1**	100
4	2-Chloropyridine	Phenylacetylene	1000	**1**	(90)
5	3-Bromopyridine	Phenylacetylene	1000	**2**	100
6	3-Bromopyridine	Phenylacetylene	10000	**2**	(75)[a]
7	3-Chloropyridine	Phenylacetylene	100	**2**	0
8	3-Chloropyridine	Phenylacetylene	100	**2**	(90)[b]
9	4-Bromopyridine[c]	Phenylacetylene	1000	**3**	(97)
10	4-Bromopyridine[c]	Phenylacetylene	10000	**3**	50
11	4-Chloropyridine[c]	Phenylacetylene	1000	**3**	(75)
12	2-Bromopyridine	Propargyl alcohol	1000	**4**	100
13	2-Bromopyridine	Propargyl alcohol	5000	**4**	(90)
14	2-Chloropyridine	Propargyl alcohol	100	**4**	(97)
15	3-Iodopyridine	Propargyl alcohol	10000	**5**	100
16	3-Iodopyridine	Propargyl alcohol	100000	**5**	(80)
17	3-Bromopyridine	Propargyl alcohol	100	**5**	(90)
18	3-Bromopyridine	Propargyl alcohol	1000	**5**	26
19	3-Chloropyridine	Propargyl alcohol	100	**5**	(30)
20	4-Bromopyridine[c]	Propargyl alcohol	1000	**6**	(60)
21	4-Chloropyridine[c]	Propargyl alcohol	100	**6**	(86)
22	2-Bromopyridine	But-3-yn-1-ol	1000	**7**	(90)
23	2-Bromopyridine	But-3-yn-1-ol	10000	**7**	20
24	2-Chloropyridine	But-3-yn-1-ol	100	**7**	100
25	2-Chloropyridine	But-3-yn-1-ol	1000	**7**	(90)
26	3-Iodopyridine	But-3-yn-1-ol	100000	**8**	100
27	3-Iodopyridine	But-3-yn-1-ol	1000000	**8**	(90)
28	3-Bromopyridine	But-3-yn-1-ol	100	**8**	100
29	3-Bromopyridine	But-3-yn-1-ol	1000	**8**	(80)
30	3-Chloropyridine	But-3-yn-1-ol	100	**8**	30
31	4-Bromopyridine[c]	But-3-yn-1-ol	1000	**9**	50
32	4-Chloropyridine[c]	But-3-yn-1-ol	100	**9**	100
33	4-Chloropyridine[c]	But-3-yn-1-ol	1000	**9**	(72)
34	2-Bromopyridine	Pent-4-yn-1-ol	100	**10**	100
35	2-Bromopyridine	Pent-4-yn-1-ol	1000	**10**	(90)
36	2-Chloropyridine	Pent-4-yn-1-ol	100	**10**	(95)
37	3-Iodopyridine	Pent-4-yn-1-ol	100000	**11**	100
38	3-Iodopyridine	Pent-4-yn-1-ol	1000000	**11**	(80)
39	3-Bromopyridine	Pent-4-yn-1-ol	100	**11**	100
40	3-Bromopyridine	Pent-4-yn-1-ol	1000	**11**	(92)
41	3-Chloropyridine	Pent-4-yn-1-ol	100	**11**	2
42	4-Bromopyridine[c]	Pent-4-yn-1-ol	1000	**12**	(75)
43	4-Chloropyridine[c]	Pent-4-yn-1-ol	100	**12**	90

Conditions: Catalyst [Pd(C$_3$H$_5$)Cl]$_2$/Tedicyp 1/2, halopyridine (1 eq.), alkyne (2 eq.), K$_2$CO$_3$ (2 eq.), CuI (0.05 eq.), DMF, 100 °C, 20 h, GC and NMR yields, yields in parenthesis are isolated.

[a] The reaction performed under similar conditions using [Pd(C$_3$H$_5$)Cl]$_2$ without Tedicyp ligand does not proceed.

[b] The reaction performed without CuI at 130 °C.

[c] 4-Bromo- or 4-chloropyridine hydrochlorides were used directly with 3 eq. of K$_2$CO$_3$.

4-(Pyridin-2-yl)-3-butyn-1-ol (**7**): (Table 1, entry 22) 2-Bromopyridine (0.95 mL, 10 mmol), but-3-yn-1-ol (1.51 mL, 20 mmol), K$_2$CO$_3$ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (10 μmol) at 100 °C gave **7** in 90% (1.32 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.50 (d, *J* = 4.8 Hz, 1H), 7.61 (dd, *J* = 7.8 and 7.8 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.18 (dd, *J* = 7.8 and 4.8 Hz, 1H), 3.83 (t, *J* = 6.4 Hz, 2H), 2.69 (t, *J* = 6.4 Hz, 2H).

4-(Pyridin-3-yl)-3-butyn-1-ol (**8**): (Table 1, entry 27) 3-Iodopyridine (2.05 g, 10 mmol), but-3-yn-1-ol (1.51 mL,

20 mmol), K$_2$CO$_3$ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (0.01 μmol) at 100 °C gave **8** in 90% (1.32 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.61 (s, 1H), 8.47 (bs, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.20 (dd, *J* = 8.0 and 4.5 Hz, 1H), 3.81 (t, *J* = 6.3 Hz, 2H), 2.68 (t, *J* = 6.3 Hz, 2H).

4-(Pyridin-4-yl)-3-butyn-1-ol (**9**): (Table 1, entry 33) 4-Chloropyridine hydrochloride (1.50 g, 10 mmol), but-3-yn-1-ol (1.51 mL, 20 mmol), K$_2$CO$_3$ (4.14 g, 30 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (10 μmol) at 100 °C gave **9** in 72% (1.05 g) isolated yield. ^{1}H NMR (300 MHz,

Table 2
Palladium-catalysed Sonogashira reactions with haloquinolines (Scheme 2)

Entry	Aryl bromide	Alkyne	Substrate/catalyst ratio	Product	Yield (%)
1	3-Bromoquinoline	Phenylacetylene	1000	**13**	100
2	3-Bromoquinoline	Phenylacetylene	10000	**13**	(79)
3	3-Bromoquinoline	Propargyl alcohol	100	**14**	(98)
4	3-Bromoquinoline	2-(Prop-2-ynyloxy)tetrahydropyran	100	**15**	(92)
5	3-Bromoquinoline	2-(Prop-2-ynyloxy)tetrahydropyran	1000	**15**	10
6	3-Bromoquinoline	But-3-yn-1-ol	100	**16**	(98)
7	3-Bromoquinoline	But-3-yn-1-ol	1000	**16**	87
8	3-Bromoquinoline	2-(But-3-ynyloxy)tetrahydropyran	100	**17**	(81)
9	3-Bromoquinoline	Pent-4-yn-1-ol	100	**18**	(96)
10	3-Bromoquinoline	Pent-4-yn-1-ol	1000	**18**	60
11	4-Bromoisoquinoline	Phenylacetylene	10000	**19**	(60)
12	4-Bromoisoquinoline	Propargyl alcohol	100	**20**	(93)
13	4-Bromoisoquinoline	But-3-yn-1-ol	100	**21**	(95)
14	4-Bromoisoquinoline	But-3-yn-1-ol	1000	**21**	20
15	4-Bromoisoquinoline	Pent-4-yn-1-ol	100	**22**	(97)
16	4-Bromoisoquinoline	Pent-4-yn-1-ol	1000	**22**	50
17	4-Bromoisoquinoline	Hex-5-yn-1-ol	1000	**23**	(96)
18	4-Bromoisoquinoline	Hex-5-yn-1-ol	10000	**23**	18
19	2-Chloroquinoline	Phenylacetylene	1000	**24**	(97)
20	2-Chloroquinoline	Phenylacetylene	10000	**24**	60
21	2-Chloroquinoline	Propargyl alcohol	100	**25**	(80)
22	2-Chloroquinoline	Propargyl alcohol	1000	**25**	49
23	2-Chloroquinoline	But-3-yn-1-ol	1000	**26**	(90)

Conditions: Catalyst [Pd(C$_3$H$_5$)Cl]$_2$/Tedicyp 1/2, haloquinoline (1 eq.), alkyne (2 eq.), K$_2$CO$_3$ (2 eq.), CuI (0.05 eq.), DMF, 100 °C, 20 h, GC and NMR yields, yields in parenthesis are isolated.

CDCl$_3$): δ = 8.40 (d, *J* = 4.9 Hz, 2H), 7.23 (d, *J* = 4.9 Hz, 2H), 3.80 (t, *J* = 6.5 Hz, 2H), 2.68 (t, *J* = 6.5 Hz, 2H).

5-(Pyridin-2-yl)-4-pentyn-1-ol (**10**): (Table 1, entry 35) 2-Bromopyridine (0.95 mL, 10 mmol), pent-4-yn-1-ol (1.86 mL, 20 mmol), K$_2$CO$_3$ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (1 μmol) at 100 °C gave **10** in 90% (1.45 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.49 (d, *J* = 4.8 Hz, 1H), 7.61 (dd, *J* = 7.8 and 7.8 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.18 (dd, *J* = 7.8 and 4.8 Hz, 1H), 3.79 (t, *J* = 6.2 Hz, 2H), 2.56 (t, *J* = 7.0 Hz, 2H), 1.86 (m, 2H).

5-(Pyridin-3-yl)-4-pentyn-1-ol (**11**): (Table 1, entry 38) 3-Iodopyridine (2.05 g, 10 mmol), pent-4-yn-1-ol (1.86 mL, 20 mmol), K$_2$CO$_3$ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (0.01 μmol) at 100 °C gave **11** in 80% (1.29 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.60 (s, 1H), 8.47 (d, *J* = 4.5 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.20 (dd, *J* = 8.0 and 4.5 Hz, 1H), 3.80 (t, *J* = 6.2 Hz, 2H), 2.57 (t, *J* = 7.0 Hz, 2H), 1.86 (m, 2H).

5-(Pyridin-4-yl)-4-pentyn-1-ol (**12**): (Table 1, entry 42) 4-Bromopyridine hydrochloride (1.94 g, 10 mmol), pent-4-yn-1-ol (1.86 mL, 20 mmol), K$_2$CO$_3$ (4.14 g, 30 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (10 μmol) at 100 °C gave **12** in 75% (1.21 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.35 (d, *J* = 4.9 Hz, 2H), 7.20 (d, *J* = 4.9 Hz, 2H), 3.79 (t, *J* = 6.2 Hz, 2H), 2.56 (t, *J* = 7.0 Hz, 2H), 1.86 (m, 2H).

Table 3
Palladium-catalysed Sonogashira reactions with 5-bromopyrimidine, 5-bromoindole and 2-bromothiazole (Scheme 3)

Entry	Aryl bromide	Alkyne	Substrate/catalyst ratio	Product	Yield (%)
1	5-Bromopyrimidine	Phenylacetylene	1000	**27**	100
2	5-Bromopyrimidine	Phenylacetylene	10000	**27**	(80)
3	5-Bromopyrimidine	Propargyl alcohol	100	**28**	(96)
4	5-Bromopyrimidine	But-3-yn-1-ol	1000	**29**	(75)
5	5-Bromoindole	Phenylacetylene	1000	**30**	(97)
6	5-Bromoindole	Phenylacetylene	10000	**30**	(60)
7	5-Bromoindole	Propargyl alcohol	100	**31**	(99)
8	5-Bromoindole	But-3-yn-1-ol	100	**32**	(99)
9	2-Bromothiazole	Phenylacetylene	1000	**33**	100
10	2-Bromothiazole	Phenylacetylene	10000	**33**	(76)
11	2-Bromothiazole	Propargyl alcohol	100	**34**	(85)
12	2-Bromothiazole	But-3-yn-1-ol	100	**35**	100
13	2-Bromothiazole	But-3-yn-1-ol	1000	**35**	(60)

Conditions: Catalyst [Pd(C$_3$H$_5$)Cl]$_2$/Tedicyp 1/2, heteroaryl halide (1 eq.), alkyne (2 eq.), K$_2$CO$_3$ (2 eq.), CuI (0.05 eq.), DMF, 100 °C, 20 h, GC and NMR yields, yields in parenthesis are isolated.

Table 4
Palladium-catalysed Sonogashira reactions with halothiophenes (Scheme 4)

Entry	Aryl bromide	Alkyne	Substrate/catalyst ratio	Product	Yield (%)
1	2-Bromothiophene	Phenylacetylene	1000	**36**	(95)[a]
2	2-Bromothiophene	Phenylacetylene	10000	**36**	56
3	2-Bromothiophene	Propargyl alcohol	100	**37**	(65)
4	2-Iodothiophene	Propargyl alcohol	1000	**37**	(80)
5	2-Bromothiophene	But-3-yn-1-ol	1000	**38**	(52)
6	2-Iodothiophene	But-3-yn-1-ol	10000	**38**	(89)
7	2-Bromothiophene	Pent-4-yn-1-ol	1000	**39**	70
8	2-Iodothiophene	Pent-4-yn-1-ol	10000	**39**	(58)
9	3-Bromothiophene	Phenylacetylene	100	**40**	100
10	3-Bromothiophene	Phenylacetylene	1000	**40**	(78)[a]
11	3-Bromothiophene	Propargyl alcohol	100	**41**	(55)
12	3-Bromothiophene	But-3-yn-1-ol	100	**42**	(95)
13	3-Bromothiophene	But-3-yn-1-ol	1000	**42**	35
14	3-Bromothiophene	Pent-4-yn-1-ol	100	**43**	(90)
15	3-Bromothiophene	Pent-4-yn-1-ol	1000	**43**	80

Conditions: Catalyst [Pd(C$_3$H$_5$)Cl]$_2$/Tedicyp 1/2, halothiophene (1 eq.), alkyne (2 eq.), K$_2$CO$_3$ (2 eq.), CuI (0.05 eq.), DMF, 100 °C, 20 h, GC and NMR yields, yields in parenthesis are isolated.

[a] The reaction performed under similar conditions using [Pd(C$_3$H$_5$)Cl]$_2$ without Tedicyp ligand does not proceed.

3-(Phenylethynyl)quinoline (**13**): (Table 2, entry 2) 3-Bromoquinoline (1.36 mL, 10 mmol), phenylacetylene (2.20 mL, 20 mmol), K$_2$CO$_3$ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (1 μmol) at 100 °C gave **13** in 79% (1.81 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.77 (s, 1H), 8.07 (s, 1H), 8.04 (d, J = 8.3 Hz, 1H), 7.60–7.53 (m, 2H), 7.51 (m, 2H), 7.40 (dd, J = 8.0 and 7.9 Hz, 1H), 7.38–7.23 (m, 3H).

3-(Quinolin-3-yl)-prop-2-yn-1-ol (**14**): (Table 2, entry 3) 3-Bromoquinoline (1.36 mL, 10 mmol), propargyl alcohol (1.12 g, 20 mmol), K$_2$CO$_3$ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (100 μmol) at 100 °C gave 14 in 98% (1.79 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.97 (s, 1H), 8.17 (s, 1H), 8.04 (d, J = 8.3 Hz, 1H), 7.68 (m, 2H), 7.48 (dd, J = 7.2 and 7.0 Hz, 1H), 4.53 (s, 2H).

2-[3-(Quinol-3-yl)-2-propyn-1-oxy]tetrahydropyran (**15**): (Table 2, entry 4) 3-Bromoquinoline (1.36 mL, 10 mmol), 2-prop-2-ynyloxytetrahydropyran (2.81 g, 20 mmol), K$_2$CO$_3$ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (100 μmol) at 100 °C gave **15** in 92% (2.46 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.79 (s, 1H), 8.00 (m, 2H), 7.60–7.53 (m, 2H), 7.40 (dd, J = 8.0 and 7.9 Hz, 1H), 4.78 (m, 1H), 4.47 (d, J = 7.0 Hz, 2H), 3.80–3.71 (m, 1H), 3.48–3.42 (m, 1H), 1.80–1.46 (m, 6H). ^{13}C NMR (CDCl$_3$): δ = 153.1, 147.6, 138.3, 129.7, 129.6, 127.6, 127.5, 126.0, 114.5, 99.1, 95.9, 78.6, 63.7, 51.0, 32.2, 28.9, 19.0. Anal. calc. for C$_{17}$H$_{17}$NO$_2$: C, 76.38; H, 6.41%. Found: C, 76.57; H, 6.62%.

4-(Quinol-3-yl)-3-butyn-1-ol (**16**): (Table 2, entry 6) 3-Bromoquinoline (1.36 mL, 10 mmol), but-3-yn-1-ol (1.51 mL, 20 mmol), K$_2$CO$_3$ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (100 μmol) at 100 °C gave **16** in 98% (1.93 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.77 (s, 1H), 8.00 (m, 2H), 7.61–7.56 (m, 2H), 7.43 (dd, J = 8.0 and 7.9 Hz, 1H), 3.85 (t, J = 6.5 Hz, 2H), 2.69 (t, J = 6.5 Hz, 2H).

2-[4-(Quinol-3-yl)-3-butyn-1-oxy]tetrahydropyran (**17**): (Table 2, entry 8) 3-Bromoquinoline (1.36 mL, 10 mmol), 2-(but-3-ynyloxy)tetrahydropyran (3.09 g, 20 mmol), K$_2$CO$_3$ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (100 μmol) at 100 °C gave **17** in 81% (2.28 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.80 (s, 1H), 8.00 (m, 2H), 7.60–7.53 (m, 2H), 7.40 (dd, J = 8.0 and 7.9 Hz, 1H), 4.63 (m, 1H), 3.83 (m, 2H), 3.58 (m, 1H), 3.45 (m, 1H), 2.68 (t, J = 6.2 Hz, 2H), 1.74–1.48 (m, 6H). ^{13}C NMR (CDCl$_3$): δ = 153.0, 147.2, 138.1, 129.7, 129.6, 127.6, 127.5, 126.0, 114.5, 100.2, 96.9, 75.2, 63.4, 62.2, 33.1, 28.2, 19.8, 18.5. MS (70 ev); *m/z* (%): 281 (14) [M$^+$]. Anal. calc. for C$_{18}$H$_{19}$NO$_2$: C, 76.84; H, 6.81%. Found: C, 76.70; H, 7.01%.

5-(Quinol-3-yl)-4-pentyn-1-ol (**18**): (Table 2, entry 9) 3-Bromoquinoline (1.36 mL, 10 mmol), pent-4-yn-1-ol (1.86 mL, 20 mmol), K$_2$CO$_3$ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (100 μmol) at 100 °C gave **18** in 96% (2.03 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.78 (s, 1H), 8.03 (s, 1H), 8.00 (d, J = 8.3 Hz, 1H), 7.71–7.61 (m, 2H), 7.48 (dd, J = 7.4 and 7.1 Hz, 1H), 3.79 (t, J = 6.2 Hz, 2H), 2.56 (t, J = 7.0 Hz, 2H), 1.86 (m, 2H).

4-(Phenylethynyl)isoquinoline (**19**): (Table 2, entry 11) 4-Bromoisoquinoline (2.08 g, 10 mmol), phenylacetylene (2.20 mL, 20 mmol), K$_2$CO$_3$ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (1 μmol) at 100 °C gave **19** in 60% (1.38 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 9.20 (s, 1H), 8.75 (s, 1H), 8.31 (d, J = 8.8 Hz, 1H), 7.99 (d, J = 8.1 Hz, 1H), 7.80 (t, J = 8.5 Hz, 1H), 7.70–7.20 (m, 6H).

3-(Isoquinol-4-yl)-2-propyn-1-ol (**20**): (Table 2, entry 12) 4-Bromoisoquinoline (2.08 g, 10 mmol), propargyl alcohol (1.12 g, 20 mmol), K$_2$CO$_3$ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (100 μmol) at 100 °C gave **20** in 93% (1.70 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 9.16 (s, 1H), 8.81 (s, 1H), 8.19 (d, J = 8.3 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.74 (dd, J = 8.3 and 7.2 Hz,

1H), 7.62 (dd, $J = 8.1$ and 7.2 Hz, 1H), 4.85 (s, 2H), 4.40 (bs, 1H).

4-(Isoquinol-4-yl)-3-butyn-1-ol (**21**): (Table 2, entry 13) 4-Bromoisoquinoline (2.08 g, 10 mmol), but-3-yn-1-ol (1.51 mL, 20 mmol), K_2CO_3 (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (100 μmol) at 100 °C gave **21** in 95% (1.87 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 9.11$ (s, 1H), 8.61 (s, 1H), 8.16 (d, $J = 8.3$ Hz, 1H), 7.90 (d, $J = 8.1$ Hz, 1H), 7.72 (dd, $J = 8.3$ and 7.2 Hz, 1H), 7.58 (dd, $J = 8.1$ and 7.2 Hz, 1H), 3.92 (t, $J = 6.5$ Hz, 2H), 2.84 (t, $J = 6.5$ Hz, 2H).

5-(Isoquinol-4-yl)-4-pentyn-1-ol (**22**): (Table 2, entry 15) 4-Bromoisoquinoline (2.08 g, 10 mmol), pent-4-yn-1-ol (1.86 mL, 20 mmol), K_2CO_3 (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (100 μmol) at 100 °C gave **22** in 97% (2.05 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 9.11$ (s, 1H), 8.61 (s, 1H), 8.16 (d, $J = 8.3$ Hz, 1H), 7.90 (d, $J = 8.1$ Hz, 1H), 7.72 (dd, $J = 8.3$ and 7.2 Hz, 1H), 7.58 (dd, $J = 8.1$ and 7.2 Hz, 1H), 3.80 (t, $J = 6.2$ Hz, 2H), 2.60 (t, $J = 7.0$ Hz, 2H), 1.89 (m, 2H). ^{13}C NMR (CDCl$_3$): $\delta = 151.3$, 146.3, 136.7, 130.4, 130.0, 127.7, 127.5, 125.9, 114.0, 96.9, 74.9, 62.2, 31.9, 14.0. Anal. calc. for $C_{14}H_{13}NO$: C, 79.59; H, 6.20%. Found: C, 79.51; H, 6.11%.

6-(Isoquinol-4-yl)-5-hexyn-1-ol (**23**): (Table 2, entry 17) 4-Bromoisoquinoline (2.08 g, 10 mmol), hex-5-yn-1-ol (2.21 mL, 20 mmol), K_2CO_3 (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (10 μmol) at 100 °C gave **23** in 96% (2.16 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 9.08$ (s, 1H), 8.56 (s, 1H), 8.16 (d, $J = 8.3$ Hz, 1H), 7.90 (d, $J = 8.1$ Hz, 1H), 7.71 (dd, $J = 8.3$ and 7.2 Hz, 1H), 7.58 (dd, $J = 8.1$ and 7.2 Hz, 1H), 3.72 (t, $J = 6.5$ Hz, 2H), 2.58 (t, $J = 6.5$ Hz, 2H), 1.83–1.78 (m, 4H). ^{13}C NMR (CDCl$_3$): $\delta = 151.2$, 146.0, 135.8, 130.9, 130.9, 127.8, 127.7, 125.1, 114.0, 97.9, 75.9, 62.2, 32.0, 25.2, 16.9. MS (70 ev); m/z (%): 225 (85) [M$^+$]. Anal. calc. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71%. Found: C, 79.89; H, 6.84%.

2-(Phenylethynyl)quinoline (**24**): (Table 2, entry 19) 2-Chloroquinoline (1.32 mL, 10 mmol), phenylacetylene (2.20 mL, 20 mmol), K_2CO_3 (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (10 μmol) at 100 °C gave **24** in 97% (2.22 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 8.03$ (m, 2H), 7.72 (d, $J = 8.3$ Hz, 1H), 7.68 (dd, $J = 8.1$ and 7.2 Hz, 1H), 7.50–7.44 (m, 4H), 7.30–7.28 (m, 3H).

3-(Quinol-2-yl)-2-propyn-1-ol (**25**): (Table 2, entry 21) 2-Chloroquinoline (1.32 mL, 10 mmol), propargyl alcohol (1.12 g, 20 mmol), K_2CO_3 (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (100 μmol) at 100 °C gave **25** in 80% (1.46 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 8.03$ (m, 2H), 7.72 (d, $J = 8.3$ Hz, 1H), 7.68 (dd, $J = 8.1$ and 7.2 Hz, 1H), 7.46 (m, 2H), 4.55 (s, 2H).

4-(Quinol-2-yl)-3-butyn-1-ol (**26**): (Table 2, entry 23) 2-Chloroquinoline (1.32 mL, 10 mmol), but-3-yn-1-ol (1.51 mL, 20 mmol), K_2CO_3 (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (10 μmol) at 100 °C gave **26** in 90% (1.77 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 8.03$ (m, 2H), 7.72 (d, $J = 8.3$ Hz, 1H), 7.68 (dd, $J = 8.2$ and

7.2 Hz, 1H), 7.46 (m, 2H), 3.92 (t, $J = 6.5$ Hz, 2H), 2.84 (t, $J = 6.5$ Hz, 2H).

5-(Phenylethynyl)pyrimidine (**27**): (Table 3, entry 2) 5-Bromopyrimidine (1.59 g, 10 mmol), phenylacetylene (2.20 mL, 20 mmol), K_2CO_3 (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (1 μmol) at 100 °C gave **27** in 80% (1.44 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 9.10$ (s, 1H), 8.82 (s, 2H), 7.58 (m, 2H), 7.40–7.33 (m, 3H).

3-(Pyrimidin-5-yl)-2-propyn-1-ol (**28**): (Table 3, entry 3) 5-Bromopyrimidine (1.59 g, 10 mmol), propargyl alcohol (1.12 g, 20 mmol), K_2CO_3 (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (100 μmol) at 100 °C gave **28** in 96% (1.29 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 9.06$ (s, 1H), 8.70 (s, 2H), 4.45 (s, 2H).

4-(Pyrimidin-5-yl)-3-butyn-1-ol (**29**): (Table 3, entry 4) 5-Bromopyrimidine (1.59 g, 10 mmol), but-3-yn-1-ol (1.51 mL, 20 mmol), K_2CO_3 (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (10 μmol) at 100 °C gave **29** in 75% (1.11 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta =$ (s, 1H), 8.70 (s, 2H), 3.86 (t, $J = 6.5$ Hz, 2H), 2.72 (t, $J = 6.5$ Hz, 2H).

5-(Phenylethynyl)indole (**30**): (Table 3, entry 5) 5-Bromoindole (1.96 g, 10 mmol), phenylacetylene (2.20 mL, 20 mmol), K_2CO_3 (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (10 μmol) at 100 °C gave **30** in 97% (2.11 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 10.10$ (s, 1H), 7.73 (s, 1H), 7.50–7.44 (m, 2H), 7.30–7.26 (m, 5H), 7.16 (d, $J = 2.6$ Hz, 1H), 6.48 (d, $J = 2.6$ Hz, 1H).

3-(Indol-5-yl)-2-propyn-1-ol (**31**): (Table 3, entry 7) 5-Bromoindole (1.96 g, 10 mmol), propargyl alcohol (1.12 g, 20 mmol), K_2CO_3 (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (100 μmol) at 100 °C gave **31** in 99% (1.69 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 10.11$ (s, 1H), 7.73 (s, 1H), 7.29–7.24 (m, 2H), 7.16 (d, $J = 2.6$ Hz, 1H), 6.48 (d, $J = 2.6$ Hz, 1H), 4.40 (s, 2H). ^{13}C NMR (CDCl$_3$): $\delta = 135.3$, 127.5, 124.9, 124.8, 123.9, 115.0, 111.1, 102.6, 89.4, 86.8, 53.1. Anal. calc. for $C_{11}H_9NO$: C, 77.17; H, 5.30%. Found: C, 76.91; H, 5.64%.

4-(Indol-5-yl)-3-butyn-1-ol (**32**): (Table 3, entry 8) 5-Bromoindole (1.96 g, 10 mmol), but-3-yn-1-ol (1.51 mL, 20 mmol), K_2CO_3 (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (100 μmol) at 100 °C gave **32** in 99% (1.83 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 10.10$ (s, 1H), 7.73 (s, 1H), 7.29–7.24 (m, 2H), 7.16 (d, $J = 2.6$ Hz, 1H), 6.48 (d, $J = 2.6$ Hz, 1H), 3.81 (t, $J = 6.3$ Hz, 2H), 2.69 (t, $J = 6.3$ Hz, 2H). ^{13}C NMR (CDCl$_3$): $\delta = 135.3$, 127.7, 125.6, 125.2, 124.5, 114.3, 111.1, 102.6, 83.9, 83.5, 61.3, 23.9. MS (70 ev); m/z (%): 185 (100) [M$^+$]. Anal. calc. for $C_{12}H_{11}NO$: C, 77.81; H, 5.99%. Found: C, 77.70; H, 6.12%.

2-(Phenylethynyl)thiazole (**33**): (Table 3, entry 10) 2-Bromothiazole (1.64 g, 10 mmol), phenylacetylene (2.20 mL, 20 mmol), K_2CO_3 (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (1 μmol) at 100 °C gave **33** in 76% (1.41 g) isolated yield. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 7.84$ (d, $J = 3.3$ Hz, 1H), 7.58 (m, 2H), 7.40–7.33 (m, 4H).

3-(Thiazol-2-yl)-2-propyn-1-ol (**34**): (Table 3, entry 11) 2-Bromothiazole (1.64 g, 10 mmol), propargyl alcohol (1.12 g, 20 mmol), K_2CO_3 (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol),

DMF (10 mL) and Pd complex (100 μmol) at 100 °C gave **34** in 85% (1.18 g) isolated yield. ^{1}H NMR (300 MHz, CDCl₃): δ = 7.74 (d, *J* = 3.2 Hz, 1H), 7.29 (d, *J* = 3.2 Hz, 1H), 4.27 (s, 2H).

4-(Thiazol-2-yl)-3-butyn-1-ol (**35**): (Table 3, entry 13) 2-Bromothiazole (1.64 g, 10 mmol), but-3-yn-1-ol (1.51 mL, 20 mmol), K₂CO₃ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (10 μmol) at 100 °C gave **35** in 60% (0.92 g) isolated yield. ^{1}H NMR (300 MHz, CDCl₃): δ = 7.75 (d, *J* = 3.2 Hz, 1H), 7.29 (d, *J* = 3.2 Hz, 1H), 3.84 (t, *J* = 6.5 Hz, 2H), 2.73 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (CDCl₃): δ = 153.4, 143.2, 120.4, 87.0, 72.2, 61.6, 20.0. Anal. calc. for C₇H₇NOS: C, 54.88; H, 4.61%. Found: C, 54.69; H, 4.42%.

2-(Phenylethynyl)thiophene (**36**): (Table 4, entry 1) 2-Bromothiophene (1.63 g, 10 mmol), phenylacetylene (2.20 mL, 20 mmol), K₂CO₃ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (10 μmol) at 100 °C gave **36** in 95% (1.75 g) isolated yield. ^{1}H NMR (300 MHz, CDCl₃): δ = 7.52–7.49 (m, 2H), 7.34–7.32 (m, 3H), 7.27 (m, 2H), 7.00 (dd, *J* = 5.1 and 3.6 Hz, 1H).

3-(Thien-2-yl)-2-propyn-1-ol (**37**): (Table 4, entry 4) 2-Iodothiophene (2.10 g, 10 mmol), propargyl alcohol (1.12 g, 20 mmol), K₂CO₃ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (10 μmol) at 100 °C gave **37** in 80% (1.11 g) isolated yield. ^{1}H NMR (300 MHz, CDCl₃): δ = 7.24 (d, *J* = 5.1 Hz, 1H), 7.19 (d, *J* = 3.6 Hz, 1H), 6.95 (dd, *J* = 5.1 and 3.6 Hz, 1H), 4.48 (s, 2H).

4-(Thien-2-yl)-3-butyn-1-ol (**38**): (Table 4, entry 6) 2-Iodothiophene (2.10 g, 10 mmol), but-3-yn-1-ol (1.51 mL, 20 mmol), K₂CO₃ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (1 μmol) at 100 °C gave **38** in 89% (1.35 g) isolated yield. ^{1}H NMR (300 MHz, CDCl₃): δ = 7.22 (d, *J* = 5.1 Hz, 1H), 7.17 (d, *J* = 3.6 Hz, 1H), 7.00 (dd, *J* = 5.1 and 3.6 Hz, 1H), 3.76 (t, *J* = 6.5 Hz, 2H), 2.62 (t, *J* = 6.5 Hz, 2H).

5-(Thien-2-yl)-4-pentyn-1-ol (**39**): (Table 4, entry 8) 2-Iodothiophene (2.10 g, 10 mmol), pent-4-yn-1-ol (1.86 mL, 20 mmol), K₂CO₃ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (1 μmol) at 100 °C gave **39** in 58% (0.96 g) isolated yield. ^{1}H NMR (300 MHz, CDCl₃): δ = 7.23 (d, *J* = 5.1 Hz, 1H), 7.18 (d, *J* = 3.6 Hz, 1H), 6.93 (dd, *J* = 3.6 and 5.1 Hz, 1H), 3.78 (t, *J* = 6.3 Hz, 2H), 2.49 (t, *J* = 7.0 Hz, 2H), 1.90–1.85 (m, 2H). 3-(Phenylethynyl)thiophene (**40**): (Table 4, entry 10) 3-Bromothiophene (1.63 g, 10 mmol), phenylacetylene (2.20 mL, 20 mmol), K₂CO₃ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (10 μmol) at 100 °C gave **40** in 78% (1.44 g) isolated yield. ^{1}H NMR (300 MHz, CDCl₃): δ = 7.55–7.50 (m, 2H), 7.36–7.32 (m, 3H), 7.30–7.27 (m, 2H), 7.01 (d, *J* = 4.9 Hz, 1H).

3-(Thien-3-yl)-2-propyn-1-ol (**41**): (Table 4, entry 11) 3-Bromothiophene (1.63 g, 10 mmol), propargyl alcohol (1.12 g, 20 mmol), K₂CO₃ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (100 μmol) at 100 °C gave **41** in 55% (0.76 g) isolated yield. ^{1}H NMR (300 MHz, CDCl₃): δ = 7.30 (d, *J* = 3.0 Hz, 1H), 7.21 (dd, *J* = 4.9 and 3.0 Hz, 1H), 7.08 (d, *J* = 4.9 Hz, 1H), 4.48 (s, 2H).

4-(Thien-3-yl)-3-butyn-1-ol (**42**): (Table 4, entry 12) 3-Bromothiophene (1.63 g, 10 mmol), but-3-yn-1-ol (1.51 mL, 20 mmol), K₂CO₃ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (100 μmol) at 100 °C gave **42** in 95% (1.45 g) isolated yield. ^{1}H NMR (300 MHz, CDCl₃): δ = 7.34 (d, *J* = 3.0 Hz, 1H), 7.20 (dd, *J* = 5.0 and 3.0 Hz, 1H), 7.04 (d, *J* = 5.0 Hz, 1H), 3.76 (t, *J* = 6.5 Hz, 2H), 2.62 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (CDCl₃): δ = 131.2, 129.1, 125.5, 124.1, 88.9, 74.6, 61.7, 20.3. MS (70 ev); *m/z* (%): 152 (32) [M⁺]. Anal. calc. for C₈H₈OS: C, 63.13; H, 5.30%. Found: C, 62.98; H, 5.14%.

5-(Thien-3-yl)-4-pentyn-1-ol (**43**): (Table 4, entry 14) 3-Bromothiophene (1.63 g, 10 mmol), pent-4-yn-1-ol (1.86 mL, 20 mmol), K₂CO₃ (2.76 g, 20 mmol), CuI (0.10 g, 0.5 mmol), DMF (10 mL) and Pd complex (100 μmol) at 100 °C gave **43** in 90% (1.50 g) isolated yield. ^{1}H NMR (300 MHz, CDCl₃): δ = 7.32 (d, *J* = 3.0 Hz, 1H), 7.20 (dd, *J* = 4.9 and 3.0 Hz, 1H), 7.04 (d, *J* = 4.9 Hz, 1H), 3.78 (t, *J* = 6.3 Hz, 2H), 2.49 (t, *J* = 7.0 Hz, 2H), 1.82 (m, 2H). ^{13}C NMR (CDCl₃): δ = 130.7, 128.5, 125.8, 123.4, 89.6, 76.9, 62.6, 32.1, 16.7. MS (70 ev); *m/z* (%): 166 (28) [M⁺]. Anal. calc. for C₉H₁₀OS: C, 65.02; H, 6.06%. Found: C, 65.19; H, 6.20%.

2.5. CAS Registry No.

1, 13141-42-9; **2**, 13238-38-5; **3**, 13295-94-8; **4**, 29768-03-4; **5**, 61266-33-9; **6**, 93524-95-9; **7**, 395652-44-5; **8**, 138487-20-4; **9**, 192643-83-7; **10**, 119981-54-3; **11**, 138745-76-3; **12**, 191725-48-1; **13**, 70437-03-5; **14**, 70437-05-7; **16**, 137417-35-7; **18**, 178762-64-6; **19**, 70437-15-9; **20**, 70437-17-1; **21**, 119981-62-3; **24**, 70437-00-2; **25**, 70437-02-4; **26**, 121277-71-2; **27**, 71418-88-7; **28**, 174456-28-1; **29**, 88940-56-1; **30**, 374818-68-5; **33**, 35070-01-0; **34**, 121356-98-7; **36**, 4805-17-8; **37**, 1194-13-4; **38**, 289652-61-5; **39**, 124855-50-1; **40**, 131423-29-5; **41**, 170859-75-3.

3. Results and discussion

Palladium chemistry involving heterocycles has its unique characteristics stemming from the heterocycles' inherently different structural and electronic properties in comparison to the corresponding carbocyclic aryl compounds. Pyridines or quinolines are π-electron deficient. Thiophenes are π-electron excessive [2]. If the oxidative addition of the aryl halides to the palladium complex is the rate-limiting step of the reaction with this catalyst, the reactions should be slower with thiophenes than with pyridines. Furthermore palladium(II) possesses strong thiophilicity. This is reflected in the poisoning effects of the sulphur atom on some palladium-catalysed reactions. This poisoning effect has also been observed in the presence of nitrogen atom. For this reason, the position of the halide on a heteroaromatic ring has an effect on the reactions.

We describe here successively the reactions of a range of alkynes with halopyridines (Scheme 1; Table 1), haloquinolines (Scheme 2; Table 2), a bromoindole, a bromopyrimidine, a bromothiazole (Scheme 3; Table 3) and halothiophenes (Scheme 4; Table 4). For this study, based on previous results [37], DMF
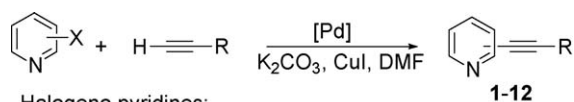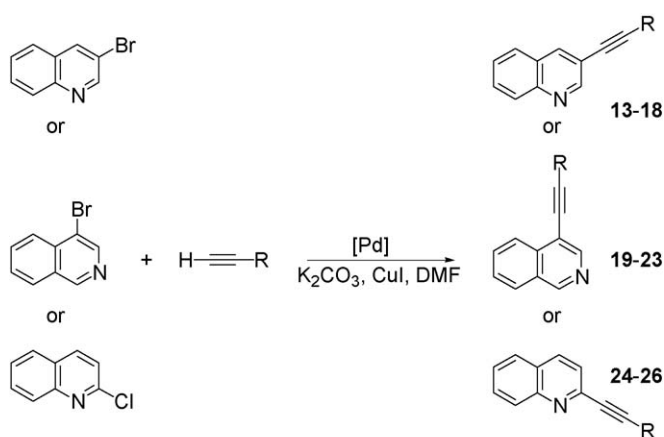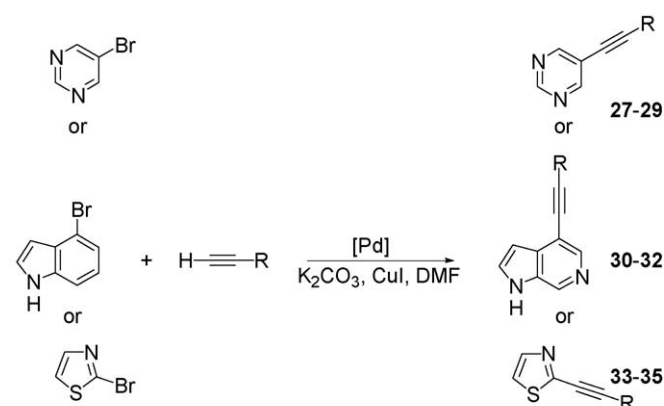
Halogeno pyridines:
2-chloropyridine
3-chloropyridine
4-chloropyridine
2-bromopyridine
3-bromopyridine
4-bromopyridine
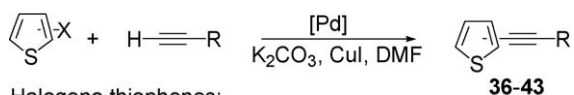3-iodopyridine

R = Ph, CH₂OH, (CH₂)₂OH, (CH₂)₃OH

Scheme 1.

R = Ph, CH₂OH, CH₂OTHP, (CH₂)₂OH, (CH₂)₂OTHP, (CH₂)₃OH

Scheme 2.

R = Ph, CH₂OH, (CH₂)₂OH

Scheme 3.

Halogeno thiophenes:
2-bromothiophene
2-iodothiophene
3-bromothiophene

R = Ph, CH₂OH, (CH₂)₂OH, (CH₂)₃OH

Scheme 4.

was chosen as the solvent, potassium carbonate as the base and CuI as co-catalyst. The reactions were performed under argon in the presence of a ratio 1/2 of [Pd(C₃H₅)Cl]₂/Tedicyp as catalyst. Some substrates and products are thermally quite unstable, so we generally performed the reactions at a moderate temperature: 100 °C. In a few cases, the partial dimerisation or polymerisation of the alkyne was observed. For this reason, we used two equivalents of alkyne in all cases in order to obtain higher substrate/catalyst ratios. However, most of the reactions should led to similar results with 1.2–1.5 equivalent of alkyne.

3.1. Reactions with halopyridines

First, we studied the influence of the position of the bromo substituent on pyridines on the reaction rates for the coupling with phenylacetylene (Scheme 1). Due to the electronegativity of the nitrogen atom, the 2 and 4 positions of bromopyridines should be the most susceptible to the oxidative addition to palladium. In fact, we observed similar results for the coupling of 3-bromopyridine than with 2- and 4-bromopyridines (Table 1, entries 1, 2, 5, 6, 9 and 10). In all cases the expected alkynylation adducts **1–3** were obtained in high TONs (5000–8000) with as little as 0.01% catalyst. We have also investigated the influence of the nature of the halogen on the reactivity of halopyridines. As expected, the reactions using 2- and 4-chloropyridines were faster than with 3-chloropyridine (Table 1, entries 3, 4, 7, 8 and 11). 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 7). However, with this substrate, a yield of 90% in adduct **2** was obtained using modified reaction conditions: 1% catalyst at 130 °C without addition of CuI (Table 1, entry 8). These results seem to indicate that the oxidative addition of chloropyridines to palladium is the rate-limiting step of the reaction with this catalyst.

Having demonstrated that phenylacetylene can be efficiently cross-coupled with halopyridines, we investigated the scope of this reaction using four alk-1-ynols (Scheme 1; Table 1). The results described in the Table 1 shown that much slower reactions were observed using propargyl alcohol instead of phenylacetylene (Table 1, entries 12–21). With this alkyne, 2-bromopyridine (Table 1, entries 12 and 13) or 4-bromopyridine (Table 1, entry 20) were coupled efficiently using 0.1% catalyst. The cross-coupling of 3-bromopyridine with propargyl alcohol required the presence of 1% catalyst in order to obtain the desired product **5** in good yield (Table 1, entry 17). A similar trend was observed using chloropyridines and propargyl alcohol. We found that 2- and 4-chloropyridines are more reactive than 3-chloropyridine (Table 1, entries 14, 19 and 21). With propargyl alcohol, the highest TON was obtained using 3-iodopyridine: 80000 (Table 1, entry 16). Better results in terms of substrate/catalyst ratio were obtained using but-3-yn-1-ol as reactant. With bromopyridines and but-3-yn-1-ol the coupling products **7–9** were obtained in medium to good yields using 0.1–0.01% catalyst (Table 1, entries 22, 23, 29 and 31). 2-Chloro or 4-chloropyridines and but-3-yn-1-ol using 0.1% catalyst gave the adducts **7** and **9** in 90 and 72% yields, respectively (Table 1, entries 25 and 33). Again, 3-

chloropyridine was found to be less reactive (TON 30) (Table 1, entry 30). With but-3-yn-1-ol, the highest TON was obtained for the reaction with 3-iodopyridine: 900,000 (Table 1, entry 27). Pent-4-yn-1-ol reacted with 2-, 3- or 4-bromopyridines led to adducts **10–12** in 750–920 TONs (Table 1, entries 35, 40 and 42). Compounds **10** and **12** were obtained in lower TONs using 2- or 4-chloropyridines and pent-4-yn-1-ol: 95 and 90, respectively (Table 1, entries 36 and 43). Only traces of coupling product **11** were observed using 3-chloropyridine (Table 1, entry 41).

3.2. Reactions with haloquinolines

For Sonogashira reactions of haloquinolines, we observed behaviour similar to that of halopyridines. The reactivity of three haloquinolines has been studied (Scheme 2, Table 2). The reaction of 3-bromoquinoline with phenylacetylene proceeds in high TON: 7900 (Table 2, entries 1 and 2). A much slower reaction was observed employing protected or unprotected propargyl alcohol (Table 2, entries 3–5). But-3-yn-1-ol or pent-4-yn-1-ol gave better results in terms of substrate/catalyst ratio. With these alkynes the reactions proceeds using 0.1% catalyst (Table 2, entries 6, 7, 9 and 10). Sterically congested 4-bromoisoquinoline led to the coupling adducts **19–23** with very similar TONs than those observed with 3-bromoquinoline (Table 2, entries 11–18). TONs of 6000 and 1800 were obtained for the coupling of 4-bromoisoquinoline with phenylacetylene or hex-5-yn-1-ol, respectively (Table 2, entries 11 and 18). 2-Chloroquinoline reacted with alkynes also gave the cross-coupling adducts in high TONs. With phenylacetylene or but-3-yn-1-ol TONs of 6000 and 900 were obtained, respectively (Table 2, entries 19, 20, 22 and 23).

3.3. Reactions with 5-bromopyrimidine, 5-bromoindole and 2-bromothiazole

Bromo-substituted indole, pyrimidine or thiazole, which have the potential to bind to palladium through nitrogen or sulphur atom, are also suitable substrates for Sonogashira reactions. TONs of 6000–8000 were obtained for the couplings of 5-bromoindole, 5-bromopyrimidine or 2-bromothiazole with phenylacetylene (Table 3, entries 1, 2, 5, 6, 9 and 10). Lower TONs were observed using propargyl alcohol or but-3-yn-1-ol as alkynes. With propargyl alcohol, we had to use 1% catalyst in order to obtain high yields of adducts **28**, **31** and **34** (Table 3, entries 3, 7 and 11). Employing but-3-yn-1-ol, satisfactory yields of products **29**, **32** and **35** were obtained using 0.1% catalyst (Table 3, entries 4, 8 and 13).

3.4. Reactions with halothiophenes

Thiophenes are π-electron-excessive heterocycles. Oxidative addition to palladium should be slower with bromothiophenes, than with the π-electron deficient heterocycles bromopyridines. However, the reactions of 2-bromopyridine or 2-bromothiophene with phenylacetylene gave the adducts **1** and **36** in similar TONs: 8000 and 5600, respectively (Table 1, entries 1 and 2; Table 4, entries 1 and 2). On the other

hand, with 3-bromopyridine or 3-bromothiophene and phenylacetylene, TONs of 7500 and 780 were obtained, respectively (Table 1, entry 6; Table 4, entry 10). The reaction of 2- or 3-bromothiophenes with but-3-yn-1-ol or pent-4-yn-1-ol gave the alkynylated adducts **38**, **39**, **42** and **43** in 350–800 TONs (Table 4, entries 5, 7, 12–15). We also performed reactions of 2-iodothiophene with propargyl alcohol, but-3-yn-1-ol or pent-4-yn-1-ol. In all cases, higher TONs than with 2-bromothiophene were obtained (Table 4, entries 4, 6 and 8). These observations suggest that, in some cases, the oxidative addition of the bromothiophenes to palladium is the rate-limiting step with this catalyst. It should be noted that the reaction or 2- or 3-bromothiophene and phenylacetylene performed with 0.1% [PdCl(C₃H₅)]₂ as catalyst, in absence of ligand, using similar reactions conditions does not proceed.

4. Conclusion

In summary, the Tedicyp-palladium complex provides a convenient catalyst for the cross-coupling of a variety of heteroaryl halides with several alkynes. Despite the presence of N and S heteroatoms, that might be expected to significantly affect the course of the Pd-catalysed reactions, heteroaromatics such as pyridines, quinolines, an indole or thiophenes, led to the alkynylated adducts in good yields. The position and the nature of the halide on the heteroaromatic have an important effect on the reaction rates. As expected, heteroaryl iodides are more reactive than heteroaryl bromides. The slowest reactions were observed using heteroaryl chlorides. The position of the bromide on these heteroaromatics generally has a minor effect on the reaction rates. Quite similar TONs of 5000–8000 were obtained for the coupling of 2-, 3-, 4-bromopyridines, 3-bromoquinoline, 4-bromoisoquinoline, 5-bromopyrimidine, 5-bromoindole, 2-bromothiazole or 2-bromothiophene with phenylacetylene. However, a lower TON of 780 was obtained for the coupling of phenylacetylene with 3-bromothiophene. With heteroaryl chlorides, most of the reactions gave the alkynylation products in satisfactory yields using 1% catalyst. 3-Chloropyridine was found to be less reactive than 2- or 4-chloropyridines. With 3-bromothiophene or 3-chloropyridine, the oxidative addition to palladium appears to be the rate-limiting step of the reactions, probably for electronic reasons. The nature of the alkyne has also a huge effect on the reaction rates. The reactions can be performed with as little as 0.01–0.001% catalyst with the most reactive alkynes. Phenylacetylene is more reactive than alkynols. Higher substrate/catalyst ratios could be used (up to 10,000) with but-3-yn-1-ol, pent-4-yn-1-ol or hex-5-yn-1-ol than with propargyl alcohol. These results represent, in most cases, economically attractive procedures and due to the high price of palladium, the practical advantage of such low catalyst loading reactions can become increasingly important for industrial processes.

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