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Novel pyridine-bis(ferrocene-isoxazole) ligand: synthesis and application to palladium-catalyzed Sonogashira cross-coupling reactions under copper- and phosphine-free conditions

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We present here the first synthesis and application to Sonogashira reaction of pyridine-bis(ferrocene-isoxazole) Pd(II) complex 5, prepared from 2,6-bis-(5-ferrocenylisoxazole-3-yl)pyridine. Under copper- and phosphine-free conditions, the stable complex 5 efficiently catalyzed the cross-coupling of aryl halides with terminal alkynes in DMF–H_2O with TBAB as an additive, hexahydropyridine as base and affording internal arylated alkynes in moderate to excellent yields. Copyright © 2008 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article.

Keywords: 2,6-bis-(5-ferrocenylisoxazole-3-yl)pyridine; palladium; catalysis; Sonogashira cross-coupling

Introduction

Ferrocene[1] derivatives have come a long way as a tool in chemistry, with applications in electrochemistry, material science, synthesis and catalysis.[2] The ferrocenyl ligands represent one of the most important classes among the different types of achiral[3] and chiral ligands[4] used in homogenous catalysis and they have been applied in a variety of transition-metal catalyzed reactions. Important examples are (P,P) ligands like the best-known DPPF,[5] (P,N) ligands, especially phosphine–oxazolines like, for instance, DIPOF,[6] and more recently (P,S) ligands like Fesulphos.[7] Ferrocene ligands have an important role to play: (i) as a backbone or substituent in ligands providing a specific and unique geometry and (ii) via their redox activity and the potential control of the reactivity of a coordinated, catalytically active metal centre.[2,8] On the other hand, bisoxazoline, box and pyridine-2, 6-bisoxazoline, pybox, have been generally used in a variety of metal-catalyzed processes.[9] Although ferrocene-containing bisoxazoline ligands have been successfully utilized in the catalytic allylation reactions,[10] to the best of our knowledge, a ferrocene-containing ligand with three N-donor groups applied in the transition-metal catalyzed reactions has not been demonstrated. Thus, as part of our ongoing quest to find new sterically hindered and redox-active ferrocene ligands, this paper features the introduction of ferrocene moiety into pyridine-bis(isoxazole) ligand, subsequent coordination to Pd(II) and an investigation into their potential as catalyst for C–C forming reactions.

Palladium-catalyzed Sonogashira cross-coupling of terminal alkynes with aryl halides is one of the most widely used carbon–carbon forming reactions.[11] It provides an efficient route to aryl alkynes, which are important intermediates for the preparation of a variety of target compounds with applications ranging from natural products,[12] pharmaceuticals[13] and biologically active molecules[14] to materials.[15] Owing to the use of the products, the development of new catalyst systems has gained much attention. The most widely used catalysts are Pd complexes of phosphine ligands such as $Pd(PPh_3)_2Cl_2$ and $Pd(PPh_3)_4$ in conjunction with CuI.[16] Phosphine ligands are usually water- and air-sensitive and expensive. One way around this problem is to develop a phosphine-free methodology, for example, palladium-*N*-heterocyclic carbene complex, and Pd–oxazoline complex and palladacycle catalyst.[17] On the other hand, the presence of CuI can result in the formation of some Cu(I) acetylides *in situ* that can readily induce oxidative homocoupling reactions of alkynes.[18] It has also been found that CuI had a deleterious effect on the Sonogashira cross-coupling reaction.[19] Hence, numerous studies focused on the elimination of CuI have been reported in the last decade.[20] Based on these findings, we wished to use the pyridine-bis(ferrocene-isoxazole) complex of Pd(II) as a highly stable and efficient palladium catalyst in Sonogashira cross-coupling under copper- and phosphine-free conditions.

In this paper we report: (i) the synthesis and characterization of 2,6-bis-(5-ferrocenylisoxazole-3-yl) pyridine; (ii) preparation

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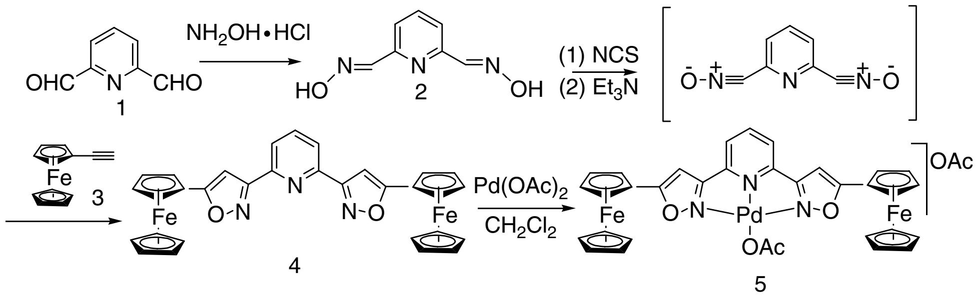


Scheme 1. The synthesis of 2,6-bis-(5-ferrocenylisoxazole-3-yl)pyridine **4** and pyridine-bis(ferrocene-isoxazole) Pd(II) complex **5**.

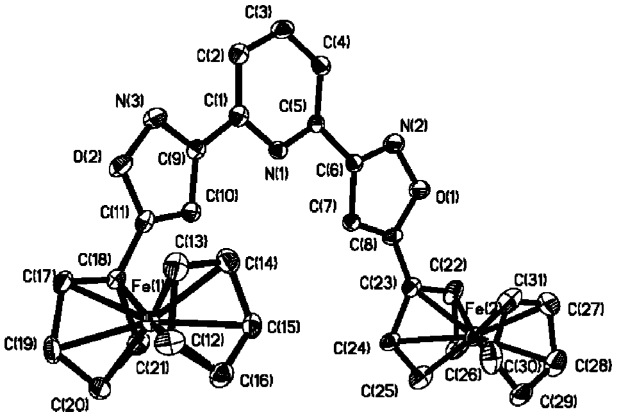


Figure 1. The single-crystal X-ray structure of 2, 6-bis-(5-ferrocenylisoxazole-3-yl) pyridine.

of new pyridine-bis-(ferrocene-isoxazole) complex of Pd(II) (Scheme 1); and (iii) its efficient catalysis of the Sonogashira cross-coupling reaction. On the basis, we will further develop the applications of the new ligand in palladium-catalyzed Heck and Suzuki reaction and other types of transition-metal catalyzed reactions.

Results and Discussion

Synthesis and characterization of 4 and 5

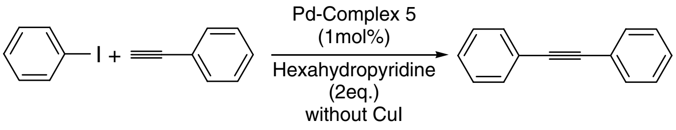
The preparation of 2, 6-bis-(5-ferrocenylisoxazole-3-yl) pyridine **4** and complex of Pd(II) **5** is shown in Scheme 1. Compound **4** was synthesized using a method similar to that reported by our groups previously.[21] And it was characterized by analytical and spectroscopic techniques. The structure of compound **4** was confirmed by X-ray single-crystal analysis (Fig. 1).

The synthesis of complex **5** was achieved by reaction of compound **4** with Pd(OAc)$_2$ in CH$_2$Cl$_2$ and was isolated in pure form as a dark red-purple powder, insensitive to air and moisture and easy to handle. Complex **5** was determined by spectroscopic analysis. The ligand is bound to palladium in a tridentate fashion via the three N atoms, forming two five-member chelate rings. The C=N bands of complex **5** were shifted to lower frequency in the IR spectrum and were shifted to higher frequency in the ^{13}C NMR spectrum compared with that of the free ligand **4**.[9c,17d] Moreover, in the ^{1}H NMR spectrum of complex **5**, the signal of pyridine-H was observed to occur an upfield shift, and the signal of the acetyl proton at 2.32ppm was also observed.

Sonogashira cross-coupling catalyzed by complex 5

Our investigation began with the coupling of iodobenzene with phenylacetylene catalyzed by 1 mol% of complex **5** in the absence of CuI as a co-catalyst. As shown in Table 1, we found that increasing the polarity of the solvent led to increased yield of cross-coupling product. A solution of DMF–H$_2$O (2 : 1) gave the highest yield (Table 1, entry 1, 88%) after 2 h at 30 °C under N$_2$ atmosphere. Moreover, adding TBAB (tetrabutylammonium bromide) to the reaction mixture enhanced the activity of the catalyst (compare conversions in Table 1, entries 1 and 5). In addition, hexahydropyridine was found to be the optimal base compared with TEA and K$_2$CO$_3$.

Table 1. Effect of the solvent and additive on the reaction of iodobenzene with phenylacetylene without CuI[a]

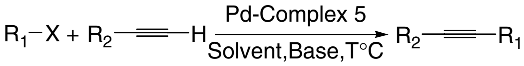


Entry	Solvent	Additive	Temperature (°C)	Time (h)	Yield[b] (%)
1	DMF–H$_2$O (2 : 1)	TBAB	30	2	88
2	DMF	–	30	2	75
3	CH$_3$CN–H$_2$O (2 : 1)	TBAB	30	2	40
4	THF–H$_2$O (2 : 1)	TBAB	30	2	10
5	DMF–H$_2$O (2 : 1)	–	30	2	67

[a] Reaction conditions: iodobenzene (1.0 equiv), phenylacetylene (1.5 equiv), TBAB (0.5 equiv), hexahydropyridine (2.0 equiv), at N$_2$ atmosphere.
[b] Isolated yields after flash chromatography.

Then, complex **5** was studied further in the coupling of a number of aryl halides and terminal alkynes. The results are summarized in Table 2. We observed that a variety of aryl halides can be successfully coupled with phenylacetylene using this new catalyst under the optimized reaction conditions. As expected, the coupling of phenylacetylene with iodides or bromides led to the desired products in moderate to high yields (Table 2, entries 1–9). In particular, the reaction of aryl iodide substituted with electron-withdrawing groups (such as $-NO_2$) was performed in high yield after 2 h at 30 °C (Table 2, entry 2). In the case of deactivated bromides, higher temperature and longer reaction time were required to push the reaction in good yields (Table 2, entries 4–9). The catalyst effect was also evident for chlorides, where only the substituted with electron-drawing group gave reasonable yield in coupling product (Table 2, entry 10). Nonactivated aryl chrolides gave a low yield in coupling reactions under similar conditions (Table 2, entries 11–13). We next investigated the effect of varying the terminal alkynes in the Sonogashira reaction using 1-iodobenzene as substrate under the optimized reaction conditions. Phenylacetylene led to high yield of the desired product (Table 2, entry 1). When ethynyl-ferrocene and several simple linear terminal alkynes were used, the desired products also formed in good yields (Table 2, entries 14–17). In all cases, the yields of the homocoupling

Table 2. Sonogashira coupling reactions of aryl halides with terminal alkynes without CuI[a]



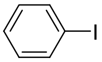
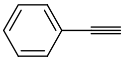
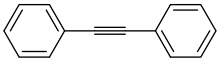
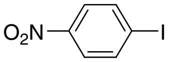
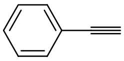
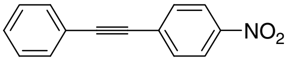
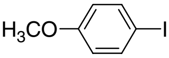
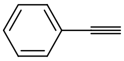
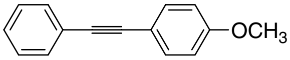
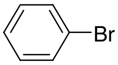
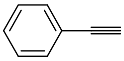
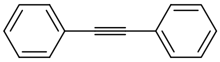
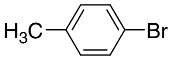
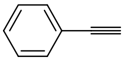
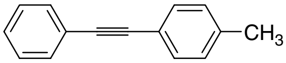
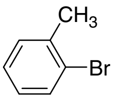
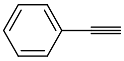
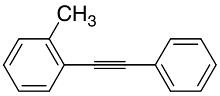
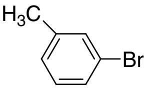
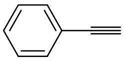
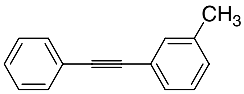
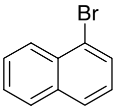
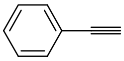
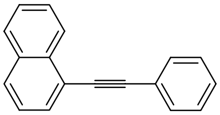
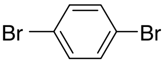
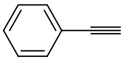
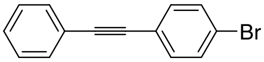
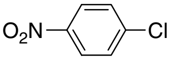
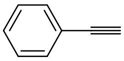
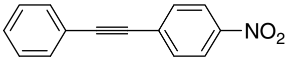
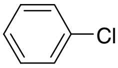
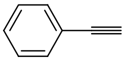
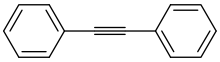
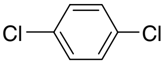
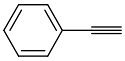
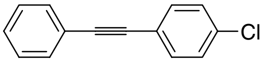
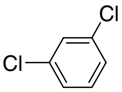
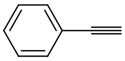
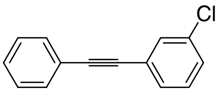
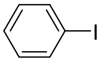
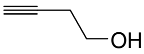
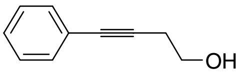
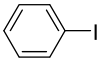
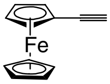
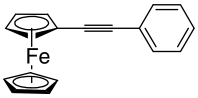
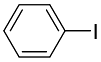
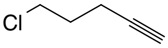
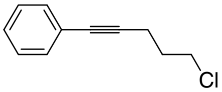
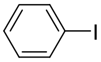
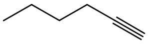
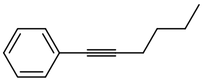
Entry	ArX	Alkyne	Product	Temperature (°C)	Time (h)	Yield[b] (%)
1				30	4	90
2[c]				30	2	97
3				90	8	60
4				90	6	76
5				90	6	75
6				90	6	74
7				90	6	76
8				90	6	70
9				90	8	71
10[d]				120	16	40
11[d]				120	16	21
12[d]				120	16	18
13[d]				120	16	20
14				60	4	75

Table 2. (*Continued*)

$$R_1{-}X + R_2{-}{\equiv}{-}H \xrightarrow[\text{Solvent,Base,T°C}]{\text{Pd-Complex 5}} R_2{-}{\equiv}{-}R_1$$

Entry	ArX	Alkyne	Product	Temperature (°C)	Time (h)	Yield[b] (%)
15				60	4	85
16				60	4	90
17				60	6	81

[a] Reaction conditions: In DMF–H_2O (2 : 1): ArHal (1.0 equiv), alkyne (1.5 equiv), Pd complex **5** (1 mol%), hexahydropyridine (2.0 equiv),TBAB (0.5 equiv), in N_2 atmosphere.
[b] Isolated yields after flash chromatography.
[c] Pd complex 5 (0.5 mol%).
[d] Tributyl amine (2.0 equiv) used as a base; Pd complex 5 (2 mol%).

products were less than 5%. In addition, it is worth noting that the catalyst seems to be stable at 100 °C, and no palladium black was observed. It is also important to mention that complex **5** was easily removed in the extraction step after the reaction because of its low solubility in most of the solvents.

Conclusions

In summary, a novel pyridine-bis (ferrocene-isoxazole) ligand, namely 2, 6-bis-(5-ferrocenylisoxazole-3-yl) pyridine, has been synthesized. As the ferrocene-containing ligand with three N-donor groups, its coordination to Pd(II) led to complex **5**, which showed good catalytic activity in the Sonogashira cross-coupling reaction of terminal alkynes with iodides and bromides under the copper- and phosphine-free reaction conditions. Further studies on the applications of complex **5** to the other reactions such as the Heck and Suzuki reactions are ongoing and will be reported in due course.

Experimental

General

All chemicals were commercially available and the preparation of 2,6-pyridinedicarboxaldehyde and aldoxime was similar to previously described procedures. IR spectra were recorded on KBr pellets on a PTIR-8400S spectrometer. ^1H NMR spectra were recorded at 300 MHz on a Bruker Avance DMX300 spectrometer and ^{13}C NMR spectra at 75 MHz on the same spectrometer in deuteriochloroform solutions. All chemical shifts are reported in parts per million from TMS as an internal standard. Coupling constants (*J* values) are given in Hz. Mass spectra (EI) were performed on an HP-5989 instrument with ionization energy maintained at 70 eV. Elemental analyses were carried out on an EA-1110 elemental analyzer. Column chromatography was carried out on Merck silica gel (230–400mesh) and solvents were distilled before use. X-ray crystallographic data were determined on a SMART APEX II X-ray diffractometer. Crystal of compound **4** was obtained by slow evaporation of a solution in DCM–hexane. The results of the structural analyses are illustrated in Table 3 and Fig. 1.

General procedure for the synthesis of 2, 6-bis-(5-ferrocenylisoxazole-3-yl) pyridine 4

Ethynylferrocene was prepared according to a previously described procedure.[8a] Hydroxylamine hydrochloride (1.2 equiv) and sodium bicarbonate (1.5 equiv) were added to 2,6-pyridinedicarboxaldehyde in ethanol. The mixture was stirred at room temperature overnight. The precipitate was removed by filtration and washed with water. After drying, 2,6-pyridinedicarboxaldoxime was obtained.

2,6-Pyridinedicarboxaldoxime (4 mmol) and chlorosuccinimide (NCS, 8 mmol) were dissolved in dry chloroform (12 ml) and DMF (6 ml). The reaction mixture was stirred at 30 °C for 3 h. Ethynylferrocene (8 mmol) was added. Triethylamine (1.2 ml in 12 ml of CH_2Cl_2) was added drop by drop over about 30 min. Then, the reaction mixture was stirred at room temperature overnight. The golden precipitate **4** was filtered and washed with CH_2Cl_2. An orange–red crystal of the compound **4** was obtained by slow evaporation of a solution in DCM–hexane.

*2, 6-Bis-(5-ferrocenylisoxazole-3-yl) pyridine (**4**)*

Yield: 2.002 g (86%); $\nu_{(C-O)} = 1107\ cm^{-1}$, $\nu_{(C=C)} = 1568\ cm^{-1}$, $\nu_{(C=N)} = 1603\ cm^{-1}$, $\nu_{(\equiv C-H)} = 3124\ cm^{-1}$. Anal. calcd for $C_{29}H_{23}O_2N_3Fe_2$: C,59.90; H,3.96; N,7.23. Found: C, 60.12; H, 4.25; N, 7.50%. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 4.18$ (s, 10 H, C_5H_5), 4.46 (s, 4 H, C_5H_4), 4.86 (s, 4 H, C_5H_4), 6.91 (s, 2 H, NOC=CH), 7.94 (t, 1 H, *J* 7.8, C_5H_3N), 8.16 (d, *J* 7.8, 2 H, C_5H_3N). ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 67, 69, 97, 122, 137, 148,163$. EIMS: 582($[M + H]^+$).

General procedure for the preparation of the palladium (II) complex (5)

To a 100 ml of CH_2Cl_2 solution of compound **4** (1 mmol) was added $Pd(OAc)_2$ (1 mmol) in open air. The mixture was stirred at 30 °C for

Table 3. Crystal data and structure refinement for compound 4

Empirical formula	$C_{29}H_{23}O_2N_3Fe_2$
Formula weight	582.0
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P21/c
Unit cell dimensions	
a (Å)	22.746(8)
b (Å)	9.554(4)
c (Å)	11.612(4)
α (deg)	90.0
β (deg)	100.473(4)
γ (deg)	90.0
Volume (Å^3)	2481.4(16)
Z	4
Calculated density (mg/m^3)	1.556
Absorption coefficient (mm^{-1})	1.205
F(000)	1192
Θ range (deg)	1.82–27.69
Maximum indices hkl	26, 12, 15
Reflections collected/unique	20146/5717
R_{int}	0.0461
Completeness (%)	98.1
Data/restraints/parameters	5717/0/344
Goodness-of-fit on F^2	1.090
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.1582$
	$wR_2 = 0.4423$
R indices (all data)	$R_1 = 0.1750$,
	$wR_2 = 0.4498$
Largest difference peak and hole (e Å^{-3})	2.606 and -1.575

6 h, during which time the solution darkened in color. After the greater part of solvent was removed under reduced pressure, to the residual solution was added Et_2O (20 ml) and a dark red-purple precipitate formed. This solid was then isolated by filtration and washed with Et_2O (2×5 ml) and CH_2Cl_2 (3×5 ml) and then dried in air. Complex **5** was thus obtained as a dark red-purple solid.

Complex 5

Yield: 0.650 g (81%); $\nu_{(C-O)} = 1105\ \text{cm}^{-1}$, $\nu_{(C{=}C)} = 1533\ \text{cm}^{-1}$, $\nu_{(C{=}N)} = 1589\ \text{cm}^{-1}$, $\nu_{({=}C-H)} = 3095\ \text{cm}^{-1}$. Anal. calcd for $C_{33}H_{29}O_6N_3Fe_2Pd$: C, 49.19; H, 3.60; N, 5.22. Found: C, 48.75; H, 3.12; N, 5.04%. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 2.32$ (s, 6 H, CH_3CO), 4.18 (s, 10 H, C_5H_5), 4.48 (s, 4 H, C_5H_4), 4.78 (s, 4 H, C_5H_4), 6.97 (s, 2 H, NOC=CH), 7.84 (t, 1 H, J 7.8, C_5H_3N), 8.10 (d, 2 H, J 7.8, C_5H_3N). ^{13}C NMR (75 MHz, DMSO-d_6) $\delta = 29$, 67, 69, 95, 122, 146, 154, 160, 179. EIMS: 806 ([M + H]$^+$).

General procedure for Sonogashira cross-coupling reaction

Under nitrogen atmosphere, a mixture of ArX (1.0 mmol), alkyne (1.5 mmol), Pd complex **5** (0.01 mmol), n-Bu_4NBr (0.5 mmol), hexahydropyridine (2.0 mmol), and DMF/H_2O (2 : 1, 6.0 ml) was stirred at certain temperature in an oil bath followed by TLC. After the reaction was finished, 15 ml water was added, and the mixture was extracted with Et_2O. The combined organic phases were washed with water, dried over anhydrous Na_2SO_4, and filtered. The solvent was removed under reduced pressure. The residue was purified by column chromatography using hexane or hexane–ethyl acetate as an eluent to afford cross-coupling products.

Supporting information

Crystallographic data has been deposited with the Cambridge Crystallographic Data Centre [CCDC 680439] for compound **4**. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax: (+44) 1223 336 033; email: deposit@ccdc.cam.ac.uk].

Supporting information may be found in the online version of this article.

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