

Palladium/1,3-bis(ferrocenylmethyl)imidazolium Chloride Catalyst for Suzuki Cross-Coupling Reactions

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Abstract

We describe here the first results on the catalytic performance of in-situ prepared $[\text{Pd}(\text{O}_2\text{CCH}_3)_2]$ / 1,3-bis(ferrocenylmethyl)imidazolium chloride. This saturated imidazole ring was successfully used in Suzuki cross-coupling reactions of various aryl bromides (bromobenzene, 2-bromobenzonitrile, 2-bromotoluene, *p*-bromobenzaldehyde, *p*-bromoacetophenone, *p*-bromoanisole, *p*-bromotoluene, and *p*-bromobenzotrifluoride) with phenylboronic acid under optimal conditions. The optimal conditions were determined to be 24 hours, 80°C, K_2CO_3 as a base, dioxane as a solvent, and 1,3-bis(ferrocenylmethyl)imidazolium chloride as an auxiliary ligand. Under these conditions, 2-bromobenzonitrile, *p*-bromoacetophenone, and *p*-bromobenzaldehyde reacted with phenylboronic acid in moderate yields of 57%, 50%, and 46%, respectively. Catalytic experiments showed that the $[\text{Pd}(\text{O}_2\text{CCH}_3)_2]$ / 1,3-bis(ferrocenylmethyl)imidazolium chloride catalytic system was moderately efficient in the Suzuki cross-coupling reaction of aryl bromides in dioxane.

Keywords: Ferrocene, 1,3-bis(ferrocenylmethyl)imidazolium salt, Palladium, Suzuki

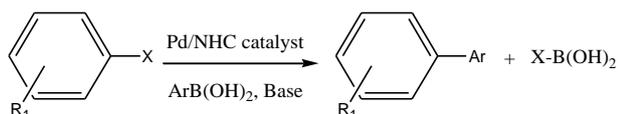
1. Introduction

The use of N-heterocyclic carbenes (NHCs) in transition metal catalysis has inspired numerous studies since it was first reported by Hermann et al. in 1995. Different metal complexes of NHCs, such as Pd, Ru, Rh, Pt, and Ir, have been extensively used to catalyze various reactions, including olefin metathesis, polymerization, hydrogenation, and C-N and C-C coupling [1-3]. Pd-NHC systems have been shown to compete with phosphane-bonded systems in reactions such as Kumada, Sonogashira, Heck, and Suzuki [4-6]. Therefore, NHCs are known as potential alternatives to phosphines.

Ferrocenyl-substituted carbenes are interesting compounds in terms of being an electron source, reversible redox chemistry, and the stereoelectronic effect of ferrocenyl groups [7]. The first study on this subject were conducted by Bildstein et al. in the late 1990s, and diferrocenylcarbene and ferrocenyl-substituted NHCs were synthesized [8-9]. After the publication of the work on carbenes containing ferrocene groups by Bildstein in 2001, great progress has been

made in the studies conducted in this field. This period is counted as the "post-Bildstein period" in carbene chemistry containing ferrocene groups [10].

The first study on *N,N'*-diferrocenyl-linked carbenes were also carried out by Bildstein et al. [8-9]. Later, imidazolium salts containing *N,N'*-diferrocenyl-linked phosphine, aryl, or silyl groups were reported [11-15]. These salts have been converted into NHC complexes with various metals (Ru(II), Ir(I), Mo), Pd(II), Rh(I), and some of the obtained complexes have been used in catalytic applications. Especially in recent years, ferrocenyl-substituted Pd-NHCs have wide applications in homogeneous catalysis [16-21]. In addition, in situ catalytic studies of $[\text{Pd}(\text{O}_2\text{CCH}_3)_2]$ / ferrocenyl NHCs are known but are very scarce in the literature [22-26]. For example, Shi et al. reported an in situ Suzuki-Miyaura coupling reaction of aryl bromides by reacting $[\text{Pd}(\text{O}_2\text{CCH}_3)_2]$ / ferrocenylimidazolium salts as shown in the general mechanism in Scheme 1 [22-24]. Dallas et al. have also investigated the catalytic properties of the $[\text{Pd}(\text{O}_2\text{CCH}_3)_2]$ / ferrocenyl azolium salt systems in the Heck reaction [25].



Scheme 1. Suzuki-Miyaura coupling reaction

We have recently reported on the catalytic activity of 1,3-bis(ferrocenylmethyl)imidazolium chloride/bromide salts (Figure 1) in the Heck coupling reaction [26]. This study represents the first example of utilizing 1,3-bis(ferrocenylmethyl)imidazolium salts, featuring a saturated imidazole ring as the auxiliary ligand, with $[Pd(O_2CCH_3)_2]$ for the Suzuki reaction. These salts performed moderately well as auxiliary ligands in the Suzuki reaction and were active in the Heck coupling reaction.

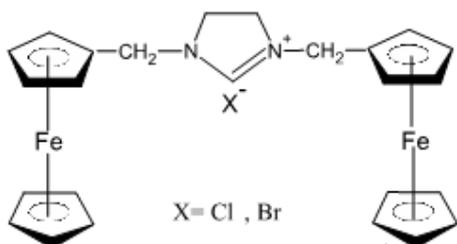


Figure 1. 1,3-bis(ferrocenylmethyl)imidazolium salts

2. Materials and Methods

1,3-bis(ferrocenylmethyl)imidazolium chloride/bromide were synthesized using previously reported procedures, and the analytical properties (FT-IR, 1H NMR, and melting point) of these salts were consistent with those reported in the literature [27]. The 1H NMR spectra of 1,3-bis(ferrocenylmethyl)imidazolium chloride/bromide and the biaryl product were recorded on a VARIAN ASW-400 spectrometer, while the melting points were measured using an Electrothermal 9200 melting point apparatus.

2.1. General procedure for the Suzuki cross-coupling reactions

A 25 mL flask was filled with 1,3-bis(ferrocenylmethyl)imidazolium salt (0.005 mmol), $[Pd(O_2CCH_3)_2]$ (0.005 mmol), $C_6H_5B(OH)_2$ (1.5 mmol), aryl bromide (1.0 mmol), solvent (2 mL), and a base (2 mmol) in an air atmosphere. The solution was stirred at the specified temperature for 2-24 hours, and the reactions were monitored using TLC. The mixture was then cooled, diluted with Et_2O , and purified via column chromatography. The purity of the compounds was confirmed using 1H NMR, and the yields were based on the amount of aryl bromide used.

2.2. Data for biaryl

2.2.1. 4-Acetylbiphenyl [28]. Mp: 118 °C. 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.04 (Ar-H, 2H, d), 7.65 (Ar-H, 2H, m), 7.48 (Ar-H, 2H, d), 7.43 (Ar-H, 3H, m), 2.64 ($COCH_3$, 3H, s) (Figure S1).

2.2.2. Biphenyl [28]. Mp: 68 °C. 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.60 (Ar-H, 4H, m), 7.46-7.42 (Ar-H, 4H, t), 7.36-7.33 (Ar-H, 2H, t) (Figure S2).

2.2.3. 4-Methoxybiphenyl [28]. Mp: 88 °C. 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.57-7.54 (Ar-H, 4H, m), 7.41 (Ar-H, 2H, m), 7.30 (Ar-H, 1H, dd), 6.98 (Ar-H, 2H, m.), 3.86 (OCH_3 , 3H, s,) (Figure S3).

2.2.4. Biphenyl-2-carbonitrile [29]. Mp: 37 °C. 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.75 (Ar-H, 2H, dd), 7.66 (Ar-H, 1H, m), 7.58 (Ar-H, 2H, m), 7.52 (Ar-H, 3H, m.), 7.44 (Ar-H, 2H, m) (Figure S4).

2.2.5. Biphenyl-4-carboxaldehyde [30]. Mp: 57 °C. 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.06 ($O=CH$, 1H, s), 7.97 (Ar-H, 2H, m), 7.77 (Ar-H, 2H, m), 7.51-7.48 (2H, m), 7.44 (1H, s) (Figure S5).

3. Results and Discussion

The reaction processes were optimized using 4-bromoacetophenone and phenylboronic acid as substrates in situ with $[Pd(O_2CCH_3)_2]$ / 1,3-bis(ferrocenylmethyl)imidazolium as the catalyst. The optimization involved varying the temperature, base, solvent, time, and auxiliary ligand. The results of the optimization are shown in Table 1.

Initially, the reaction was carried out without the auxiliary ligand, and only $[Pd(O_2CCH_3)_2]$ was used as a catalyst. However, a trace amount of product was formed. The addition of 1,3-bis(ferrocenylmethyl)imidazolium chloride/bromide as an auxiliary ligand produced 50% and 38% yield, respectively (Table 1, entries 1-2, 4). Thus, it was decided to use 1,3-bis(ferrocenylmethyl)imidazolium chloride as the auxiliary ligand.

The effect of varying temperatures was studied, and it was found that the yield was moderate at a higher temperature of 80°C. No product was obtained at room temperature, and the yield did not change at the highest temperature of 110°C (Table 1, entries 4-5). The optimum temperature was determined to be 80°C as it is advantageous to work at lower temperatures.

The effect of different solvents, dioxane, toluene, and DMF- H_2O , on the yield was studied. (Table 1, entries 4, 6-7). Dioxane was chosen as the solvent as it gave the highest yield.

Different bases were investigated to optimize the yield of the transformation. K_2CO_3 gave a 50% yield, while Cs_2CO_3 and $NaOH$ produced 54% and 43% yield, respectively. Na_2CO_3 , Li_2CO_3 , and CH_3COONa did not work for the present coupling reaction (Table 1, entries 4, 8-12). K_2CO_3 was preferred as a base due to its effectiveness and lower cost.

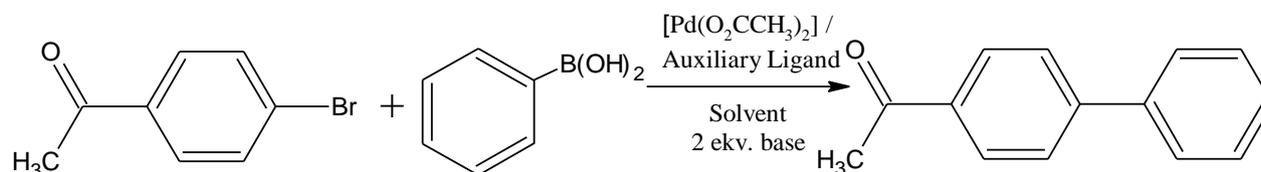
The yield was found to increase with the reaction time, and trace amounts of product were obtained at 2, 4, 6, and 8 hours. The optimum time was determined as 24 hours, as the yield increased with reaction time (Table 1, entries 4, 13-16).

Optimum conditions were determined as 24 hours at $80^\circ C$, with K_2CO_3 as the base, dioxane as the solvent, and 1,3-bis(ferrocenylmethyl)imidazolium chloride as the auxiliary ligand. Under these conditions, moderate yields of 57%, 50%, 46%, 13%, and 8% were obtained for the reactions of 2-bromobenzonitrile, *p*-bromoacetophenone,

p-bromobenzaldehyde, bromobenzene, and *p*-bromoanisole, respectively, with phenylboronic acid (Table 2, entries 1-5). No product was obtained when using 2-bromotoluene, *p*-bromotoluene, and *p*-bromobenzotrifluoride (Table 2, entries 6-8). Unfortunately, the in situ $[Pd(O_2CCH_3)_2]$ / 1,3-bis(ferrocenylmethyl)imidazolium catalyst system was not effective in the Suzuki reaction.

The proposed mechanism for the Suzuki coupling reaction of biaryl products using the Pd/NHC catalytic system is outlined in Scheme 2. This reaction follows a sequence of three steps: oxidative addition, transmetalation, and reductive elimination. In the first step, Pd(0) species are oxidized by organic halides to form Pd(II), which is the rate-determining step of the reaction. Next, transmetalation occurs between Pd(II) and the alkyl borate complex. Finally, Pd(0) is regenerated by the reductive cleavage of the C-C sigma bond.

Table 1. Optimizations of Suzuki cross-coupling reaction



Entry ^a	Base	Solvent	T (°C)	Time (h)	Yield ^{b,c} (%)
1 ^d	K_2CO_3	1,4-Dioxane	80	24	Trace
2 ^e	K_2CO_3	1,4-Dioxane	80	24	38
3	K_2CO_3	1,4-Dioxane	RT	24	ND
4	K_2CO_3	1,4-Dioxane	80	24	50
5	K_2CO_3	1,4-Dioxane	110	24	48
6	K_2CO_3	Toluene	80	24	40
7	K_2CO_3	DMF-H ₂ O	80	24	36
8	Cs_2CO_3	1,4-Dioxane	80	24	54
9	$NaOH$	1,4-Dioxane	80	24	43
10	Na_2CO_3	1,4-Dioxane	80	24	Trace
11	Li_2CO_3	1,4-Dioxane	80	24	ND
12	CH_3COONa	1,4-Dioxane	80	24	Trace
13	K_2CO_3	1,4-Dioxane	80	2	Trace
14	K_2CO_3	1,4-Dioxane	80	4	Trace
15	K_2CO_3	1,4-Dioxane	80	6	Trace
16	K_2CO_3	1,4-Dioxane	80	8	Trace

a Reaction conditions: $[Pd(O_2CCH_3)_2]$ (0.05 mmol), 1,3-bis(ferrocenylmethyl)imidazolium chloride (0.05 mmol), *p*-bromoacetophenone (1.0 mmol), $C_6H_5B(OH)_2$ (1.5 mmol), base (2 mmol), solvent (2 mL). ND: Not determined.

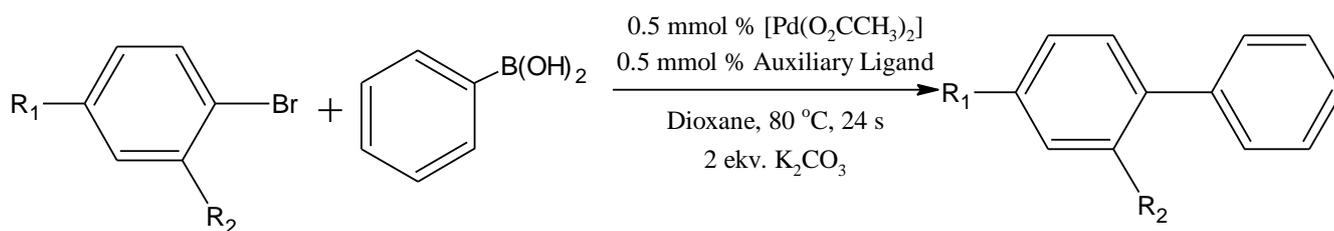
b Isolated yields based on *p*-bromoacetophenone.

c All reactions were monitored by TLC.

d $[Pd(O_2CCH_3)_2]$ was used as catalyst.

e 1,3-bis(ferrocenylmethyl)imidazolium bromide was used as an auxiliary ligand.

Table 2. Suzuki cross-coupling reaction of aryl bromides with $C_6H_5B(OH)_2$



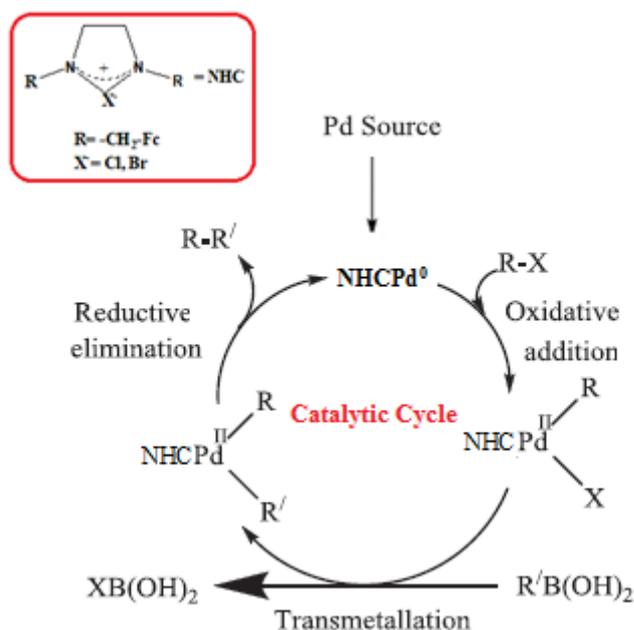
Entry ^a	R ₁	R ₂	Yield ^{b,c} (%)
1	H	CN	57
2	COCH ₃	H	50
3	CHO	H	46
4	H	H	13
5	OCH ₃	H	8
6	H	CH ₃	ND
7	CH ₃	H	ND
8	CF ₃	H	ND

a Reaction conditions: $[Pd(O_2CCH_3)_2]$ (0.05 mmol), 1,3-bis(ferrocenylmethyl)imidazolium chloride (0.05 mmol), *p*-bromoacetophenone (1.0 mmol), $C_6H_5B(OH)_2$ (1.5 mmol), K_2CO_3 (2 mmol), and 1,4-Dioxane (2 mL), 24 h. ND: Not determined.

b Isolated yields based on aryl bromide.

c All reactions were monitored by TLC.

Suzuki-Miyaura Cross Coupling Reaction Mechanism



Scheme 2. General mechanism of Suzuki reaction for Pd/NHC catalytic systems



4. Conclusion

In summary, the in situ $[Pd(O_2CCH_3)_2]$ / 1,3-bis(ferrocenylmethyl)imidazolium chloride catalyzed Suzuki reaction has been described. Optimum conditions were determined as 24 h, 80 °C, K_2CO_3 as a base, dioxane as a solvent, and 1,3-bis(ferrocenylmethyl)imidazolium chloride as auxiliary ligand. Under these conditions, 2-bromobenzonitrile, *p*-bromoacetophenone, and *p*-bromobenzaldehyde react with phenylboronic acid in moderate yields of 57%, 50%, and 46%, respectively. While this catalytic system performed moderately in the Suzuki reaction, the results provide a good basis for studies targeting efficient catalyst activity.

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Author's Contributions

Mehmet Günaltay: Performed the experiment.

Hülya Avcı Özbek: Performed the experiment and result analysis; and wrote the manuscript.

Funda Demirhan: Supervised the progress of the experiment, the interpretation of the results, drafted the manuscript.

Ethics

There are no ethical issues after the publication of this manuscript.

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Supporting Information

¹H NMR Spectra for biaryl compounds

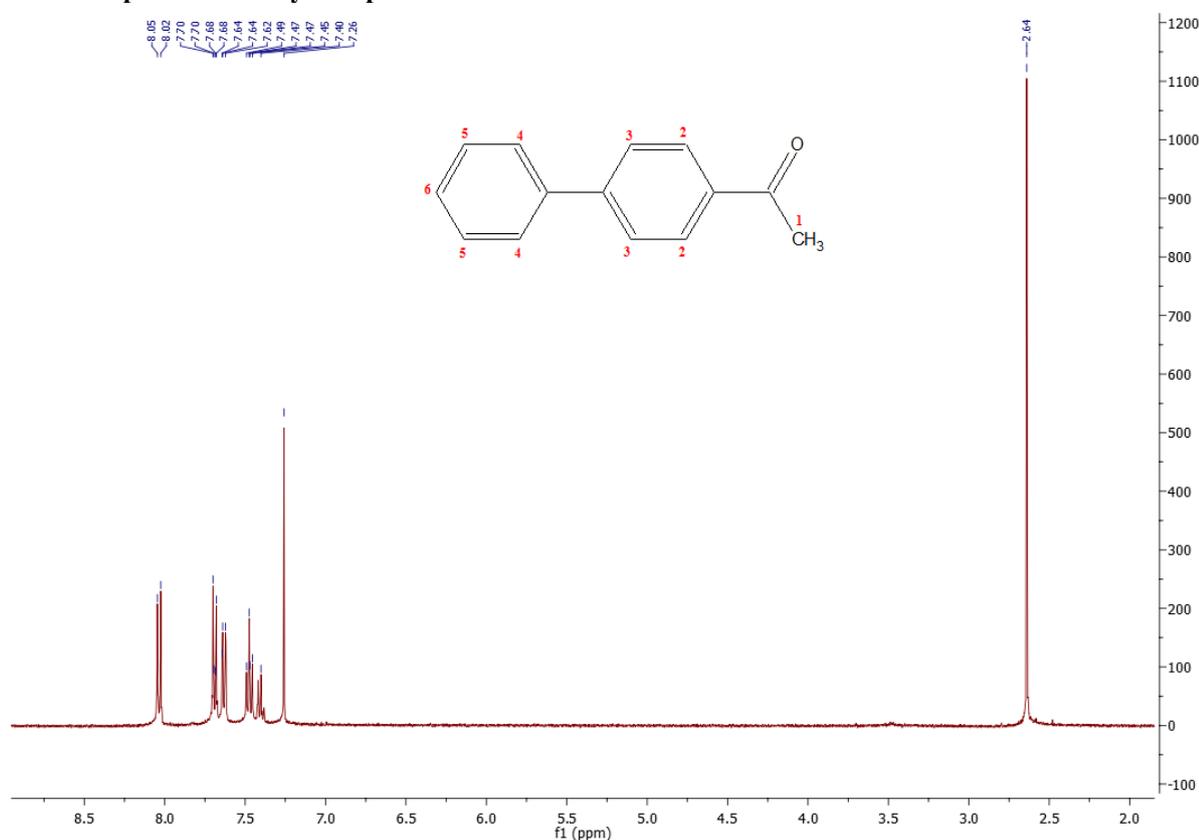


Figure S1. ¹H NMR spectra of 4-acetylbiphenyl

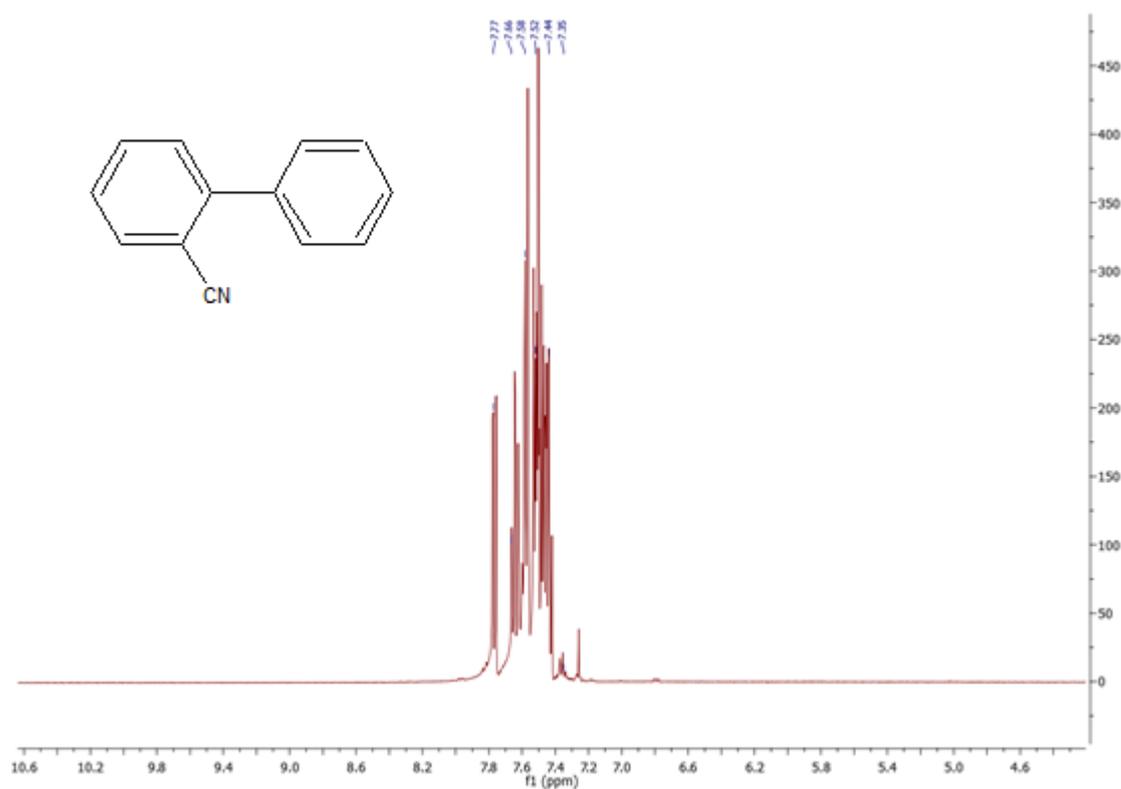


Figure S4. ¹H NMR spectra of biphenyl-2-carbonitrile

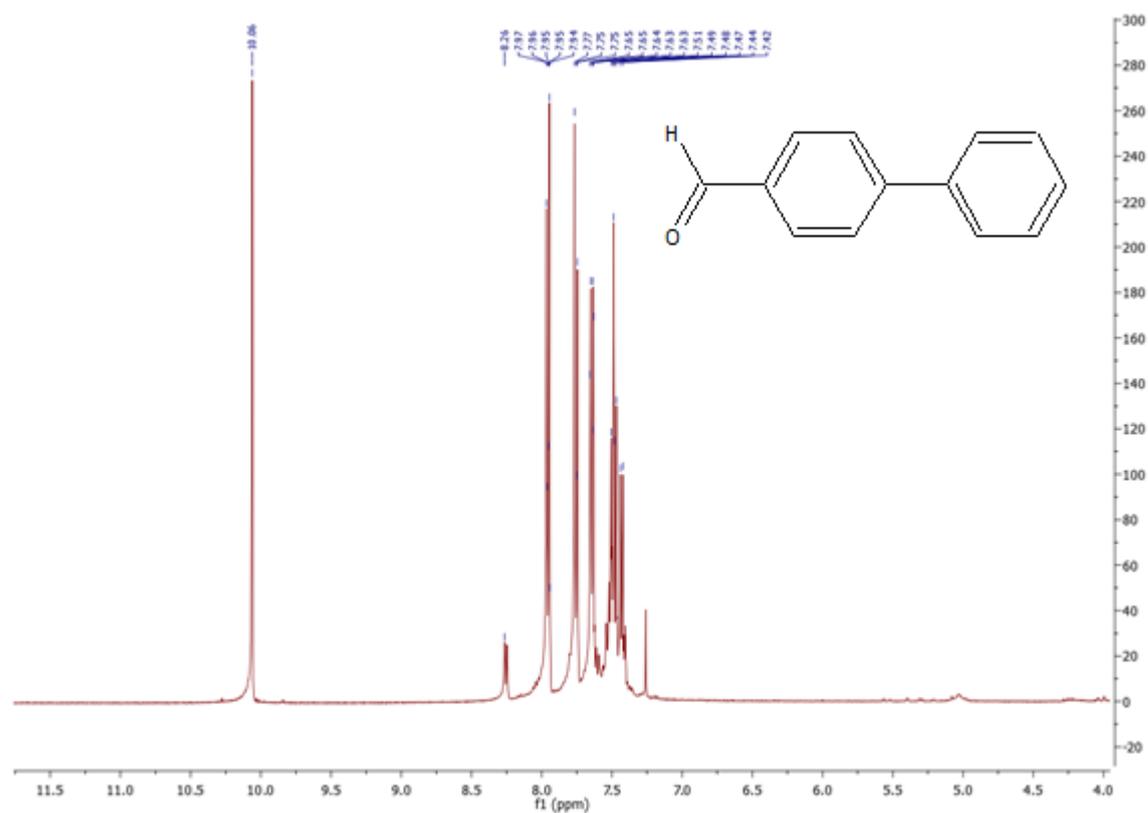


Figure S5. ¹H NMR spectra of biphenyl-4-carboxaldehyde