A $Ni(OAc)_2{\cdot}4H_2O$-catalysed Sonogashira-type coupling reaction of aryl iodides and terminal alkynes in the presence of CuI

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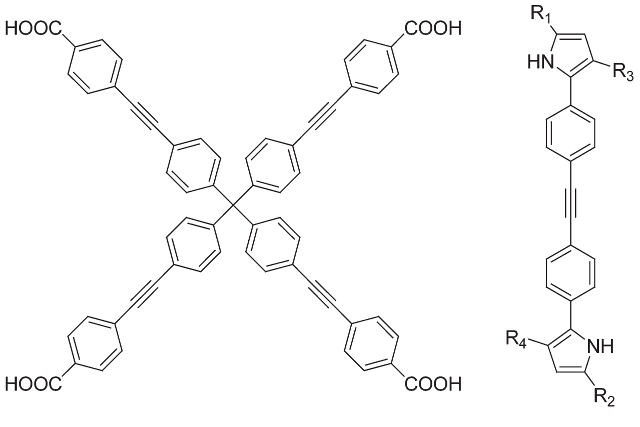
An effective and promising Ni/Cu catalytic system for the coupling of aryl iodides with various terminal alkynes has been developed. For the first time the readily available chiral amino alcohol has been employed as the ligand for the Pd-free Sonogashira coupling reaction.

Keywords: aryl iodides, terminal alkynes, Sonogashira coupling, cross-coupling, palladium-free

It is well known that transition metal-catalysed cross-coupling reactions are very powerful processes for the formation of carbon–carbon bonds[1,3] Among them, the Sonogashira-type coupling between terminal alkynes and aryl or vinyl halides is one of the important and widely used procedures for the synthesis of molecules containing an acetylenic moiety, which is found in many fine chemicals and biologically active substances.[4] For example, compound **1**[5] was synthesised for the research on three-dimensional metal-organic frameworks (MOFs) and compound **2** and its derivatives[6] were proved to be potential hepatitis C virus (HCV) inhibitors (Fig. 1).

The traditional Sonogashira coupling is carried out in the presence of $PdCl_2(PPh_3)_2$, $PdCl_2/PPh_3$, or $Pd(PPh_3)_4$ together with CuI as the cocatalyst and larger amount of amines as the solvents or cosolvents.[7] In the past decades, many efficient modified protocols have been developed, such as copper-free,[8–12] Pd/Ni bimetallic systems,[13] Au complex[14] and Ru/Al_2O_3 systems.[15] However, they were limited in industrial use due to the expensive cost. Thus, the alternative way to solve this problem was raised by using cheaper and lower-toxicity metal instead of palladium, for example, copper-catalysed coupling reactions in the presence of ligands[16–18] or an iron-based catalytic system[19] for the reaction. Recently, we reported a highly efficient example of Fe/Cu co-catalysed alkynylation of aryl halides in the absence of any ligands.[20] As an extension of this work, we have tried to find other efficient palladium-free catalytic systems for the Sonogashira coupling reaction. In 2005, Wang and Li reported that an ultrafine particle nickel(0) could catalyse this coupling in the presence of CuI with PPh_3 as the ligand. They also found that Ni(0) of a special size (*ca* 100 nm) could show the best catalytic activity.[21] We now report that readily available $Ni(OAc)_2{\cdot}4H_2O$ has proved to be a promising catalyst for the Sonogashira coupling reaction together with CuI and with chiral amino alcohol (**12**) (Scheme 1) as the ligand.



1 **2**

Fig. 1 Examples for structures containing the arylene-ethynylene motif.

Experimental

All reactions were carried out under an argon atmosphere. Solvents were dried and degassed by standard methods and all aryl halides were purchased from Aldrich or Alfa. Aryl alkynes and various nickel resources were purchased from Aldrich, Acros or Alfa. Flash column chromatography was performed using silica gel (300–400 mesh). Analytical TLC was performed using glass plates pre-coated with 200–300 mesh silica gel impregnated with a fluorescent indicator (254 nm). NMR spectra were recorded in $CDCl_3$ on a Varian Inova-400 NMR spectrometer (400 MHz) with TMS as an internal reference. Products were characterised by comparison with ^{1}H NMR, ^{13}C NMR and TOF-MS data in the literatures.[22–24]

Sonogashira reaction of alkynes and halides; general procedure

A flask was charged with $Ni(OAc)_2{\cdot}4H_2O$ (0.075 mmol), (–)-ephedrine (**12**) (0.15 mmol), CuI (0.075 mmol), ^{t}BuOK (1.0 mmol) and any remaining solids (aryl halide). The flask was evacuated and backfilled with argon (this procedure was repeated three times). Aryl iodides (0.5 mmol, if liquid), alkyne (0.6 mmol), and DMSO (2 mL) were added to the flask under an argon atmosphere. The flask was sealed and the mixture was stirred at the shown temperature for the indicated period of time. At the end of the reaction, the reaction mixture was cooled to room temperature, diluted with diethyl ether and washed with water. The combined organic phase was dried over anhydrous Na_2SO_4. The solvent of the filtrate was removed with the aid of a rotary evaporator, and the residue was purified by column chromatography on silica gel, using a mixed solvent (petroleum ether/ethyl acetate) as eluent to provide the desired product.

1-(2-(4-Methoxyphenyl)ethynyl)benzene (**3**): Yellow solid; m.p. 57–59 °C (lit.[22] 59–60 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.50 (m, 2H, ArH), 7.47 (d, $J = 8.8$ Hz, 2H, ArH), 7.36–7.32 (m, 3H, ArH), 6.88 (d, $J = 8.8$ Hz, 2H, ArH), 3.83 (s, 3H, CH_3); HRMS (ESI$^+$): Calcd. for $[C_{15}H_{12}O]^+$ requires m/z 208.0888, found 208.0896.

1-(2-Phenylethynyl)naphthalene (**4**) [22]: Yellow solid. m.p. 74–75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, $J = 8.0$ Hz, 1H, ArH), 7.86 (t, $J = 8.0$ Hz, 2H, ArH), 7.77 (d, $J = 0.8$ Hz, 1H, ArH), 7.67 (d, $J = 0.2$ Hz, 1H, ArH), 7.65 (d, $J = 0.2$ Hz, 1H, ArH), 7.59 (d, $J = 6.8$ Hz, 1H, ArH), 7.56 (d, $J = 0.8$ Hz, 1H, ArH), 7.53 (d, $J = 0.8$ Hz, 1H, ArH), 7.48–7.39 (m, 3H, ArH); HRMS (ESI$^+$): Calcd for $[C_{18}H_{12}]^+$ requires *m/z* 228.0939; found 228.0938.

1-Fluoro-4-(2-phenylethynyl)benzene (**5**): Yellow solid; m.p. 108–109 °C (lit.[23] 105–109 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.50 (m, 4H, ArH), 7.36–7.34 (m, 3H, ArH), 7.05 (t, $J = 8.6$ Hz, 2H, ArH); ^{13}C NMR (100 MHz, CDCl3) δ 165.4 (d, $J = 249.5$ Hz, C), 135.2 (d, $J = 8.3$ Hz, CH), 133.2 (CH), 130.0 (d, $J = 3.7$ Hz, CH), 124.7 (C), 121.0 (d, $J = 3.4$ Hz, CH), 117.4 (C), 117.2 (C), 90.7 (C), 89.2 (C); HRMS (ESI$^+$): Calcd for $[C_{14}H_9F]^+$requires *m/z* 196.0688; found 196.0690.

1,2-Diphenylethyne (**6**): White solid; m.p. 58–59 °C lit.[23] 63–64 °C); ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm):7.25–7.35 (m, 6H), 7.52–7.54 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 89.84, 128.87. 129.69, 132.09, 132.98; HRMS (ESI$^+$): Calcd for $[C_{14}H_{10}]^+$ requires *m/z* 178.0783; found 178.0791.

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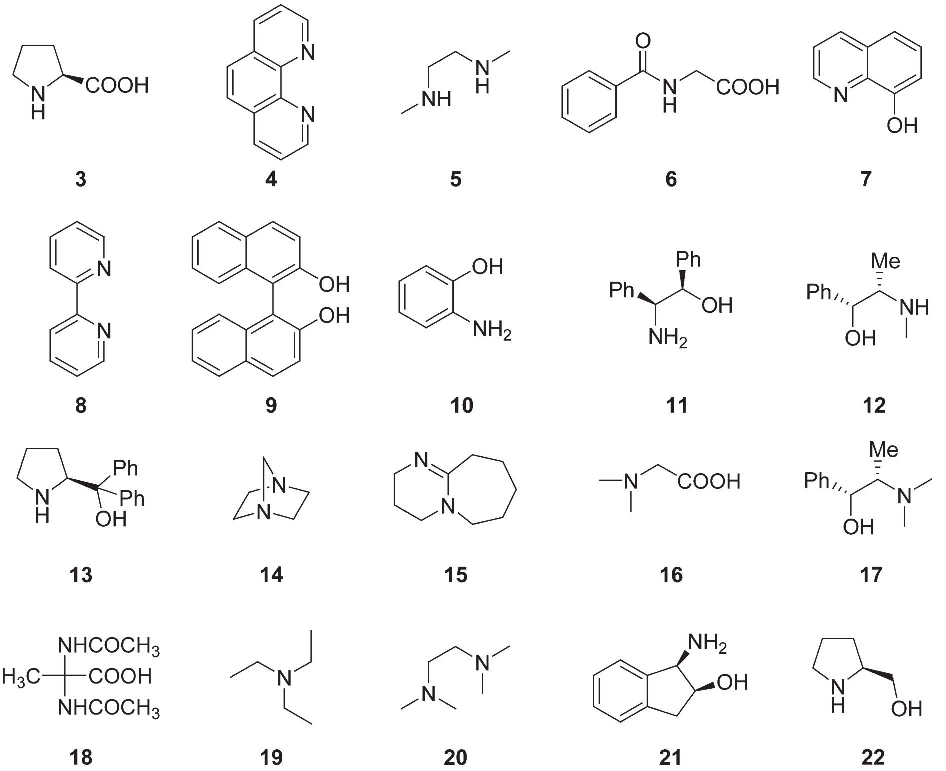


Scheme 1 The ligands evaluated in the study.

1-Chloro-4-(2-phenylethynyl)benzene (**7**): Yellow solid; m.p. 83–84 °C (lit.[24] 83–84 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (t, J = 7.6 Hz, 2H, ArH), 7.46 (d, J = 8.4 Hz, 2H, ArH), 7.36–7.34 (m, 4H, ArH), 7.32 (s, 1H, ArH); HRMS (ESI$^+$): Calcd for $[C_{14}H_9{}^{35}Cl]^+$ requires *m/z* 212.0393; found 212.0396.

1-Methyl-4-(2-phenylethynyl)benzene (**8**): White solid; m.p. 113–115 °C (lit.[24] 113–114 °C);^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.52 (m, 2H, ArH), 7.43 (d, J = 8.0 Hz, 2H, ArH), 7.37–7.33 (m, 3H, ArH), 7.16 (d, J = 8.0 Hz, 2H, ArH), 2.37 (s, 3H, CH_3); HRMS (ESI$^+$)Calcd for $[C_{15}H_{12}]^+$ requires *m/z* 192.0939, found 192.0926.

Results and discussion

Firstly, various commercially available ligands (**3–22**) were directly employed into the model coupling between *p*–iodoanisole and phenylacetylene in the presence of $Ni(OAc)_2{\cdot}4H_2O$ as the catalyst precursor, ^{t}BuOK as the base and DMSO (dimethyl sulfoxide) as the solvent, at 130 °C for 24 h. As shown in Scheme 1, these ligands include L-proline (**3**), 1,10-phenanthroline (**4**), *N*,*N′*-dimethylethylenediamine (**5**), hippuric acid (**6**), 8-hydroxyquinoline (**7**), 2,2′-bipyridine (**8**), *rac*-1,1′-bi-2-naphthol (**9**), 2-aminophenol (**10**), (1*R*,2*S*)-2-amino-1,2-diphenylethanol (**11**), (–)-ephedrine (**12**), diphenyl [(*S*)-pyrrolidin-2-yl] methanol (**13**), DABCO (1,4-diazabicycol[2.2.2]octane) (**14**), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) (**15**), *N*,*N*-dimethylglycine (**16**), *N*-methyl-(–)-ephedrine (**17**), 2,2-(diacetamido) propionic acid (**18**), triethylamine (**19**), TMEDA (tetramethylethylenediamine) (**20**), (1*R*, 2*S*)-1-amino-2-indanol (**21**) and L-prolinol (**22**). The results were shown in Fig. 2. Recently, we have reported that inexpensive hippuric acid (**6**) is a novel ligand for amination of nitrogen-containing heterocycles with various aryl halides in moderate to excellent yields.[25] In our screening experiment, hippuric acid also showed good catalytic effect in the Sonogashira coupling reaction. From Fig. 2, it can be seen that (–)-ephedrine (**12**) afforded the desired product in highest yield.

Thus, **12** was considered as the best ligand for the following screening experiments. The results are listed in Table 1. As shown, various widely used inorganic bases such as Cs_2CO_3, K_2CO_3, K_3PO_4, KOH, NaOH, ^{t}BuOLi, KF, Na_2CO_3, NaOAc, LiOAc, LiOAc, Bu_4NOAc, TMSNLi and ^{t}BuOK had remarkable effect on the coupling reactions (Table 1, entries 1–12), and ^{t}BuOK was the best among the bases. In addition, an organic base (triethylamine) was also employed, but here the coupling did not occur (Table 1, entry 13). Furthermore, several commonly-used solvents, including dimethylformamide (DMF), PEG-400 (poly(ethylene)glycol), NMP (*N*-methyl-2-pyrrolidone), toluene, dioxane, isopropanol and acetonitrile, were screened in the model reaction under suitable temperatures (Table 1, entries 14–20). The results suggested that DMSO was the best solvent.

Then different additives were employed in the coupling reaction between iodoanisole and phenylacetylene as shown in Table 2. Firstly, 15 mol% of CuI showed an obvious acceleration role in the reaction and an enhanced yield of the desired

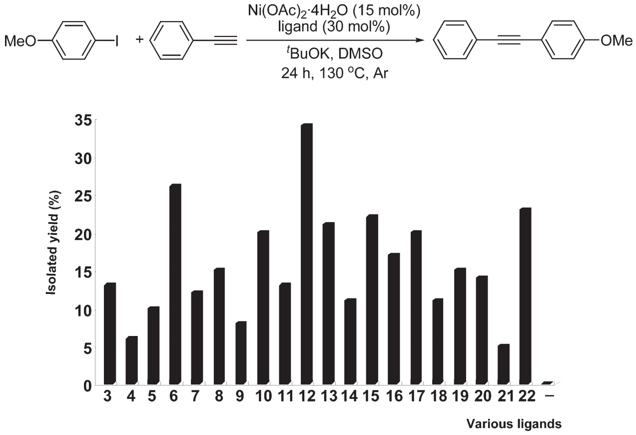
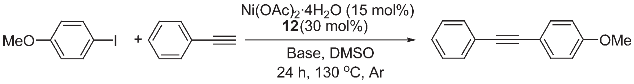


Fig. 2 The relationship between ligands and catalytic effect. The catalytic reaction conditions: iodoanisole (0.5 mmol), phenylacetylene (0.6 mmol), ^{t}BuOK (2 equiv.), $Ni(OAc)_2{\cdot}4H_2O$ (15 mol %), ligand (30 mol%), DMSO (2 mL), 130 °C, 24 h, Ar.

Table 1 Screening different bases and solvents in the nickel-catalysed Sonogashira reaction[a]



Entry	Cat.	Base	Solvent (T/°C)	Yield/%[b]
1	$Ni(OAc)_2 \cdot 4H_2O$	Cs_2CO_3	DMSO (130)	NR
2	$Ni(OAc)_2 \cdot 4H_2O$	K_2CO_3	DMSO (130)	NR
3	$Ni(OAc)_2 \cdot 4H_2O$	KOH	DMSO (130)	13
4	$Ni(OAc)_2 \cdot 4H_2O$	NaOH	DMSO (130)	10
5	$Ni(OAc)_2 \cdot 4H_2O$	^{t}BuOLi	DMSO (130)	7
6	$Ni(OAc)_2 \cdot 4H_2O$	KF	DMSO (130)	NR
7	$Ni(OAc)_2 \cdot 4H_2O$	Na_2CO_3	DMSO (130)	8
8	$Ni(OAc)_2 \cdot 4H_2O$	NaOAc	DMSO (130)	9
9	$Ni(OAc)_2 \cdot 4H_2O$	LiOAc	DMSO (130)	6
10	$Ni(OAc)_2 \cdot 4H_2O$	Bu_4NOAc	DMSO (130)	5
11	$Ni(OAc)_2 \cdot 4H_2O$	TMSNLi	DMSO (130)	10
12	$Ni(OAc)_2 \cdot 4H_2O$	^{t}BuOK	DMSO (130)	34
13	$Ni(OAc)_2 \cdot 4H_2O$	Et_3N	DMSO (130)	NR
14	$Ni(OAc)_2 \cdot 4H_2O$	^{t}BuOK	DMF (130)	13
15	$Ni(OAc)_2 \cdot 4H_2O$	^{t}BuOK	PEG-400 (130)	9
16	$Ni(OAc)_2 \cdot 4H_2O$	^{t}BuOK	NMP (130)	8
17	$Ni(OAc)_2 \cdot 4H_2O$	^{t}BuOK	Toluene (100)	Trace
18	$Ni(OAc)_2 \cdot 4H_2O$	^{t}BuOK	Dioxane (100)	5
19	$Ni(OAc)_2 \cdot 4H_2O$	^{t}BuOK	CH_3CN (100)	25
20	$Ni(OAc)_2 \cdot 4H_2O$	^{t}BuOK	^{i}PrOH (100)	NR

[a] The catalytic reaction conditions: aryl iodide (0.5 mmol), alkyne (0.6 mmol), base (2 equiv), $Ni(OAc)_2 \cdot 4H_2O$ (15 mol%), **12** (30 mol%), solvent (2 mL), 130 °C, 24 h, Ar.
[b] Isolated yield.

product was obtained (Table 2, entry 1). Varying the reaction temperature from 130 to 140 °C, we got a higher isolated yield (53%) (Table 2, entry 2). The control experiment suggested that CuI alone afforded the corresponding product in low yield (Table 2, entry 3). Therefore, it can be seen that the combination of $Ni(OAc)_2 \cdot 4H_2O$ and CuI showed higher catalytic activity. In addition, other types of additives were studied in the coupling reaction, including iodine, TBAB (tetra-*n*-butylammonium bromide), LiCl, zinc powder, copper powder and sodium borohydride. However, we did not observe enhanced results (Table 2, entries 4–9). Various nickel resources were also used in the coupling reactions and the results were still disappointing (Table 2, entries 10–12). The lower temperature led to a decreased yield of the desired product (Table 2, entry 13). In order to avoid to generating homocoupling product of alkynes, all of the experiments were conducted under an argon atmosphere.

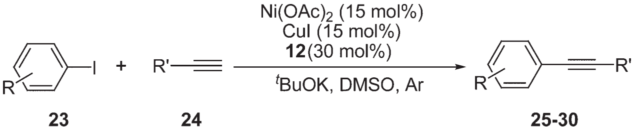
Table 2 Screening different additives and nickel sources in the nickel-catalysed Sonogashira reaction[a]

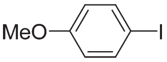
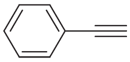
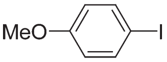
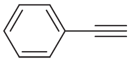
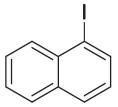
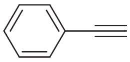
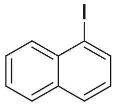
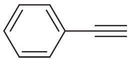
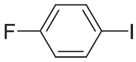
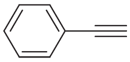
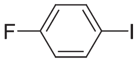
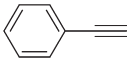
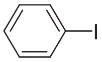
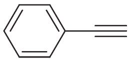
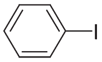
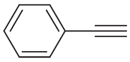
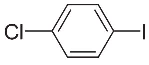
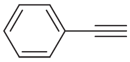
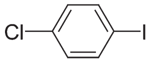
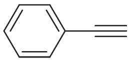
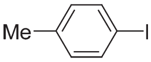
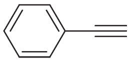
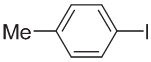
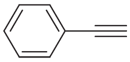
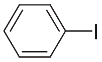
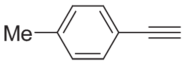
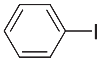
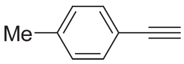
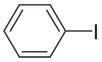
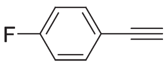
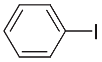
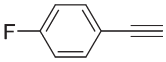
Entry	Cat.	Additive/mol%	Temp./°C	Yield/%[b]
1	$Ni(OAc)_2 \cdot 4H_2O$	CuI (15)	130	44
2	$Ni(OAc)_2 \cdot 4H_2O$	CuI (15)	140	53
3	–	CuI (15)	140	28
4	$Ni(OAc)_2 \cdot 4H_2O$	I_2 (100)	130	NR
5	$Ni(OAc)_2 \cdot 4H_2O$	TBAB (100)	130	13
6	$Ni(OAc)_2 \cdot 4H_2O$	LiCl (100)	130	Trace
7	$Ni(OAc)_2 \cdot 4H_2O$	Zn (30)	130	23
8	$Ni(OAc)_2 \cdot 4H_2O$	Cu (30)	130	36
9	$Ni(OAc)_2 \cdot 4H_2O$	$NaBH_4$ (150)	130	Trace
10	$NiCl_2$	CuI (15)	130	30
11	$NiCl_2 \cdot 6H_2O$	CuI (15)	130	32
12	$Ni(acac)_2$	CuI (15)	130	20
13	$Ni(OAc)_2 \cdot 4H_2O$	CuI (15)	110	43

[a] The catalytic reaction conditions: aryl iodide (0.5 mmol), alkyne (0.6 mmol), ^{t}BuOK (2 equiv), Ni cat. (15 mol %), **12** (30 mol%), DMSO (2 mL), 130 °C, 24 h, Ar.
[b] Isolated yield.

The results that we obtained encouraged us to investigate the applied scope of this catalytic system summarised in Table 3. The reaction times were 24 h and 48 h, respectively. It can be seen that the Ni/Cu system efficiently promotes cross-coupling reactions between aryl iodides and terminal alkynes. Generally, the longer reaction time resulted in higher yields of the corresponding products (Table 3, entries 2, 4, 6, 8, 10, 12, 14 and 16). Furthermore, for the aryl idodides, unsubstituted examples usually afforded better results than substituted ones (Table 3, entries 3–4, 7–8).

Table 3 $Ni(OAc)_2 \cdot 4H_2O$-catalysed Sonogashira coupling of alkynes and aryl iodides[a]



Entry	RX	R′C≡CH	Product	Time /h	Yield /%[b]
1			**25**	24	53
2			**25**	48	56
3			**26**	24	45
4			**26**	48	55
5			**27**	24	33
6			**27**	48	35
7			**28**	24	54
8			**28**	48	66
9			**29**	24	30
10			**29**	48	35
11			**30**	24	44
12			**30**	48	56
13			**30**	24	51
14			**30**	48	52
15			**27**	24	36
16			**27**	48	43

[a] The catalytic reaction conditions: aryl halide (0.5 mmol), alkyne (0.6 mmol), ^{t}BuOK (2 equiv), $Ni(OAc)_2 \cdot 4H_2O$ (15 mol %), CuI (15 mol%) **12** (30 mol%), DMSO (2 mL), 140 °C, 24–48 h, Ar.
[b] Isolated yield.

Conclusions

In summary, we have developed an effective and promising Ni/Cu catalytic system for the coupling of aryl iodides with various terminal alkynes. It is noteworthy that for the first time a readily available chiral amino alcohol was employed as the ligand without the amines for the Pd-free Sonogashira coupling reaction. Although the catalytic effect of Ni/Cu is not better than Pd/Cu, air-stable N,O ligands are only used, which avoids using air-sensitive phosphine ligands. It remains a possibility that other metals could catalyse the traditional Sonogashira coupling with promising results. Further work is in progress in this laboratory with the aim of mechanistic studies and the development of more effective catalytic systems.

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