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An efficient copper-free $Pd(OAc)_2$/Ruphos-catalyzed Sonogashira coupling of 1-chloroisoquinolines in the formation of 1-alkynyl-3-substituted isoquinolines

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ABSTRACT

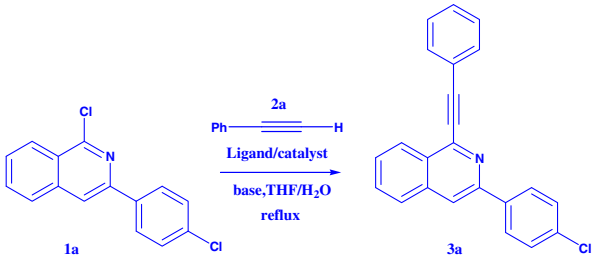
An efficient, copper-free Sonogashira coupling reaction of 1-chloroisoquinolines and terminal alkynes, catalyzed by $Pd(OAc)_2$/Ruphos, in the presence of Et_3N and tetrahydrofuran leads to the formation of 1-alkynyl-3-substituted isoquinolines in good yields.

Sonogashira coupling represents the most straightforward and an easy method for the synthesis of internal acetylenic compounds involving Pd-catalysis.[1] Since its discovery by Sonogashira[2–6] in 1975, several modifications[7–14] have been made including ligand variation, palladium sources, solvents, amines, the amount of catalyst loading, and use of microwave in order to promote the C–C bond formation.[15–17] The most important modification is the elimination of copper salt and hence diacetylenes are formed in situ during the reaction of copper acetylide and oxygen or oxidant.[18–22]

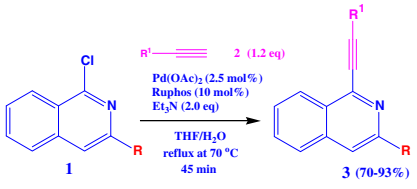
Based on the above facts, we decided to explore an efficient catalytic system for the synthesis of 1-alkynyl-3-substituted isoquinolines (Schemes 1 and 2) by replacing triphenylphosphine with other phosphines to enhance the catalyst efficiency.

In continuation of our work on isoquinolines,[23–29] we report the synthesis of, 1,3-disubstituted isoquinolines through copper-free Sonogashira coupling. The reaction of 1-chloroisoquinolines, **1** with various terminal acetylenes, **2** in tetrahydrofuran and in the presence of palladium acetate catalyst, Ruphos ligand and triethylamine in aqueous medium at 70 °C afforded 1,3-disubstituted isoquinolines **3** in good yields (Scheme 2, Table 4).

Optimization of the reaction conditions was achieved by choosing Sonogashira coupling of 1-chloro-3-(4-chlorophenyl)isoquinoline, **1a** and phenylacetylene, **2a** as model reaction (Scheme 1) and screening of various ligands (Fig. 1) in the presence of palladium acetate catalyst as shown in Table 1. The reaction proceeds



Scheme 1. Sonogashira coupling of 1-chloro-3-(4-chlorophenyl)isoquinoline, **1a** with phenyl acetylene, **2a**. Catalyst = $Pd(OAc)_2$, bases = Et_3N, pyrrolidine, piperidine, $(i\text{-}Pr)_2NH$, K_2CO_3, KOAc.



R = 4-chlorophenyl, phenyl, 2-thiophenyl

R^1 = phenyl, 2-aminophenyl, *p*-tolyl, cyclopropyl, cyclopentyl, cyclohexyl, 4-fluorophenyl

Scheme 2. Synthesis of 1-alkynyl-3-substituted isoquinolines.

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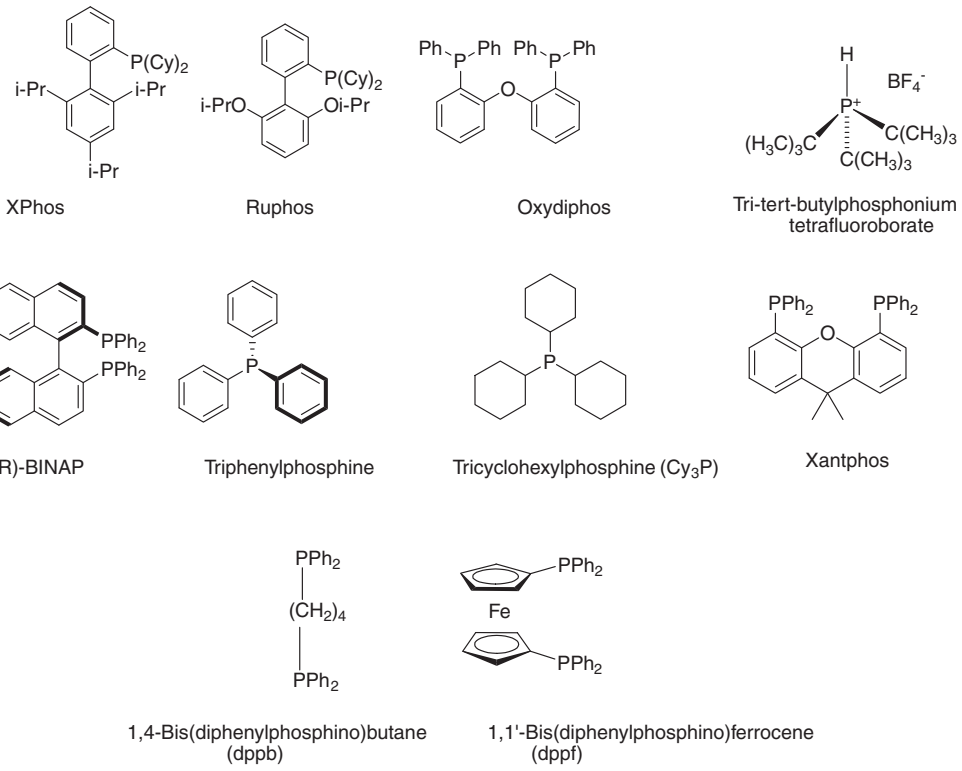


Figure 1. Ligands.

Table 1
Effect of ligands on the Sonogashira coupling[a] of **1a** and **2a**

Entry	Ligand	Yield (%)
1	PPh_3	45
2	BINAP	35
3	Xantphos	NR
4	Dppb	23
5	Dppf	25
6	Cy_3P	20
7	$(n\text{-Bu})_3P$	47
8	Oxydiphos	76
9	XPhos	73
10	Ruphos	93

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), Et_3N (2 equiv), Pd $(OAc)_2$ (2.5 mol %), ligand (10 mol %), degassed water (0.5 mL) at 70 °C for 45 min.

Table 2
Effect of catalyst loading on the Sonogashira coupling[a] of **1a** and **2a**

Entry	Additive/catalyst	Yield (%)
1	Ruphos (50 mol %)/Pd$(OAc)_2$ (25 mol %)	20
2	Ruphos (40 mol %)/Pd$(OAc)_2$ (20 mol %)	23
3	Ruphos (30 mol %)/Pd$(OAc)_2$ (15 mol %)	36
4	Ruphos (20 mol %)/Pd$(OAc)_2$ (10 mol %)	55
5	Ruphos (10 mol %)/Pd$(OAc)_2$ (05 mol %)	70
6	Ruphos (5 mol %)/Pd$(OAc)_2$ (2.5 mol %)	60
7	Ruphos (2.5 mol %)/Pd$(OAc)_2$ (1.25 mol %)	45
8	Ruphos (10 mol %)/Pd$(OAc)_2$ (2.5 mol %)	93

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), Et_3N (2 equiv), degassed water (0.5 mL) at 70 °C for 45 min.

well in the presence of Ruphos ligand (Table 1, entry 10) with over 90% yield. Other ligands, such as oxydiphos and XPhos produced moderate yields (Table 1, entries 8 and 9), and the effect of the rest of the ligands was found to be poor.

The influence of the amount of ligand, and the catalyst was further investigated using the reaction of **1a** with **2a** (Scheme 1, Table 2). The results indicated that increase in the amount of both ligand and palladium catalyst could bring about dechlorination of **1a**, and resulted in low yield of the desired product **3a** (Table 2, entries 1–3). Low catalyst and ligand loading and prolonged reaction time decreased the yield (Table 2, entry 7).

The influence of bases in the reaction of **1a** and **2a** was also explored as shown in Table 3. Among the bases tested, triethylamine (Table 3, entry 1) proved to be an excellent base at 70 °C in tetrahydrofuran-water mixture. Pyrrolidine and dialkylamine were found to be moderately efficient bases (Table 3, entries 2 and 4) and the rest of the bases (piperidine, K_2CO_3, KOAc) were less effective (Table 3, entries 3, 5 and 6). While smaller quantity of base resulted in lower yield of product **3a**, (Table 3, entries 7–9) the amount of base by more than 2.0 equiv did not make any difference in the yield (Table 3, entry 10).

Table 3
Effect of base on the Sonogashira coupling[a] of **1a** and **2a**

Entry	Base	Base equivalents	Yield (%)
1	Et_3N	2.0	93
2	Pyrrolidine	2.0	67
3	Piperidine	2.0	59
4	$(i\text{-Pr})_2NH$	2.0	75
5	K_2CO_3	2.0	40
6	KOAc	2.0	35
7	Et_3N	0.5	65
8	Et_3N	1.0	70
9	Et_3N	1.5	81
10	Et_3N	3.0	92

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), base, Pd $(OAc)_2$ (2.5 mol %), Ruphos (10 mol %), degassed water (0.5 mL) at 70 °C for 45 min.

Table 4
Sonogashira coupling of 1-chloroisoquinolines, **1** in the synthesis of internal alkynes (1-alkynyl-3-substituted isoquinolines, **2**)[a]

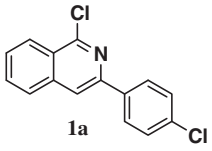
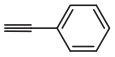
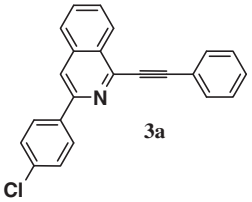
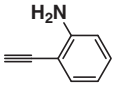
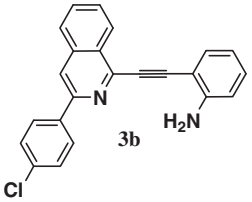
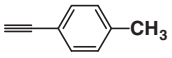
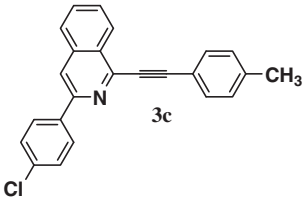
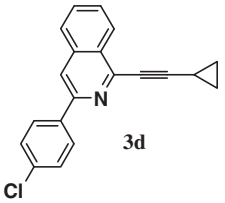
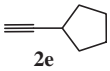
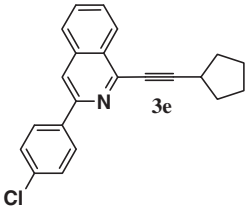
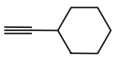
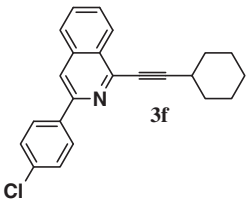
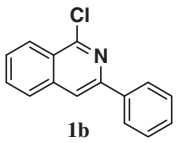
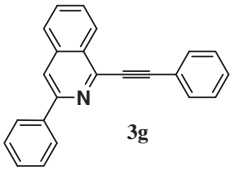
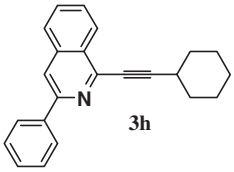
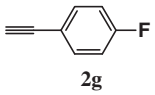
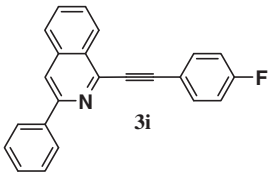
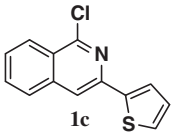
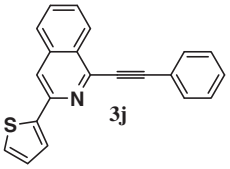
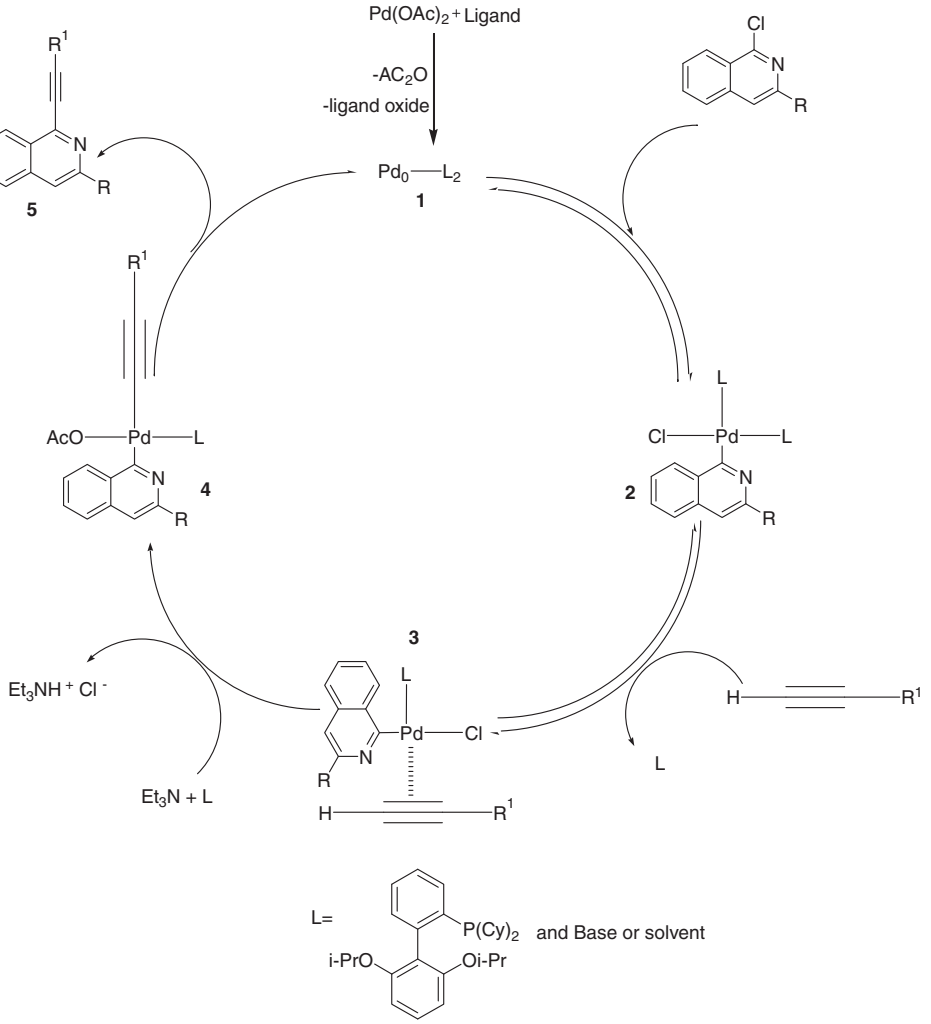
Entry	1-Chloroisoquinolines **1** **R**	Alkynes **2** R_1	Product **3**	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	93
2	**1a**	 **2b**	 **3b**	70
3	**1a**	 **2c**	 **3c**	82
4	**1a**	 **2d**	 **3d**	87
5	**1a**	 **2e**	 **3e**	72
6	**1a**	 **2f**	 **3f**	65
7	 **1b**	**2a**	 **3g**	92
8	**1b**	**2f**	 **3h**	57

Table 4 (*continued*)

Entry	1-Chloroisoquinolines **1** R	Alkynes **2** R_1	Product **3**	Yield[b] (%)
9	**1b**	 **2g**	 **3i**	71
10	 **1c**	**2a**	 **3j**	70

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), triethylamine (2 equiv), Pd $(OAc)_2$ (2.5 mol %), Ruphos (10 mol %), degassed water (0.5 mL) at 70 °C for 45 min.
[b] Isolated yield.



R = 4-chloro phenyl, phenyl, 2-thiophenyl; R_1= phenyl, 2-amino phenyl, p-tolyl, cyclopropyl, cyclopentyl, cyclohexyl, 4-fluorophenyl

Scheme 3. Mechanism of the reaction.

With the optimized conditions, various 1-alkynyl-3-substituted isoquinolines were synthesized and the results are reported in Scheme 2, Table 4. The desired products **3a–j** were obtained in high yields (70–93%) and purity.

The proposed mechanism of the reaction is depicted in Scheme 3. The catalytically active Pd^0species **I** is stabilized by the ligands present. The catalytic cycle is initiated by oxidative addition of aryl halide to species **I**, forming the adduct **II** as a homogeneous-Pd^{II} species followed by a reversible coordination of the alkyne to **II** producing an alkyne–Pd^{II} complex **III**. The base then abstracts a proton from the coordinated alkyne, forming the palladium–acetylide complex **IV**, from which the cross-coupled product **V** is obtained by reductive elimination regenerating the catalyst species **I**.

Our method presents a direct route for the sp–sp^2 bond formation and eliminates the oxidative dimerization of the alkyne which occurs as a side reaction in copper catalysis. The ready availability of catalyst, high catalytic activity and water as the co-solvent make the present methodology very attractive for the exploitation of substituted isoquinolines which possess extensive range of biological activities.[30,31] The typical procedure of the reaction and analysis data are presented.[32,33]

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.040.

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32. *General procedure for the synthesis*: A mixture of 1-chloroisoquinoline, **1** (0.5 mmol), acetylenes, **2** (0.6 mmol), Ruphos (10 mol %), triethylamine (2.0 equiv), water (0.5 mL) and tetrahydrofuran (5 mL) was degassed twice using nitrogen gas. Then $Pd(OAc)_2$ (2.5 mol %) was added, again degassed twice and heated at 70 °C in a sealed tube under nitrogen atmosphere for 45 min. After completion of the reaction, the resulting solution was filtered off using Celite pad (to remove catalyst) and the filtrate was concentrated in vacuo. The crude products were subjected to silica-gel (230–400 mesh) flash column chromatography using hexane/ethyl acetate (90:10) eluent to afford the pure products (Table 4). The compounds were confirmed by ^{1}H NMR, ^{13}C NMR, FTIR LC–MS and elemental analysis techniques.
33. The analysis data of **3a**, **3b** are given below, remaining data are presented in Supplementary data attached with this manuscript.
3-(4-Chlorophenyl)-1-(phenylethynyl)isoquinoline, **3a**.
Yellow solid, mp 110–112.5 °C, ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.53–8.51 (d, J = 8.4 Hz, 1H), 8.13–8.10 (d, J = 13.6 Hz, 2H), 8.02 (s, 1H), 7.90–7.88 (d, J = 8.0 Hz, 1H), 7.77–7.71 (m, 3H), 7.69–7.65 (t, J = 8.4 Hz, 1H), 7.49–7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 150.1, 144.4, 137.6, 136.7, 134.8, 132.3, 130.9, 129.3, 128.9, 128.6, 128.5, 128.4, 128.0, 127.3, 127.0, 122.2, 116.7; IR (ν cm^{-1}) 3058, 2924, 2850, 2211, 2164, 1999, 1961, 1557, 1494, 1439, 1391, 1334, 1261, 1148, 1092, 1017, 831, 753, 527; LC–MS: m/e 340.2, $C_{23}H_{14}ClN$ requires Mol. Wt.: 339.08. Elemental analysis, calculated: C, 81.29; H, 4.15; Cl, 10.43; N, 4.12%. Found: C, 81.22; H, 4.12; N, 4.14%.
3-[((4-Chlorophenyl)isoquinolin-1-yl)ethynyl]aniline, **3b**.
Yellow solid, mp 153–154 °C, ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.53 (s, 1H), 8.44–8.42 (d, J = 8.0 Hz, 1H), 8.27–8.25 (d, J = 8.4 Hz, 2H), 8.11–8.09 (d, J = 8.0 Hz, 1H), 7.89–7.86 (t, J = 7.4 Hz, 1H), 7.82–7.78 (t, J = 7.6 Hz, 1H), 7.62–7.60 (d, J = 8.4 Hz, 2H), 7.18–7.14 (t, J = 7.8 Hz, 1H), 6.97–6.92 (t, J = 9.8 Hz, 2H), 6.73–6.71 (d, J = 8.0 Hz, 1H), 5.4 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 149.5, 149.0, 143.8, 137.5, 136.8, 134.1, 131.8, 129.9, 129.3, 129.3, 128.8, 128.3, 126.5, 121.7, 119.8, 117.2, 117.1, 116.1, 95.1, 86.0; IR (ν cm^{-1}) 3850, 3727, 3605, 3347, 3054, 2924, 2853, 2234, 2210, 2151, 2132, 2049, 2026, 2017, 1998, 1973, 1928, 1619, 1597, 1556, 1493, 1439, 1391, 1305, 1091, 1012, 751, 520; LC–MS: m/e 355.2, $C_{23}H_{15}ClN_2$ requires Mol. Wt.: 354.09. Elemental analysis, calculated: C, 77.85; H, 4.26; Cl, 9.99; N, 7.89%. Found: C, 77.77; H, 4.21; N, 7.84%.