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Efficient *in situ* N-heterocyclic carbene palladium(II) generated from Pd(OAc)₂ catalysts for carbonylative Suzuki coupling reactions of arylboronic acids with 2-bromopyridine under inert conditions leading to unsymmetrical arylpyridine ketones: synthesis, characterization and cytotoxic activities†

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N,N-Substituted benzimidazole salts were successfully synthesized and characterized by ¹H-NMR, ¹³C {¹H} NMR and IR techniques, which support the proposed structures. Catalysts generated *in situ* were efficiently used for the carbonylative cross-coupling reaction of 2 bromopyridine with various boronic acids. The reaction was carried out in THF at 110 °C in the presence of K₂CO₃ under inert conditions and yields unsymmetrical arylpyridine ketones. All *N,N*-substituted benzimidazole salts **2a–i** and **4a–i** studied in this work were screened for their cytotoxic activities against human cancer cell lines such as MDA-MB-231, MCF-7 and T47D. The *N,N*-substituted benzimidazoles **2e** and **2f** exhibited the most cytotoxic effect with promising cytotoxic activity with IC₅₀ values of 4.45 µg mL^{−1} against MDA-MB-231 and 4.85 µg mL^{−1} against MCF7 respectively.

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1. Introduction

Ketones are vital building blocks in organic synthesis as well as an important functionality found in pharmaceutical compounds.^{1,2} The Friedel–Crafts (F–C) acylation of aromatic compounds is the most frequent route for the synthesis of aromatic ketones.² However, it has intrinsic limitations such as the substituent-directing effects, reactive substrate requirements and the fact that recovery and recycling of the catalyst is seldom possible after aqueous work-up and a large amount of toxic wastes is generated. On the other hand, Pd-catalyzed cross-coupling reactions of acyl halides with organometallic reagents provides a direct procedure for the synthesis of isomeric ketones; a drawback is that Pd-catalysts are expensive and they are not recovered.^{3–8} In 1993, Suzuki's group⁹ reported a direct method (*i.e.*, the carbonylative Suzuki coupling reaction) for the synthesis of aromatic ketones by the reaction of CO with an aryl

halide and an arylboronic acid in the presence of PdCl₂ and Pd(dba)₂ (bis(dibenzylideneacetone)palladium). This reaction provides a versatile platform for the direct synthesis of aromatic ketones using boronic acids, which are generally non-toxic and stable to air and moisture. Ishiyama *et al.*¹⁰ used a variety of different catalysts to affect this carbonylative Suzuki reaction, including PdCl₂ (PPh₃)₂ and PdCl₂ (dppf) ([1,1'-bis(diphenylphosphino) ferrocene] dichloropalladium(II)). However, the conversion and selectivity of these reactions are low and require the presence of a ligand to proceed effectively.^{11,12} On the other hand, pyridine and its derivatives have a wide range of chemical and biological potentialities that are useful intermediates in the syntheses of various natural products and drugs.¹³ Several, different protocols have been developed for the synthesis of this important class of products.¹⁴ However, most of these protocols used unfriendly reagents and gave poor overall yields.

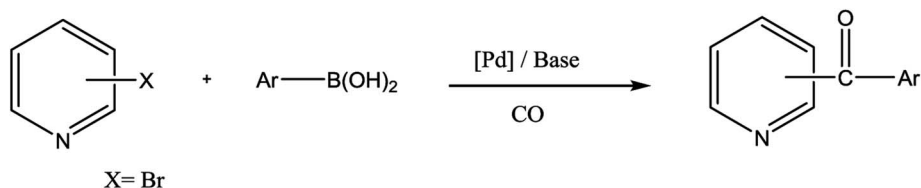
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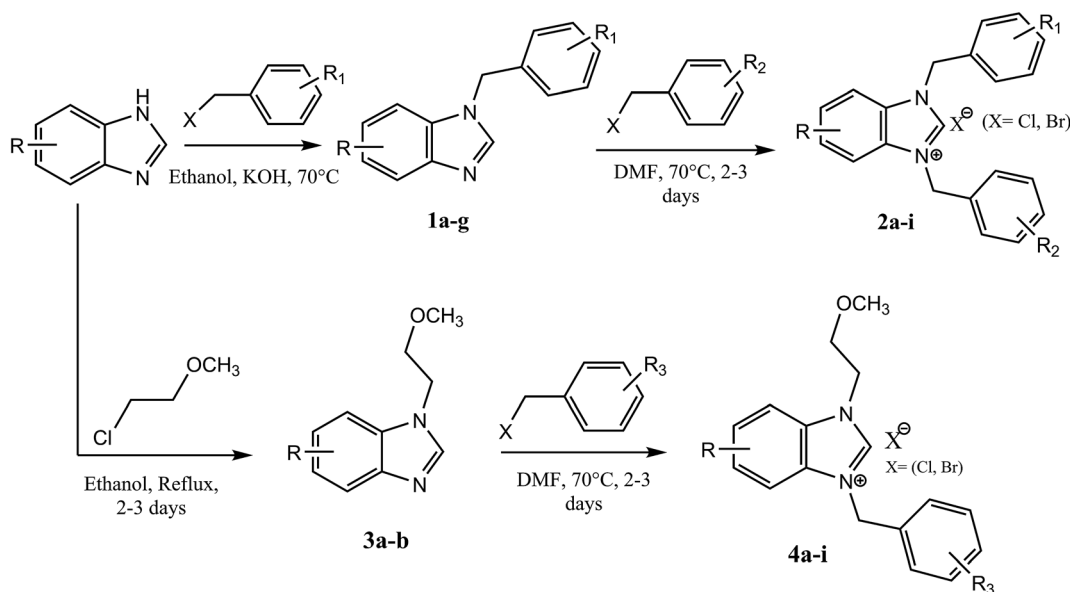


Scheme 1 Carbonylative cross-coupling reaction of chloropyridines with arylboronic acids.

The carbonyl coupling of bromopyridine with arylboronic acids (carbonyl version of the Suzuki reaction) has recently been shown to provide simple access to arylpyridine ketones with good yields after optimization of the operating conditions¹⁵ (Scheme 1).

Since the discovery of N-heterocyclic carbenes by Arduengo in 1991, NHCs have become one of the most versatile class of ligands for a wide range of transition metals^{16,17} and begun to replace phosphine ligands^{18–21} due to their unique properties.^{22–24} To date, various NHC complexes have been synthesised with different transition metals²⁵ and have demonstrated unique activities as catalysts in different organic transformations.²⁶

The palladium NHC complexes are one of the most interesting and widely investigated complexes in different catalytic transformations, especially C–C bond formation reactions such as Suzuki,²⁷ Heck,²⁸ and Sonogashira²⁹ reactions. Thus, the use of N-heterocyclic carbenes associated to palladium has been reported as efficient catalysts for the carbonyl coupling under mild and varied conditions.^{30–35} Herein, we report the use of the two families of benzimidazolium salts already synthesized^{36–38} as a ligand in the carbonylative cross coupling of 2-bromopyridine with different boronic acids under inert condition to form unsymmetrical arylpyridine ketones (Scheme 2). In addition, the cytotoxic activities against the cancer human cell lines such

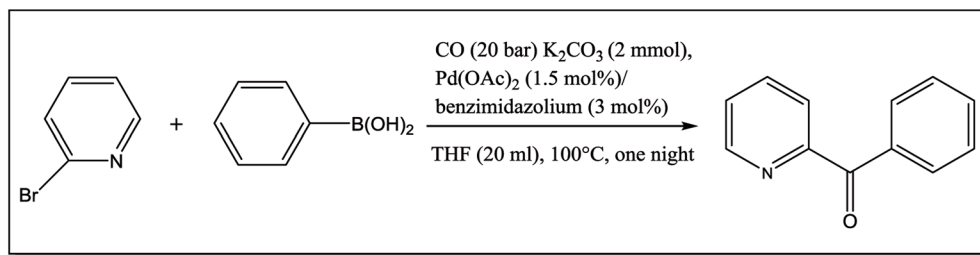


- 2a:** R = 5,6-dimethyl, R₁=R₂= 2,3,4,5,6-pentamethyl
2b: R = H, R₁=R₂= 2,3,4,5,6-pentamethyl
2c: R = H, R₁=R₂= 4-tertbutyl
2d: R = 5,6-dimethyl, R₁= 2,3,4,5,6-pentamethyl, R₂= 2,4,6-trimethyl
2e: R = 5,6-dimethyl, R₁=R₂= 2,4,6-trimethyl
2f: R = 5,6-dimethyl, R₁= 4-tertbutyl, R₂= 4-methyl
2g: R = 5,6-dimethyl, R₁=R₂= 3,5-dimethyl
2h: R = 5,6-dimethyl, R₁=R₂= 4-tertbutyl
2i: R = H, R₁=R₂= H

- 4a:** R = H, R₃= 2,3,4,5,6-pentamethyl
4b: R = H, R₃= 2,4,6-trimethyl
4c: R = H, R₃= 3,5-dimethyl
4d: R = H, R₃= 4-methyl
4e: R = 5,6-dimethyl, R₃= 2,3,4,5,6-pentamethyl
4f: R = 5,6-dimethyl, R₃= 2,4,6-trimethyl
4g: R = 5,6-dimethyl, R₃= 3,5-dimethyl
4h: R = 5,6-dimethyl, R₃= 4-methyl
4i: R = 5,6-dimethyl, R₃= 4-tertbutyl

Scheme 2 General preparation and structure formulae of benzimidazoles salts 2a–i and 4a–i





Scheme 3 Carbonylative cross-coupling reaction of 2-bromopyridine with phenylboronic acid in presence of different benzimidazolium salts **2**, **4**.

us MDA-MB-231, MCF-7 and T47D of the compounds **2** and **4** were also determined.

2. Results and discussion

2.1 Preparation of benzimidazolium salts **2a-i** and **4a-i**

The formation of *N,N*-disubstituted azolium salts is mostly done through the introduction of alkyl/benzylhalide to an *N*-alkyl/benzylazole *via* quaternization reaction.

In the present study, the precursors **2a-i** and **4a-i** were prepared by the quaternization of the intermediate **1** and **3** with a variety of benzyl chlorides or benzyl bromides in DMF at 70 °C (Scheme 2) as previously described^{36,37,39} in almost quantitatively yields. All compounds showed good solubility in water

and common organic solvents, such as dichloromethane, chloroform, methanol, acetonitrile, and *N,N*-dimethylformamide.

The synthesized compounds were purified by crystallization/column chromatography and were identified by FTIR and NMR spectral data analysis (Experimental section) in particular NMR spectra of all the benzimidazolium salts **2a-i** and **4a-i** were recorded in CDCl₃.

¹³C NMR chemical shifts were consistent with the proposed structure, the imino carbon appeared as a typical singlet in the ¹H-decoupled mode at 141.3, 143.0, 143.0, 142.1, 142.7, 141.6, 141.8, 141.8 and 132.5 ppm respectively for imidazolinium salts **2a-i**. The ¹H NMR spectra of the benzimidazolium salts further supported the assigned structures; the resonances for C(2)-H

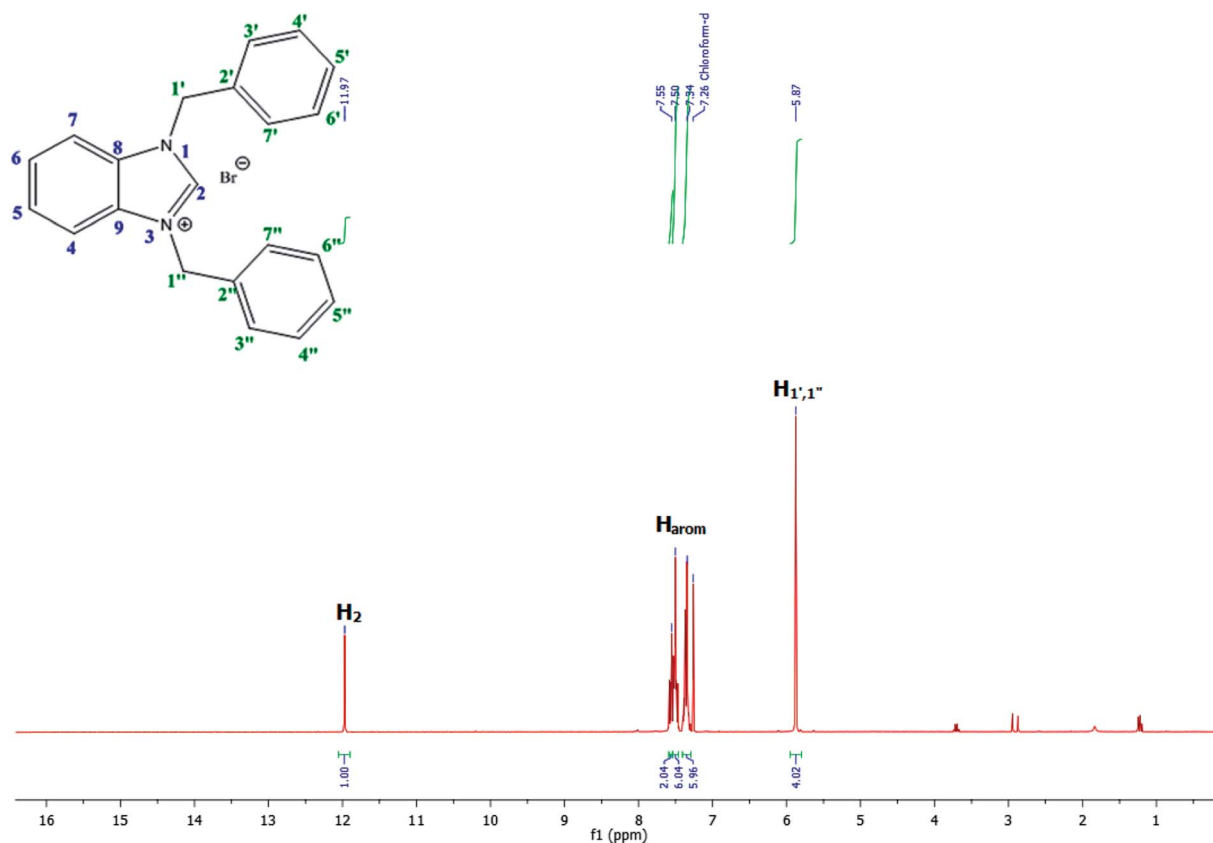


Fig. 1 ¹H NMR spectra of benzimidazole salt **2i** (CDCl₃, 300 MHz).



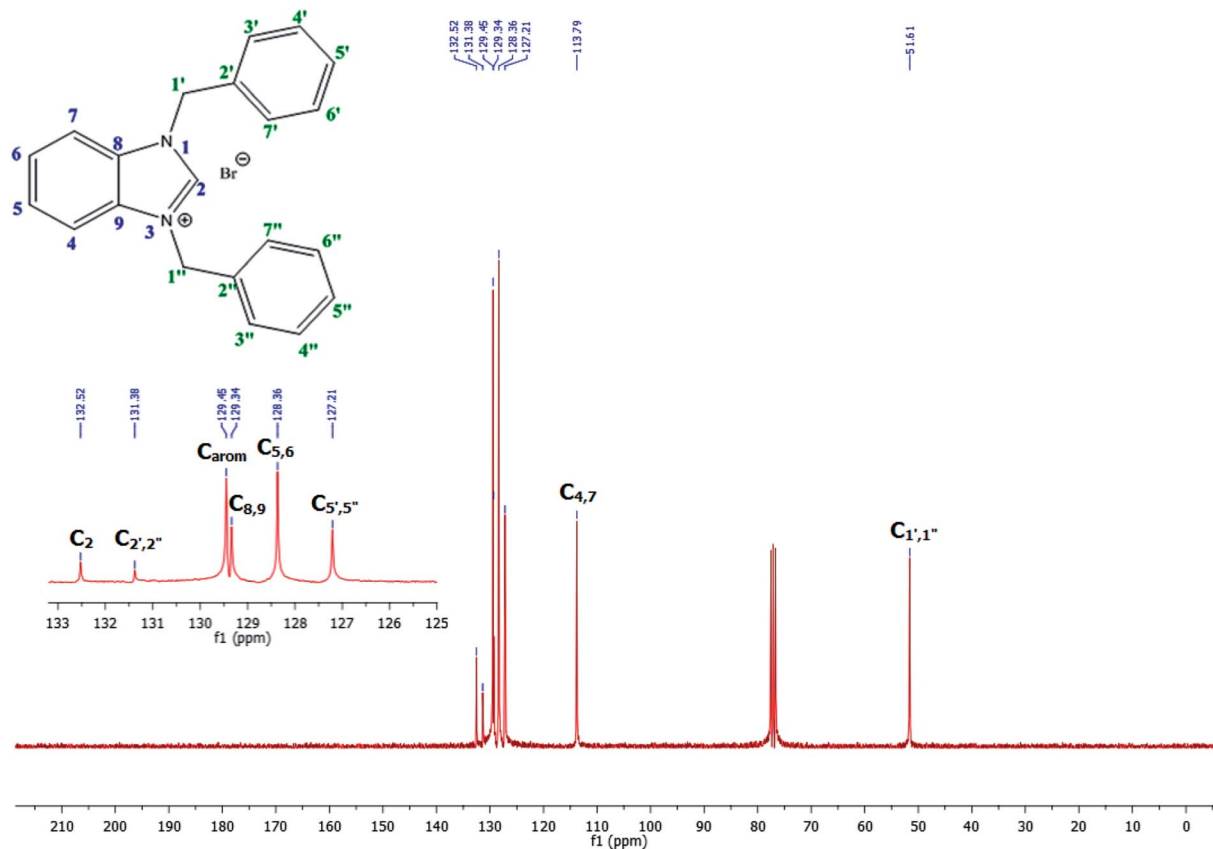


Fig. 2 ^{13}C NMR spectra of benzimidazole salt **2i** (CDCl_3 , 75 MHz).

were observed as sharp singlets in the 9.85, 10.34, 11.83, 10.41, 10.92, 11.51, 11.42, 11.63 and 11.47 ppm respectively for **2a-i**.

The characteristic $\text{IR}_{(\text{CN})}$ bond in the compounds was obtained as 1440.9, 1553.9, 1562.8, 1567.83, 1567.86, 1561.6, 1562.4, 1558.1 and 1559.02 cm^{-1} for **2a-i**, respectively.

For example, the NCHN proton signal for the benzimidazole salt **2i** was observed as singlet at 11.97 ppm that is in accordance with previous reports.^{36,37} The benzylic protons ($\text{N-CH}_2\text{-Ar}$) appeared at 5.87 ppm (Fig. 1).

The NCHN carbone of the benzimidazole salts **2i** in the ^{13}C NMR spectra was obtained in low fields at $\delta = 132.5$ ppm. Fig. 2 Palladium based N-heterocyclic carbene ligands have previously allowed the effective carbonylative coupling of different chloropyridines with phenylboronic acid^{40,41} but the results illustrate that commercial Pd-based catalyst is not effective towards this transformation, probably because the activity of the catalysts is strongly hindered by the strongly π -accepting CO ligand.⁴² Thus, we have studied the behavior of benzimidazolium salts **2a-i** and **4a-i** in the carbonylative cross coupling of 2-bromopyridine with phenylboronic acid under standard conditions previously described (Scheme 3).¹⁶

The corresponding results are summarized in the Table 1.

From Table 1 all the complexes gave the corresponding carbonyl product with moderate yields. Good yields were obtained for the less sterically hindered benzimidazoles salts (Table 1, entries 3, 6–13, 16–18). However, lower yields were

obtained for the rest of benzimidazoles having most sterically hindered groups (Table 1, entries 1–2, 4–5, 14–15). These results can be explained by the difference in the steric effects stem from the bulky groups on the carbene ring. Based on these results, we tried to improve the selectivity of the reactions by optimizing the reaction conditions. We chose 2-bromopyridine and phenylboronic acid as model substrates to explore the viability of the process. Various solvents, bases and CO pressures were tested in combination with $\text{Pd}(\text{OAc})_2$ precursor and benzimidazole **2i** as ligand (Scheme 4).

Selected results are shown in Table 2.

Solvents play a significant role in determining the conversion. Thus, a series of solvents were tested, such as 1,4-dioxane, THF and DMF, (Table 2, entries 1–3). With polar aprotic solvents such as DMF, no reaction took place (Table 2, entry 1). Even, the direct coupling is working in DMF, the presence of CO in the reaction medium could so be the cause. The absence of reaction can be explained by the fact that, in our reaction conditions, the coordination of the combination DMF-CO on the palladium caused the delay of its nucleophilic attack on the halogenated derivative. On the other hand, the use of the ethereal solvent 1,4-dioxane, afforded the carbonylative product in 42% yield (Table 2, entry 2) when we use 1,4-dioxane. However, when the reaction was carried out in tetrahydrofuran (THF), the selectivity was increased and the desired product was obtained with a yield of 53% (Table 2, entry 3).



Table 1 Study of the carbonylative cross-coupling reaction between 2-bromopyridine and phenylboronic acid catalysed by benzimidazolium salts **2a–i** and **4a–i**^a

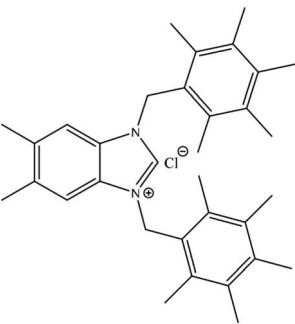
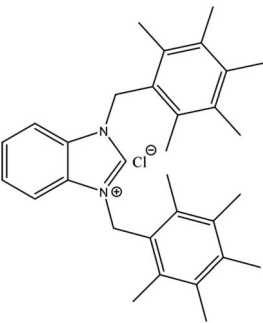
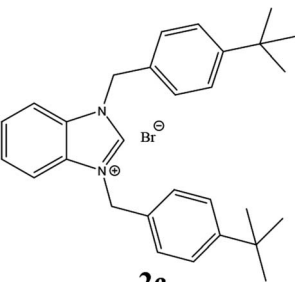
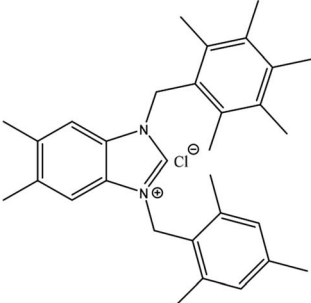
Entry	Benzimidazolium salt	Yield
1		27%
2		22%
3		55%
4		21%

Table 1 (Contd.)

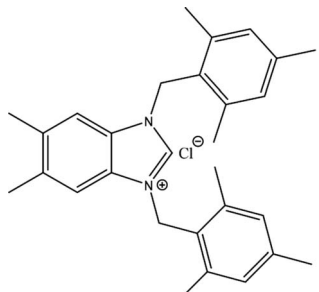
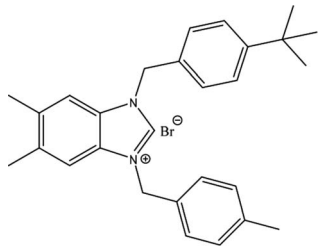
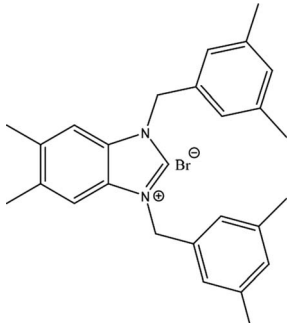
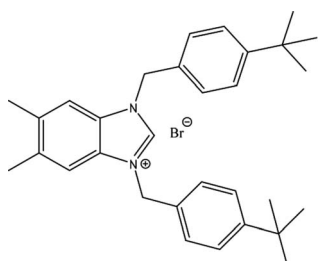
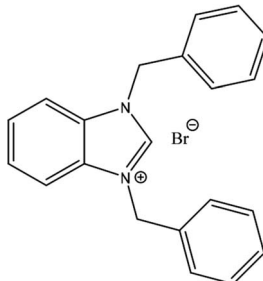
Entry	Benzimidazolium salt	Yield
5		21%
6		57%
7		45%
8		45%
9		53.0%



Table 1 (Contd.)

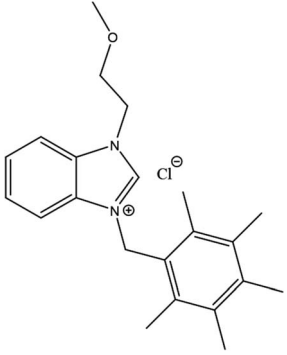
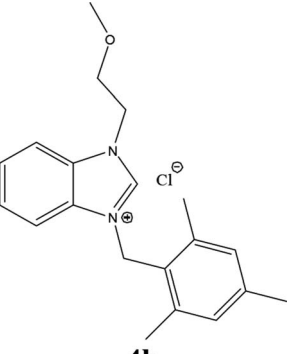
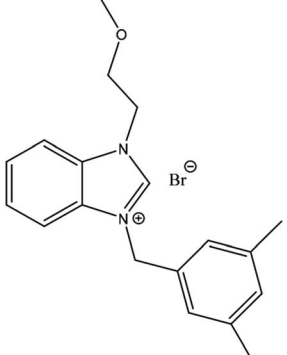
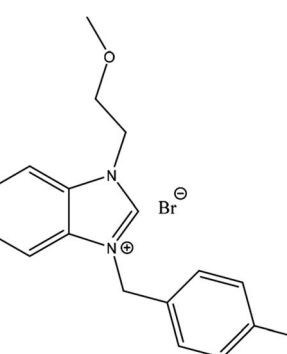
Entry	Benzimidazolium salt	Yield
10	 4a	54%
11	 4b	53%
12	 4c	57%
13	 4d	46%

Table 1 (Contd.)

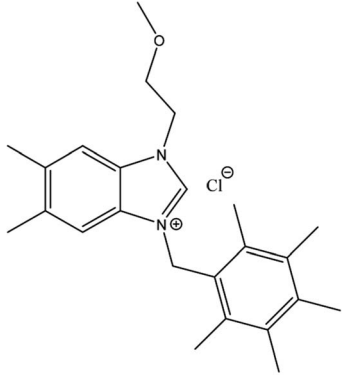
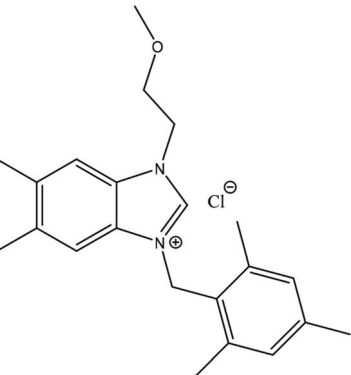
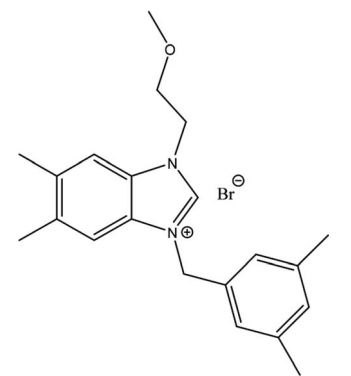
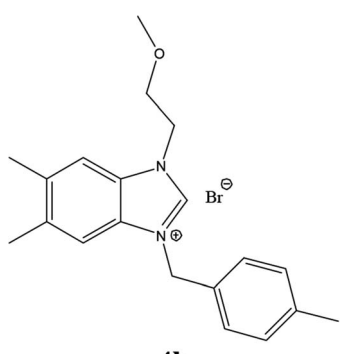
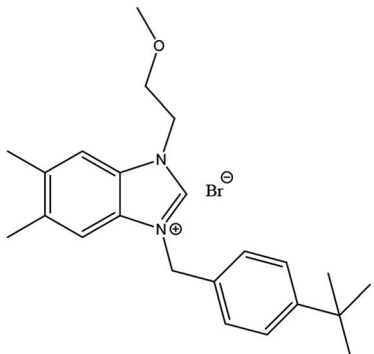
Entry	Benzimidazolium salt	Yield
14	 4e	27%
15	 4f	21%
16	 4g	57%
17	 4h	49%



Table 1 (Contd.)

Entry	Benzimidazolium salt	Yield
18	 4i	55%

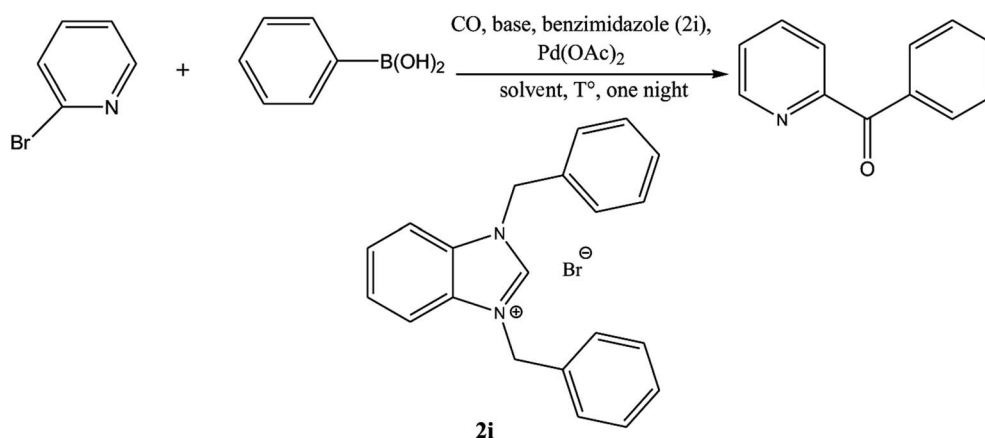
^a Conditions: 2-Br-Py (1 mmol), Pd(OAc)₂ (0.015 mmol), K₂CO₃ (2 mmol), ligand (0.03 mmol), PhB(OH)₂ (1.1 mmol), CO (20 bars), THF (10 mL), 100 °C, one night.

Next, the base-screening study was commenced. With the *t*-BuOK no reaction was observed (Table 2, entry 4). However, alkaline carbonates such as K₂CO₃ and CsCO₃ gave good yields (Table 2, entries 3 and 5). The impact of the reaction temperature for reaction efficiency was investigated. The best yield was obtained for a temperature of 110 °C (Table 2, entry 8). An increase of the temperature to 120 °C, caused a decrease in the yield to 41.11% (Table 2, entry 9) 110 °C was thus chosen as the optimal temperature for the rest of the study.

Various ligand concentrations were also investigated (Table 2, entries 10–12). Optimum ligand loading was found to be 5 mol% (Table 2, entry 10). The increase of the ligand concentration to 6 mol% has caused a slightly drop in the activity (Table 2, entry 12).

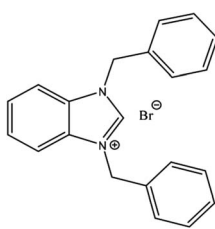
The coupling reaction being carried out under a flow of CO, the influence of this parameter on the yield of the reaction was studied. According to Table 1, low yields were obtained using low and very high carbon monoxide pressure (Table 1, entries 6 and 7) while the best yield was obtained using a pressure of 20 bar (Table 2, entry 3).

Based on these results, the optimized reaction conditions were determined to be as follows: 2-bromopyridine (1.0 mmol),



Scheme 4 Carbonylative cross-coupling reaction of 2-bromopyridine with phenylboronic acid.

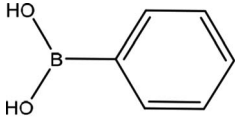
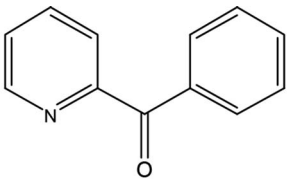
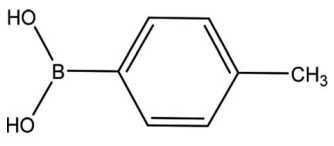
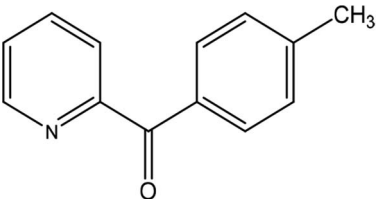
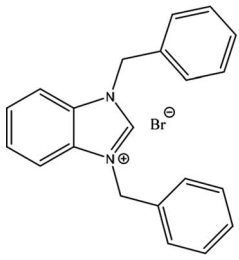
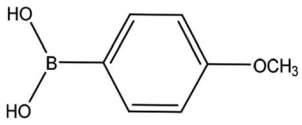
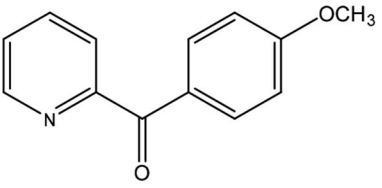
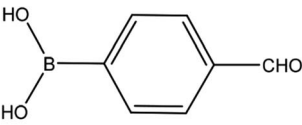
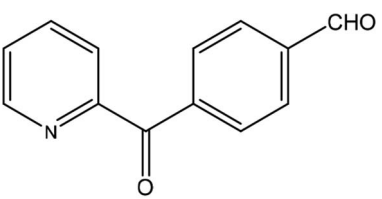
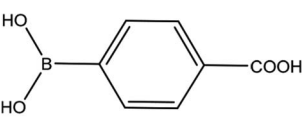
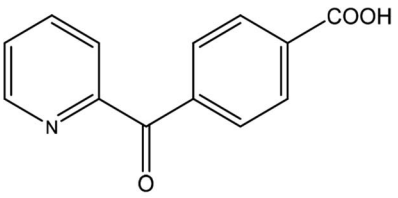
Table 2 Optimization of reaction conditions for the carbonylative cross-coupling reaction of 2-bromopyridine with phenyl boronic acid^a

Entry	Benzimidazolium salt	Ligand (mol%)	Base	Temperature	CO pressure (bar)	Solvent	Yield
1	 2i	3 mol%	K ₂ CO ₃	100 °C	20	DMF	—
2		3 mol%	K ₂ CO ₃	100 °C	20	1,4-Dioxane	42%
3		3 mol%	K ₂ CO ₃	100 °C	20	THF	53%
4		3 mol%	<i>t</i> -BuOK	100 °C	20	THF	—
5		3 mol%	Cs ₂ CO ₃	100 °C	20	THF	55%
6		3 mol%	K ₂ CO ₃	100 °C	10	THF	26%
7		3 mol%	K ₂ CO ₃	100 °C	40	THF	34%
8		3 mol%	K ₂ CO ₃	110 °C	20	THF	56%
9		3 mol%	K ₂ CO ₃	120 °C	20	THF	41%
10		5 mol%	K ₂ CO ₃	110 °C	20	THF	70%
11		5 mol%	K ₂ CO ₃	120 °C	20	THF	56%
12		6 mol%	K ₂ CO ₃	110 °C	20	THF	68%

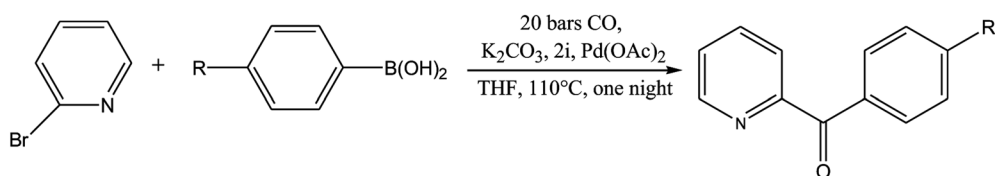
^a Conditions: 2-Br-Py (1 mmol), Pd(OAc)₂, base (2 mmol), **2i**, PhB(OH)₂ (1.1 mmol), CO, solvent (10 mL), T°, one night.



Table 3 Results of carbonylative cross-coupling reaction of 2-bromopyridine with different arylboronic acids^a

Entry	Benzimidazolium salt	Boronic acid	Carbonyl product	Yield
1		 phenylboronic acid	 phenyl(pyridin-2-yl)methanone	70%
2		 p-tolylboronic acid	 pyridin-2-yl(p-tolyl)methanone	51%
3	 2i	 (4-methoxyphenyl)boronic acid	 (4-methoxyphenyl)(pyridin-2-yl)-methanone	51%
4		 (4-formylphenyl)boronic acid	 4-picolinoylbenzaldehyde	10%
5		 4-boronobenzoic acid	 4-picolinoylbenzoic acid	Trace

^a Conditions: 2-Br-Py (1 mmol), Pd(OAc)₂ (0.025 mmol), K₂CO₃ (2 mmol), ligand (5 mol%), arylboronic acid (1.1 mmol), CO (20 bars), 110 °C, THF (10 mL), one night.

**Scheme 5** Carbonylative cross-coupling reaction of 2-bromopyridine with different arylboronic acids.

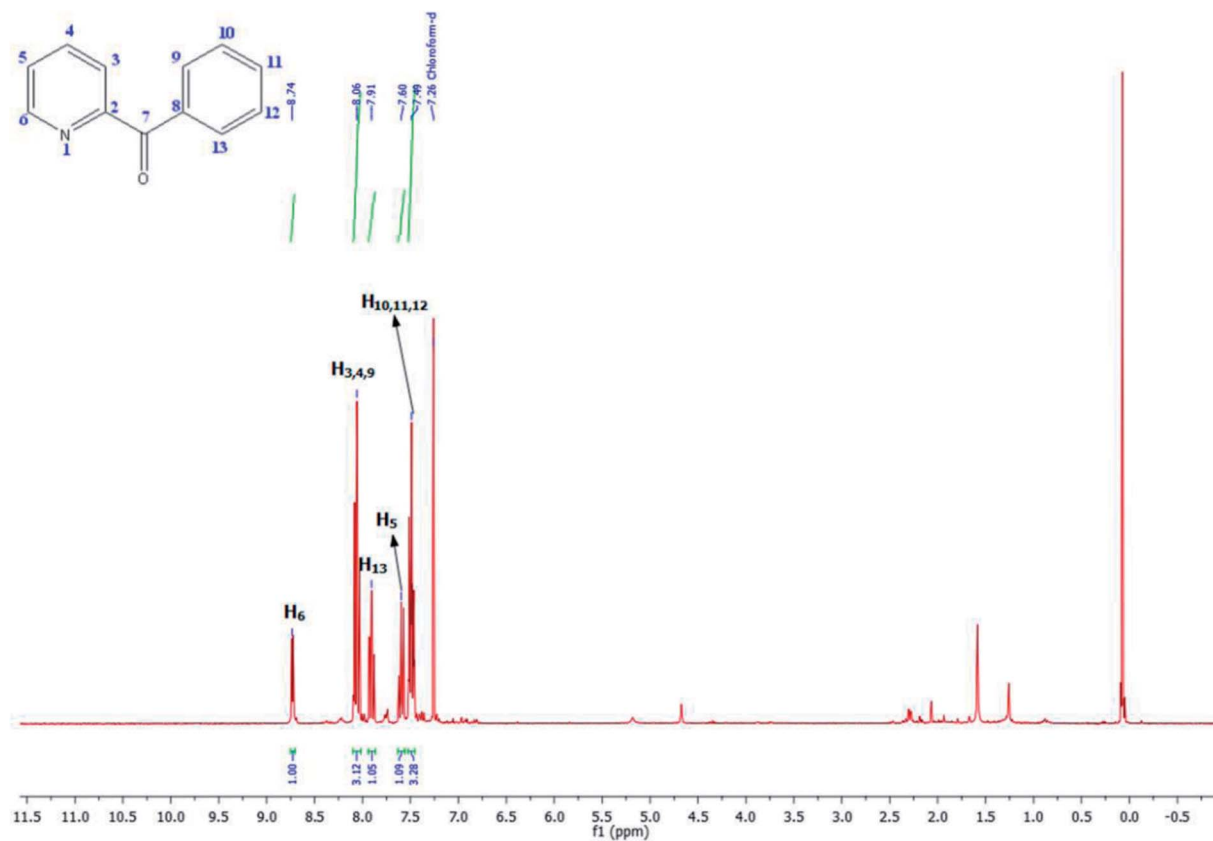


Fig. 3 ^1H NMR spectra of phenyl(pyridin-2-yl)methanone (CDCl_3 , 300 MHz).

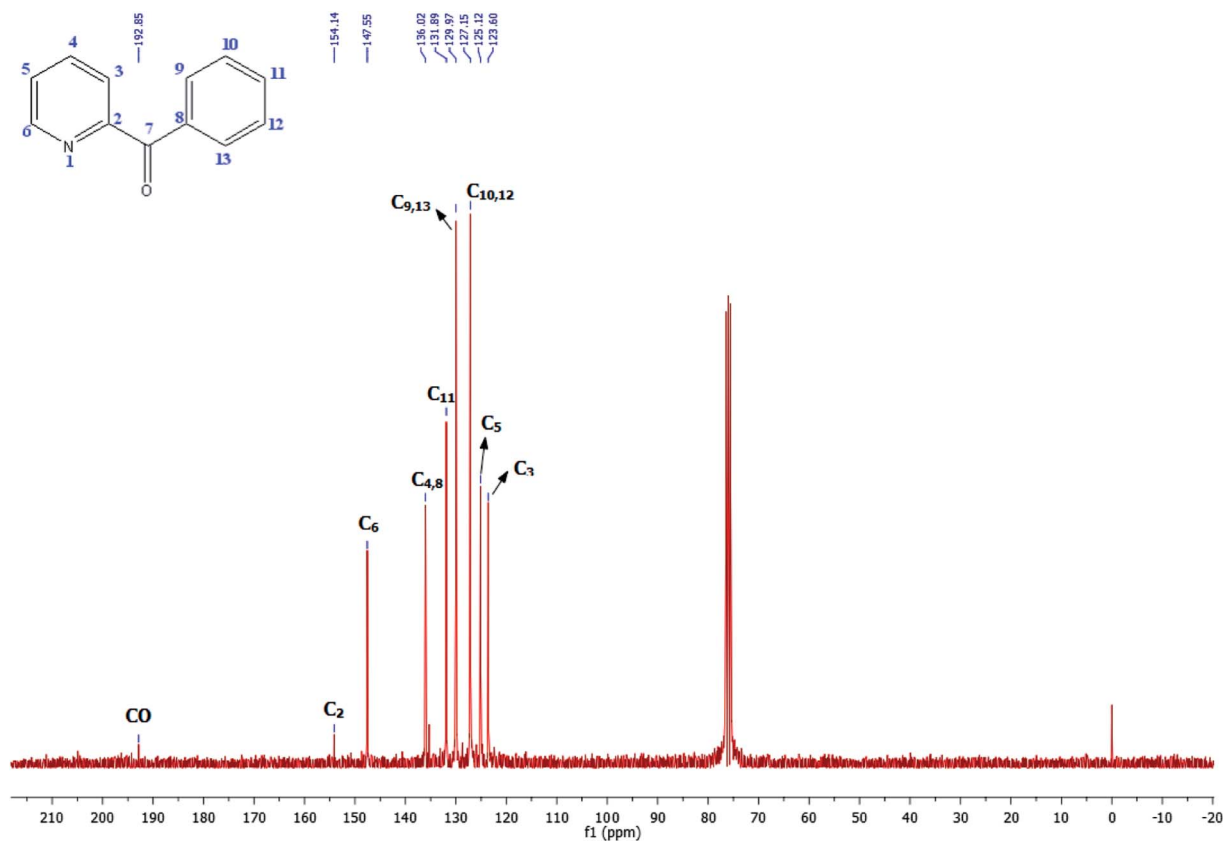


Fig. 4 ^{13}C NMR spectra of phenyl(pyridin-2-yl)methanone (CDCl_3 , 75 MHz).



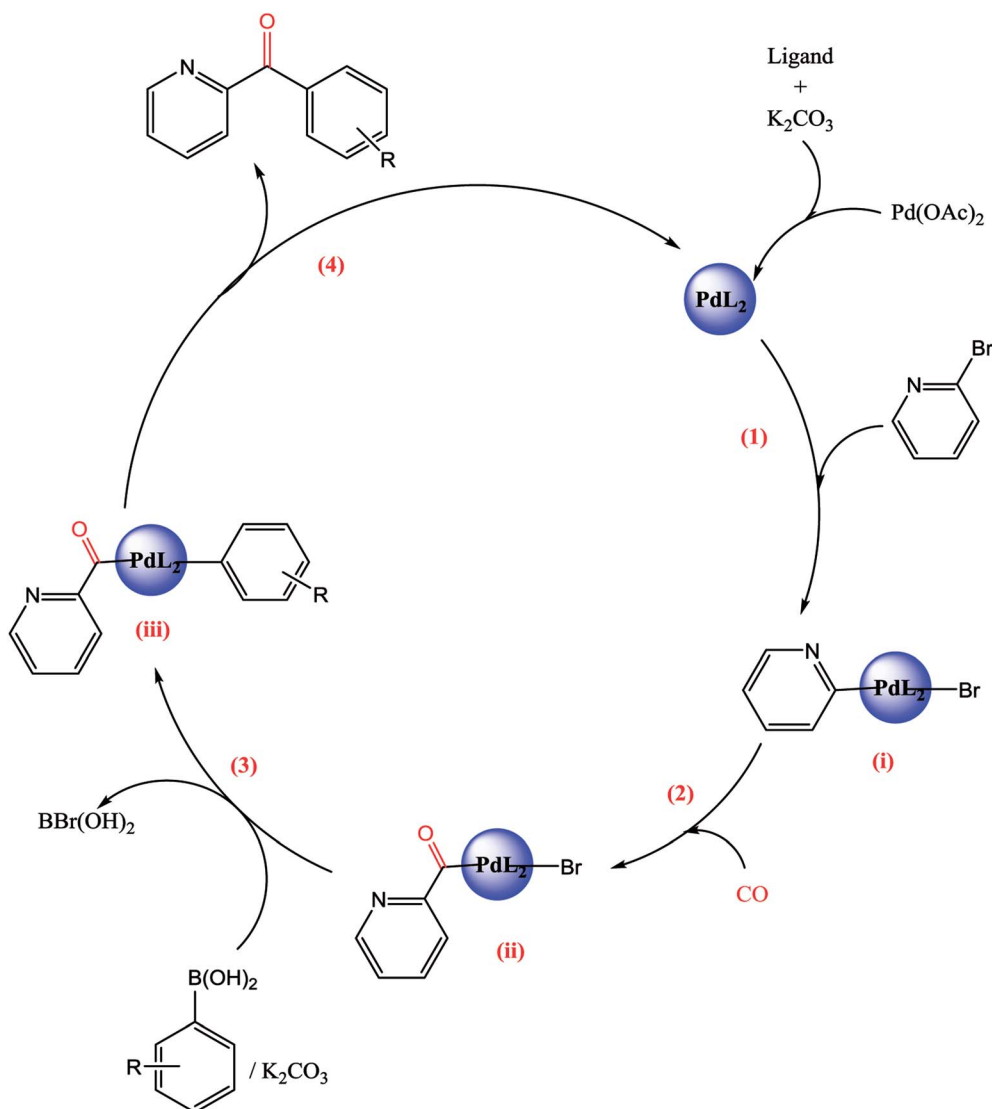
arylboronic acid (1.1 mmol), ligand (5 mol%) $\text{Pd}(\text{OAc})_2$ (0.025 mmol) and K_2CO_3 (2.0 mmol) in THF at 110 °C under CO atmosphere (20 bar).

In order to generalize this reaction, a range of arylboronic acids were subjected to the standard conditions (Table 3), regarding their electronic properties and steric effects these reactions were executed smoothly, giving the corresponding products in good yields (Scheme 5).

The results are summarized in Table 3.

As shown in Table 3, the yield of arylpyridine ketones was depending on the nature of the used arylboronic acid. The best result was obtained with phenylboronic acid giving carbonylated coupling product with a high yield of 70% (Table 3, entry 1). When we used *p*-tolylboronic acid and 4-carboxyphenylboronic acid, having a strong electrodonor effects, very similar results were obtained (Table 3, compare entries 2 and 3) and an important amount of by-product was found in the reaction

medium for the two reactions resulting from the deboronation of the corresponding boronic acid under basic conditions and high temperatures. Thus, the modest conversion obtained in this case was probably due to the lack of reagent. Other boronic acids with electron-withdrawing groups ($-\text{CHO}$, $-\text{COOH}$) were also tested on the carbonylative cross-coupling reaction of 2-bromopyridine with arylboronic acids. A low yield of 10% was obtained for the 4-formylphenylboronic acid (Table 3, entry 4) whereas, no carbonyl product was formed using 4-bromobenzoic acid only a small amount of direct coupling product (Table 3, entry 5) was detected. Thus, we can conclude that the differences in the activity for the arylboronic acids are presumably due to the difference in the electronic properties of the substituents. The chemical structures of unsymmetrical arylpyridine ketones were established using spectroscopic methods including FTIR, ^1H -NMR and ^{13}C -NMR. For example



Scheme 6 The fundamental steps involved in palladium-catalyzed carbonylative cross-coupling.



^1H -NMR spectra of phenyl(pyridin-2-yl)methanone revealed aromatic protons between 7.26 ppm and 8.74 ppm (Fig. 3).

Its ^{13}C -NMR spectrum of phenyl(pyridin-2-yl)methanone revealed $\text{C}=\text{O}$ at δ 192.8 ppm, aromatic carbons between 123.8 ppm and 154.1 ppm (Fig. 4).

3. Reaction mechanism for the carbonylative Suzuki–Miyaura coupling reaction

A plausible mechanism is given in the following Scheme 6.

The first step of the catalytic cycle consists of an oxidative addition of the halide on the palladium species leading to the formation of palladium pyridine complex. The next step is the insertion and coordination of CO to palladium pyridine complex. The step after insertion is transmetallation. The final step of the catalytic cycle is reductive elimination. This step proceeds through a three-centered transition state in order to form a new C–C bond between the electrophilic acyl group and the nucleophile leading to the formation of the expected unsymmetrical arylpyridine ketones.

In order to compare the efficiency of our catalysts (NHC–Pd complex) generated *in situ* from benzimidazolium salts **2** and **4** with literature further tests were established. The results are given in Table 4.

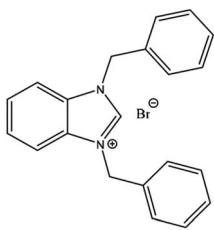
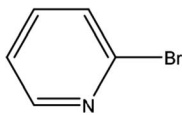
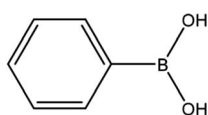
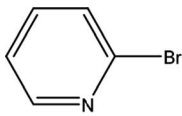
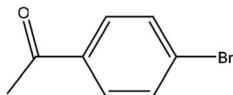
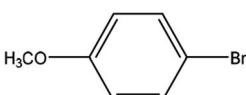
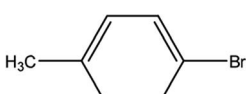
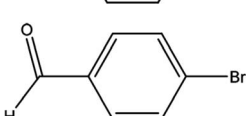
First, we thought that the obtained moderate yields are due to the lack of boronic acid in the medium caused by decomposition of boronic acid at high temperatures. In this way by increasing the amount of boronic acid the yields of the obtained products decrease (Table 4, entries 1 and 2) so we conclude that the lack of boronic acid not affect the yields. Then we tried to test benzimidazole salt **2i** with others aryl bromides used in Suzuki couplings. As shown in Table 4, using bromoacetophenone, bromoanisole and bromotoluene, only the direct coupling product was obtained (Table 4, entries 3–5). While in the case of bromobenzaldehyde low yields of carbonyl product and direct coupling product were obtained.

Previous researchers have reported induction periods for Suzuki reactions promoted by $\text{Pd}(\text{OAc})_2$ /imidazolium salts. It was proposed that during these induction periods $\text{Pd}(\text{II})/\text{NHC}$ complexes were formed and were then slowly reduced to catalytically active $\text{Pd}(\text{0})/\text{NHC}$ complexes.⁴³ It is important to note that these induction periods could be avoided with our present catalyst system.

4. Anticancer cytotoxic activity

The cytotoxic activity of the synthesized compounds **2a–i** and **4a–i** was tested *in vitro* against cancer human cell lines such as MDA-MB-231, MCF-7 and T47D.^{44,45} The results are summarized in Table 5.

Table 4 Tests for results comparison^a

Entry	Catalyst	Arylbromide	Arylboronic acid	Direct coupling yield	Carbonylative coupling yield
1	 2i			4.8%	69.9%
2 ^b				3.9%	27.7%
3				20.2%	—
4				4.1%	—
5				3.7%	—
6				17.7%	35.17%

^a Conditions: 2-Br-Py (1 mmol), $\text{Pd}(\text{OAc})_2$ (0.025 mmol), K_2CO_3 (2 mmol), ligand (5 mol%), $\text{PhB}(\text{OH})_2$ (1.1 mmol), CO (20 bars), 110 °C, THF (10 mL), one night. ^b $\text{PhB}(\text{OH})_2$ (1.5 mmol).



Table 5 Cytotoxic activity (IC₅₀, in $\mu\text{g mL}^{-1}$)^a of compounds 2a–i

Benzimidazoles salts 2	MDA-MB-231	MCF-7	T47D
2a	18 ± 4	17 ± 2	20 ± 4
2b	19.37 ± 0.85	18.36 ± 0.85	20.38 ± 0.85
2c	8.45 ± 3	10.55 ± 3	11.55 ± 5.75
2d	10.75 ± 2	10.75 ± 2	10.75 ± 2
2e	5.95 ± 1	4.85 ± 1	14.96 ± 1
2f	4.45 ± 0.95	8.08 ± 0.95	14.42 ± 0.95
2g	19.30 ± 2	20.35 ± 2	25.32 ± 1
2h	20.25 ± 1	20.25 ± 2	20.25 ± 3.10
2i	18.45 ± 2	16.42 ± 2	22.43 ± 2
4a	16 ± 4	15 ± 2	18 ± 4
4b	18 ± 0.85	17 ± 0.85	19 ± 0.85
4c	9.23 ± 2	13.55 ± 3	14.55 ± 4
4d	14.75 ± 3	15.75 ± 2	13.75 ± 2
4e	7.95 ± 1	6.85 ± 1	13.96 ± 1
4f	7.45 ± 0.95	10.08 ± 0.95	15.42 ± 0.95
4g	18.30 ± 2	22.35 ± 2	25.32 ± 1
4h	20.25 ± 1	20.25 ± 2	24.25 ± 2
4i	19.45 ± 2	17.42 ± 2	23.43 ± 3

^a The IC₅₀ values represent an average of three independent experiments (mean ± SD).

All synthesized compounds showed good cytotoxic activity against MDA-MB-231, MCF-7 and T47D cell lines. The most actives compounds are 2e and 2f against MDA-MB-231 and MCF-7.

5. Conclusion

In conclusion, two families of benzimidazolium salts 2a–i and 4a–i have been prepared and characterized. We have demonstrated that carbonylative cross-coupling reaction of arylboronic acids with 2-bromopyridine is a versatile route to prepare unsymmetrical arylpyridine ketones in the presence of a catalyst formed *in situ* from Pd(OAc)₂ and K₂CO₃. The efficiency of the reaction was especially related to the nature of the arylboronic acid. The cytotoxic activity of the compounds (2–4) were also determined against a panel of cell lines such as MDA-MB-231, MCF-7 and T47D. The most actives compounds are 2e, 2f, 4e and 4f against MDA-MB-231 and MCF-7.

6. Experimental section

6.1 General information

All manipulations were performed using Standard Schlenck techniques under Argon atmosphere. Chemicals were purchased from Sigma Aldrich and used without further purification. All solvents were purified and dried by MBraun SPS 800 solvent purification system. Column chromatography was performed using silica gel 60 (70–230 mesh). NMR spectra were recorded at 300 and 400 MHz for ¹H NMR and 75 and 100 MHz for ¹³C NMR. Chemical shifts, δ , are reported in ppm relative to the internal standard TMS for both ¹H and ¹³C NMR. The products were characterized by GC (gas chromatography). Quantitative GC analyses were performed gas chromatography (CHROMPACK CP-9002, ENSCL, France). The NMR studies were

carried out in high-quality 5 mm NMR tubes. Signals are quoted in parts per million as δ downfield from tetramethylsilane (δ = 0.00) as an internal standard. NMR multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, m = multiplet signal. IR spectra were recorded on a 398 spectrophotometer (Perkin-Elmer, Malatya University, Turkey). Melting points were determined with Stuart automatic melting point apparatus (SMP-40) at Malatya University, Turkey.

6.2 Synthesis of compounds 1a–g and benzimidazoles 2a–i

Compounds 1a–f were synthesized according to our previous works.^{36,39}

5,6-Dimethyl-1-(2,3,4,5,6-pentamethylbenzyl)-1H-benzo[d]imidazole (1a). Rdt 97%, C₂₁H₂₆N₂, M = 306.5 g mol⁻¹, p.f 173 °C. $\nu(\text{CN})$ = 1448.65 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 2.11 (s, 6H, CH₃(c,g)), 2.19 (s, 6H, CH₃(d,f)), 2.23 (s, 3H, CH₃(e)), 2.32 (s, 3H, CH₃(a)), 2.37 (s, 3H, CH₃(b)), 5.16 (s, 2H, CH₂(1')), 7.20 (s, 1H, Harom(7)), 7.24 (s, 1H, Harom(4)), 7.30 (s, 1H, H2). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 16.51 (C(c,g)), 16.87 (C(d,f)), 17.16 (C(e)), 20.33 (C(a)), 20.66 (C(b)), 44.27 (C1'), 109.77 (C7), 120.29 (C4), 127.37(C5,8), 131.21 (C4',5',6'), 131.97 (C6), 133.38 (C3',7'), 133.56 (C9), 136.13 (C2'), 141.10 (C2).

1-(2,3,4,5,6-Pentamethylbenzyl)-1H-benzo[d]imidazole (1b). Rdt 95%, C₁₉H₂₂N₂, M = 278.4 g mol⁻¹, p.f 121 °C. $\nu(\text{CN})$ = 1454.84 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 2.21 (s, 6H, CH₃(a,e)), 2.27 (s, 6H, CH₃(b,d)), 2.31 (s, 3H, CH₃(c)), 5.31 (s, 2H, CH₂(1')), 7.35 (t, 2H, Harom(5,6)), 7.43 (s, 1H, Harom(7)), 7.56 (s, 1H, Harom(4)), 7.85 (s, 1H, H2). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 16.55 (C(a,e)), 16.89 (C(b,d)), 17.19 (C(c)), 44.42 (C1'), 109.77 (C7), 120.29 (C4), 122.37 (C5), 122.87 (C6), 127.12 (C8,9), 133.47 (C4',5',6'), 133.55 (C3',7'), 136.28 (C2'), 141.96 (C2).

1-(4-(tert-Butyl)benzyl)-1H-benzo[d]imidazole (1c). Rdt 92%, C₁₈H₂₀N₂, M = 264.4 g mol⁻¹, p.f 123.6 °C. $\nu(\text{CN})$ = 1457.59 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 1.22 (s, 9H, CH₃(a,b,c)), 5.25 (s, 2H, CH₂(1')), 7.06 (d, 2H, Harom(3',7')), 7.20 (d, 2H, Harom(5,6)), 7.29 (d, 3H, Harom(4',6',7')), 7.77 (s, 1H, Harom(4)), 7.88 (s, 1H, H2). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 31.28 (C(a,b,c)), 34.60 (C8'), 48.53 (C1'), 110.08 (C7), 120.39 (C4), 122.25 (C5), 123.06 (C6), 125.97 (C4',6'), 126.92 (C3',7'), 132.46 (C2',8), 143.20 (C2,9), 151.40 (C5').

5,6-Dimethyl-1-(2,4,6-trimethylbenzyl)-1H-benzo[d]imidazole (1d). Rdt 94%, C₁₉H₂₂N₂, M = 278.4 g mol⁻¹, p.f 292.3 °C. $\nu(\text{CN})$ = 1497.89 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 2.16 (s, 6H, CH₃(c,e)), 2.25 (s, 3H, CH₃(d)), 2.31 (s, 3H, CH₃(a)), 2.35 (s, 3H, CH₃(b)), 5.11 (s, 2H, CH₂(1')), 6.88 (s, 2H, Harom(4',6')), 7.17 (s, 1H, Harom(7)), 7.22 (s, 1H, Harom(4)), 7.49 (s, 1H, H2). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 18.52 (CH₃(c,e)), 19.26 (C(d)), 19.62 (C(a)), 20.01 (C(b)), 41.99 (C1'), 108.74 (C7), 119.23 (C4), 126.29 (C5), 128.59 (C4',6'), 130.19 (C8), 131.02 (C6), 136.83 (C5',9), 137.70 (C3',7'), 139.86 (C2'), 141.47 (C2).

1-(3,5-Dimethylbenzyl)-5,6-dimethyl-1H-benzo[d]imidazole (1e). Rdt 93%, C₁₈H₂₀N₂, M = 264.4 g mol⁻¹, p.f 124.3 °C. $\nu(\text{CN})$ = 1446.05 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 2.18 (s, 6H, CH₃(c,d)), 2.27 (s, 3H, CH₃(a)), 2.29 (s, 3H, CH₃(b)), 5.13 (s, 2H, CH₂(1')), 6.70 (s, 2H, Harom(3',7')), 6.85 (s, 1H, Harom(5')), 7.01 (s,



1H, Harom(7)), 7.51 (s, 1H, Harom(4)), 7.75 (s, 1H, H₂). ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 20.28 (C(a)), 20.61 (C(b)), 21.26 (C(c,d)), 48.62 (C(1')), 110.14 (C4), 120.26 (C7), 124.8 (C3',5',7'), 129.78 (C5), 133.11 (C8), 133.22 (C6), 135.70 (C9,2'), 138.65 (C4',6'), 142.46 (C2).

1-(4-(tert-Butyl)benzyl)-5,6-dimethyl-1H-benzo[d]imidazole (1f). Rdt 92%, C₂₀H₂₄N₂, *M* = 292.4 g mol⁻¹, p.f 121 °C. ν(CN) = 1493.72 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 1.21 (s, 9H, CH₃(c,d,e)), 2.26 (s, 3H, CH₃(a)), 2.28 (s, 3H, CH₃(b)), 5.19 (s, 2H, CH₂(1')), 7.08 (s, 3H, Harom(7,3',7')), 7.27 (s, 2H, Harom(4',6')), 7.51 (s, 1H, Harom(4)), 7.76 (s, 1H, H₂). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 20.28 (C(a)), 20.60 (C(b)), 31.29 (C(c,d,e)), 34.58 (C8'), 48.38 (C1'), 110.16 (C7), 120.31 (C4), 125.92 (C4',6'), 126.78 (C3',7'), 131.17 (C8,9), 132.25 (C5,6), 132.80 (C2'), 142.45 (C2), 151.22 (C5').

1-Benzyl-1H-benzo[d]imidazole (1g). Rdt 94%, C₁₄H₁₂N₂, *M* = 208.3 g mol⁻¹, p.f 105 °C. ν(CN) = 1472.09 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 5.27 (s, 2H, H1'), 7.09–7.26 (m, 8H, Harom), 7.74 (s, 1H, H4), 7.88 (s, 1H, H2). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 48.90 (C1'), 110.07 (C7), 120.47 (C4), 122.31 (C5,6), 123.13 (C5'), 127.13 (C3',7'), 128.30 (C4',6'), 129.07 (C8), 135.49 (C2'), 144.05 (C2).

Benzimidazoles **2a–h** were synthesized according to the literature^{36,37}

5,6-Dimethyl-1,3-bis(2,3,4,5,6-pentamethylbenzyl)-1H-benzo[d]imidazol-3-ium chloride (2a). Rdt 96%, C₃₃H₄₃N₂Cl, *M* = 503.2 g mol⁻¹, p.f 307.7 °C. ν(CN) = 1440.99 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 2.22 (s, 30H, CH₃), 2.28 (s, 6H, CH₃(a,b)), 5.8 (s, 4H, CH₂(1',1'')), 7.11 (s, 2H, Harom(4,7)), 9.85 (s, 1H, H2). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 17.01 (C(c,g,c',g')), 17.01 (C(d,f,d',f')), 17.28 (C(e,e')), 20.77 (C(a,b)), 48.10 (C1';1''), 113.41 (C4;7), 125.58 (C8;9), 130.42 (C4';5';6';4'';5'';6''), 133.50 (C3';7';3'';7''), 133.74 (C5;6), 136.88 (C2';2''), 141.35 (C2).

1,3-Bis(2,3,4,5,6-pentamethylbenzyl)-1H-benzo[d]imidazol-3-ium chloride (2b). Rdt 92%, C₃₁H₃₉N₂Cl, *M* = 475.1 g mol⁻¹, p.f. 210.6 °C. ν(CN) = 1553.91 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 2.15 (s, 12H, CH₃(a,e,a',e')), 2.18 (s, 12H, CH₃(b,d,b',d')), 2.20 (s, 6H, CH₃(c,c')), 5.84 (s, 4H, CH₂), 7.2 (d, 2H, Harom(5,6)), 7.34 (d, 2H, Harom(4,7)), 10.34 (s, 1H, H2). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 16.95 (C(a,e,a',e')), 17.06 (C(b,d,b',d')), 17.30 (C(c,c')), 48.58 (C1';1''), 113.72 (C4;7), 125.36 (C5;6), 126.88 (C8;9), 131.85 (C5';5''), 133.49 (C4';6';4'';6''), 133.82 (C3';7';3'';7''), 137.07 (C2';2''), 143.0 (C2).

1,3-Bis(4-(tert-butyl)benzyl)-1H-benzo[d]imidazol-3-ium bromide (2c). Rdt 89%, C₂₉H₃₅N₂Br, *M* = 491.5 g mol⁻¹, p.f 296.5 °C. ν(CN) = 1562.86 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 1.2 (s, 18H, CH₃), 5.75 (s, 4H, CH₂), 7.33 (d, 4H, Harom(4',6',4'',6'')), 7.39 (d, 4H, Harom(3';7'3'',7'')), 7.46 (d, 2H, Harom(5;6)), 7.55 (d, 2H, Harom(4;7)), 11.83 (s, 1H, H2). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 31.18 (CH₃), 34.67 (C8';8''), 51.27 (C1';1''), 113.78 (C4;7), 126.34 (C4';6';4'';6''), 127.09 (C5;6), 128.17 (C3';7';3'';7''), 129.56 (C8;9), 131.41 (C2';2''), 143.0 (C2), 152.46 (C5';5'').

5,6-Dimethyl-1-(2,3,4,5,6-pentamethylbenzyl)-3-(2,4,6-trimethylbenzyl)-1H-benzo[d]imidazol-3-ium chloride (2d). Rdt 94%, C₃₁H₃₉N₂Cl, *M* = 475.1 g mol⁻¹, p.f 272.2 °C. ν(CN) = 1567.83 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 2.17 (s, 6H,

CH₃(a,b)), 2.21 (s, 24H, CH₃), 5.68 (s, 2H, CH₂(1')), 5.80 (s, 2H, CH₂(1'')), 6.83 (s, 2H, Harom(4'';6'')), 7.04 (s, 1H, Harom(4)), 7.20 (s, 1H, Harom(7)), 10.41 (s, 1H, H₂). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 16.96 (C(d,f)), 17.09 (C(c,g)), 17.30 (C(e)), 20.17 (C(a,b)), 20.75 (C(h,j)), 21.03 (C(i)), 47.46 (C1'), 47.82 (C1''), 113.09 (C7), 113.54 (C4), 125.19 (C8), 125.75 (C9), 129.96 (C4'';6''), 130.3 (C5'), 133.52 (C4';6'), 133.92 (C3';7'), 136.83 (C5''), 136.90 (C2''), 137.15 (C3'';7''), 137.88 (C5;6), 139.32 (C2'), 142.17 (C2).

5,6-Dimethyl-1,3-bis(2,4,6-trimethylbenzyl)-1H-benzo[d]imidazol-3-ium chloride (2e). Rdt 96%, C₂₉H₃₅N₂Cl, *M* = 447.1 g mol⁻¹, p.f 245.6 °C. ν(CN) = 1567.86 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 2.23 (s, 6H, CH₃(a,b)), 2.29 (s, 18H, CH₃), 5.79 (s, 4H, CH₂(1',1'')), 6.91 (s, 6H, Harom), 10.92 (s, 1H, H2). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 20.21 (C(c,e,c',e')), 20.74 (C(a,b)), 21.06 (C(d,d')), 47.23 (C1';1''), 113.29 (C4;7), 125.4 (C8;9), 130.07 (C4';6';4'';6''), 130.25 (C5';5''), 136.88 (C2';2''), 137.91 (C3';7';3'';7''), 139.56 (C5;6), 142.7 (C2).

1-(4-(tert-Butyl)benzyl)-5,6-dimethyl-3-(4-methylbenzyl)-1H-benzo[d]imidazol-3-ium bromide (2f). Rdt 91%, C₂₈H₃₃N₂Br, *M* = 477.5 g mol⁻¹, p.f 230.9 °C. ν(CN) = 1561.62 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 1.2 (s, 9H, CH₃(c,d,e)), 2.24 (s, 3H, CH₃(f)), 2.27 (s, 6H, CH₃(a,b)), 5.68 (s, 4H, CH₂(1',1'')), 7.1 (s, 2H, Harom(4,7)), 7.17–7.41 (m, 8H, Harom), 11.51 (s, 1H, H2). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 20.69 (C(a,b)), 21.19 (C(f)), 31.19 (C(c,d,e)), 34.66 (C8'), 50.94 (C1'), 51.13 (C1''), 113.32 (C4;7), 126.28 (C4';6'), 127.98 (C8;9), 128.20 (C3';7'), 129.99 (C3'';4'';6'';7''), 137.32 (C2';2''), 139.12 (C5;6), 141.69 (C2), 152.29 (C5';5'').

1,3-Bis(3,5-dimethylbenzyl)-5,6-dimethyl-1H-benzo[d]imidazol-3-ium bromide (2g). Rdt 91%, C₂₇H₃₁N₂Br, *M* = 463.5 g mol⁻¹, p.f 246.4 °C. ν(CN) = 1562.47 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 2.21 (s, 12H, CH₃), 2.27 (s, 6H, CH₃(a,b)), 5.65 (s, 4H, CH₂), 6.89 (s, 2H, Harom(5',5'')), 6.96 (s, 4H, Harom(3',7',3'',7'')), 7.22 (s, 2H, Harom(4,7)), 11.42 (s, 1H, H2). ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 20.72 (C(a,b)), 21.24 (C(d,e,d',e')), 51.26 (C1';1''), 113.31 (C4;7), 125.66 (C3';7';3'';7''), 129.97 (C5';5''), 130.8 (C8;9), 132.68 (C2';2''), 137.32 (C5;6), 139.06 (C4';6';4'';6''), 141.8 (C2).

1,3-Bis(4-(tert-butyl)benzyl)-5,6-dimethyl-1H-benzo[d]imidazol-3-ium bromide (2h). Rdt 91%, C₃₁H₃₉N₂Br, *M* = 519.6 g mol⁻¹, p.f 277.1 °C. ν(CN) = 1558.18 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 1.3 (s, 18H, CH₃), 2.37 (s, 6H, CH₃(a,b)), 5.77 (s, 4H, H1',1''), 7.29–7.50 (m, 10H, Harom), 11.63 (s, 1H, H2). ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 20.9 (C(a,b)), 31.2 (C(c,d,e,c',d',e')), 34.76 (C8';8''), 50.93 (C1';1''), 113.26 (C4;7), 126.32 (C4';6';4'';6''), 127.99 (C3';7';3'';7''), 129.78 (C8;9), 129.96 (C5;6), 137.32 (C2';2''), 141.83 (C2), 152.37 (C5';5'').

1,3-Dibenzyl-1H-benzo[d]imidazol-3-ium bromide (2i). Rdt 95%, C₂₁H₁₉N₂Br, *M* = 379.3 g mol⁻¹, p.f 150 °C. ν(CN) = 1559.02 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ (ppm) 5.87 (s, 4H, CH₂(1',1'')), 7.26–7.55 (m, 14H, Harom), 11.47 (s, 1H, H2). ¹³C NMR (CDCl₃, 75 MHz) δ (ppm) 51.61 (C1';1''), 113.79 (C4;7), 127.21 (C5';5''), 128.36 (C5;6), 129.34 (C8;9), 129.45 (Carom), 131.38 (C2';2''), 132.52 (C2).



6.3 Compounds 3a-b and benzimidazoles 4a-i were synthesized according to our previous works³⁸

1-(2-Methoxyethyl)-1H-benzo[d]imidazole (3a). Rdt: 94%, $C_{10}H_{12}N_2O$, $M = 176.22 \text{ g mol}^{-1}$, $\nu(\text{CN}) = 1446.43 \text{ cm}^{-1}$, $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ (ppm) 3.23 (s, 3H, $\text{CH}_3(4')$), 3.63 (s, 2H, H_2'), 4.24 (s, 2H, H_1'), 7.20 (s, 1H, H_7), 7.35 (s, 1H, H_5), 7.60 (s, 1H, H_6), 7.73 (s, 1H, H_4), 7.92 (s, 1H, H_2). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ (ppm) = 45.03 (C_1'), 59.07 ($\text{CH}_3(4')$), 70.68 (C_2'), 109.64 ($\text{C}_4,7$), 120.17 (C_5), 122.23 ($\text{C}_5,6$), 122.52, 123.0 ($\text{C}_8,9$), 143.63 (C_2).

1-(2-Methoxyethyl)-5,6-dimethyl-1H-benzo[d]imidazole (3b). Rdt: 98%, $C_{12}H_{16}N_2O$, $M = 204.27 \text{ g mol}^{-1}$, p.f. 218.2°C , $\nu(\text{CN}) = 1434.30 \text{ cm}^{-1}$, $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ (ppm) 2.29, (s, 3H, ($\text{CH}_3(a)$)), 2.31 (s, 3H, $\text{CH}_3(b)$), 3.21 (s, 3H, $\text{CH}_3(4')$), 3.60 (s, 2H, H_2'), 4.17 (s, 2H, H_1'), 7.08 (s, 1H, H_7), 7.48 (s, 1H, H_4), 7.77 (s, 1H, H_2). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ (ppm) = 19.19 ($\text{C}(a)$), 19.55 ($\text{C}(b)$), 43.87 (C_1'), 58.0 ($\text{CH}_3(4')$), 69.71 (C_2'), 108.65 ($\text{C}_4,7$), 119.26 ($\text{C}_5,6$), 129.85 (C_8), 130.92 (C_9), 141.87 (C_2).

6.4 Synthesis of benzimidazoles (4a-i)

A mixture of benzimidazolium salt (**3a-b**) (1 g) and the corresponding benzyl bromide or chloride (1 eq.) in DMF (2 mL) was stirred at 70°C for 2–3 days. After that time, the white solid formed was washed with diethyl ether (20 mL) and stirred for couple hours. Then the reaction mixture was filtered through filter paper and the white solid was dried under vacuum.

1-Methoxyethyl-3-(2,3,4,5,6-pentamethylbenzyl)benzimidazolium chloride (4a). Rdt: 93%, $C_{22}H_{29}N_2\text{OCl}$, $M = 372.94 \text{ g mol}^{-1}$, p.f. 199.1°C , $\nu(\text{CN}) = 1557.72 \text{ cm}^{-1}$. $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ (ppm) = 2.23 (s, 6H, $\text{CH}_3(a,e)$), 2.26 (s, 9H, $\text{CH}_3(b,c,d)$), 3.27 (s, 3H, $\text{CH}_3(4')$), 3.86 (t, 2H, H_2'), 4.94 (t, 2H, H_1'), 5.76 (s, 2H, H_1''), 7.39 (d, 1H, H_7), 7.48 (t, 1H, H_6), 7.57 (t, 1H, H_5), 7.88 (d, 1H, H_4), 10.96 (s, 1H, H_2). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ (ppm) = 17.00 ($\text{C}(a,e)$), 17.06 ($\text{C}(b,d)$), 17.34 ($\text{C}(c)$), 47.89 (C_1'), 47.93 (C_1''), 58.95 ($\text{CH}_3(4')$), 70.50 (C_1'), 113.11 (C_7), 114.33 (C_4), 124.75 (C_5), 126.97 (C_6), 131.19 (C_8), 132.47 (C_9), 133.58 ($\text{C}_3'',5'',7''$), 134.01 ($\text{C}_4'',6''$), 137.42 (C_2''), 142.98 (C_2).

1-Methoxyethyl-3-(2,4,6-trimethylbenzyl)benzimidazolium chloride (4b). Rdt: 96%, $C_{20}H_{25}N_2\text{OCl}$, $M = 344.88 \text{ g mol}^{-1}$, p.f. 246.7°C , $\nu(\text{CN}) = 1555.39 \text{ cm}^{-1}$. $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ (ppm) = 2.30 (s, 3H, $\text{CH}_3(b)$), 2.33 (s, 6H, $\text{CH}_3(a,c)$), 3.32 (s, 3H, $\text{CH}_3(4')$), 3.92 (t, 2H, H_2'), 4.91 (t, 2H, H_1'), 5.83 (s, 2H, H_1''), 6.94 (s, 2H, $\text{H}_4'',6''$), 7.29 (d, 1H, H_7), 7.46 (t, 1H, H_6), 7.57 (t, 1H, H_5), 7.87 (d, 1H, H_4), 11.06 (s, 1H, H_2). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ (ppm) = 20.17 ($\text{C}(a,c)$), 21.08 ($\text{CH}_3(b)$), 47.14 (C_1'), 47.76 (C_1''), 59.00 (C_4'), 70.28 (C_2'), 113.35 (C_7), 114.11 (C_4), 125.02 (C_5), 127.04 (C_6), 13.21 ($\text{C}_4'',6''$), 131.6 (C_8), 132.31 (C_9), 137.97 ($\text{C}_3'',5'',7''$), 139.78 (C_2''), 143.67 (C_2).

1-Methoxyethyl-3-(3,5-dimethylbenzyl)benzimidazolium bromide (4c). Rdt: 92%, $C_{19}H_{23}N_2\text{OBr}$, $M = 375.31 \text{ g mol}^{-1}$, p.f. = 311.1°C . $\nu(\text{CN}) = 1560.26 \text{ cm}^{-1}$. $^1\text{H NMR}$ (CDCl_3 , 400 MHz, δ , ppm): 2.28 (s, 6H, $\text{CH}_3(a,b)$), 3.36 (s, 3H, $\text{CH}_3(4')$), 3.98 (t, 2H, H_2'), 4.89 (t, 2H, H_1'), 5.73 (s, 2H, H_1''), 6.96 (s, 1H, H_5''), 7.06 (s, 2H, $\text{H}_3'',7''$), 7.55 (m, 3H, $\text{H}_5,6,7$), 7.82 (d, 1H, H_4), 11.40 (s, 1H, H_2). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz, δ , ppm) 21.3 ($\text{C}(b,d)$), 47.9 (C_1'), 51.7 (C_1''), 59.2 (C_4'), 70.5 (C_2'), 113.5 (C_7), 114.1 (C_4), 126.1

($\text{C}_3'',5'',7''$), 127.0 (C_5), 127.1 (C_6), 131.0 (C_8), 131.0 (C_9), 132.3 (C_2''), 139.2 ($\text{C}_4'',6''$), 142.6 (C_2).

1-Methoxyethyl-3-(4-methylbenzyl)benzimidazolium chloride (4d). Rdt: 90%, $C_{18}H_{21}N_2\text{OBr}$, $M = 361.28 \text{ g mol}^{-1}$, p.f. 302.5°C . $\nu(\text{CN}) = 1557.32 \text{ cm}^{-1}$. $^1\text{H NMR}$ (CDCl_3 , 400 MHz, δ , ppm): 2.29 (s, 3H, $\text{CH}_3(a)$), 3.35 (s, 3H, $\text{CH}_3(4')$), 3.95 (t, 2H, H_2'), 4.87 (t, 2H, H_1'), 5.83 (s, 2H, H_1''), 7.10 (s, 2H, $\text{H}_3'',7''$), 7.29 (d, 2H, $\text{H}_4'',6''$), 7.52 (d, 1H, H_7), 7.58 (d, 1H, H_6), 7.61 (d, 1H, H_5), 7.86 (d, 1H, H_4), 11.24 (s, 1H, H_2). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz, δ , ppm): 21.2 ($\text{C}(a)$), 47.9 (C_1'), 51.3 (C_1''), 59.1 (C_4'), 70.1 (C_2'), 113.6 (C_7), 114.1 (C_4), 127.1 ($\text{C}_5,6$), 128.4 ($\text{C}_3'',4'',6'',7''$), 129.9 (C_8), 130.9 (C_9), 132.2 (C_2''), 139.3 (C_5''), 142.98 (C_2).

1-Methoxyethyl-3-(2,3,4,5,6-pentamethylbenzyl)-5,6-dimethylbenzimidazolium chloride (4e). Rdt: 97%, $C_{24}H_{33}N_2\text{OBr}$, $M = 400.99 \text{ g mol}^{-1}$, p.f. 132.3°C . $\nu(\text{CN}) = 1558.00 \text{ cm}^{-1}$. $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ (ppm) = 2.19 (s, 6H, $\text{CH}_3(c,g)$), 2.21 (s, 6H, $\text{CH}_3(d,f)$), 2.22 (s, 3H, $\text{CH}_3(e)$), 2.31 (s, 3H, $\text{CH}_3(a)$), 2.36 (s, 3H, $\text{CH}_3(b)$), 3.21 (s, 3H, $\text{CH}_3(4')$), 3.78 (t, 2H, H_2'), 4.83 (t, 2H, H_1'), 5.59 (s, 2H, H_2''), 7.21, (s, 1H, H_7), 7.56 (s, 1H, H_4), 10.01 (s, 1H, H_2). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ (ppm) = 16.99 ($\text{C}(c,g)$), 17.02 ($\text{C}(d,f)$), 17.31 ($\text{C}(e)$), 20.66 ($\text{C}(a)$), 20.80 ($\text{C}(b)$), 47.36 (C_1'), 47.70 (C_1''), 58.93 (C_4'), 70.52 (C_2'), 112.66 (C_7), 113.85 (C_4), 124.28 (C_8), 129.73 (C_9), 130.95 (C_5''), 133.58 ($\text{C}_3'',7''$), 134.00 ($\text{C}_4'',6''$), 137.05 (C_2''), 137.19 (C_6), 137.37 (C_5), 141.38 (C_2).

1-Methoxyethyl-3-(2,4,6-trimethylbenzyl)-5,6-dimethylbenzimidazolium chloride (4f). Rdt: 94%, $C_{22}H_{29}N_2\text{OCl}$, $M = 372.94 \text{ g mol}^{-1}$, p.f. 241.2°C , $\nu(\text{CN}) = 1554.12 \text{ cm}^{-1}$. $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ (ppm) = 2.30 (s, 12H, $\text{CH}_3(b,c,d,e)$), 2.38 (s, 3H, $\text{CH}_3(a)$), 3.29 (s, 3H, $\text{CH}_3(4')$), 3.87 (s, 2H, H_2'), 4.81 (s, 2H, H_1'), 5.74 (s, 2H, H_1''), 6.92 (s, 2H, $\text{H}_4'',6''$), 6.99 (s, 1H, H_7), 7.53 (s, 1H, H_4), 10.81 (s, 1H, H_2). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ (ppm) = 20.11 ($\text{C}(c,e)$), 20.63 ($\text{C}(d)$), 20.79 ($\text{C}(a)$), 21.07 ($\text{C}(b)$), 46.71 (C_1'), 47.48 (C_1''), 58.98 (C_4'), 70.36 (C_2'), 112.92 (C_7), 113.54 (C_4), 125.14 (C_6), 129.68 (C_5), 130.12 ($\text{C}_4'',6''$), 130.83 (C_5''), 137.05 (C_2''), 137.96 ($\text{C}_3'',7''$), 139.70 ($\text{C}_5,6$), 142.32 (C_2).

1-Methoxyethyl-3-(3,5-dimethylbenzyl)-5,6-dimethylbenzimidazolium bromide (4g). Rdt: 89%, $C_{21}H_{27}N_2\text{OBr}$, $M = 403.4 \text{ g mol}^{-1}$, p.f. 267.6°C . $\nu(\text{CN}) = 1563.49 \text{ cm}^{-1}$. $^1\text{H NMR}$ (CDCl_3 , 400 MHz, δ , ppm): 2.22 (s, 6H, $\text{CH}_3(c,d)$), 2.31 (s, 3H, $\text{CH}_3(a)$), 2.35 (s, 3H, $\text{CH}_3(b)$), 3.29 (s, 3H, $\text{CH}_3(4')$), 3.89 (t, 2H, H_2'), 4.73 (t, 2H, H_1'), 5.59 (s, 2H, H_1''), 6.90 (s, 1H, H_5''), 6.95 (s, 2H, $\text{H}_3'',7''$), 7.22 (s, 1H, H_7), 7.47 (s, 1H, H_4), 11.05 (s, 1H, H_2). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz, δ , ppm): 20.6 ($\text{C}(a)$), 20.7 ($\text{C}(b)$), 21.2 ($\text{C}(c,d)$), 47.5 (C_1'), 51.2 (C_1''), 59.1 (C_4'), 70.3 (C_2'), 113.0 (C_7), 113.5 (C_4), 125.7 ($\text{C}_3'',5'',7''$), 130.8 (C_8), 132.6 (C_9), 132.6 (C_2''), 137.2 ($\text{C}_5,6$), 139.1 ($\text{C}_4'',6''$), 141.81 (C_2).

1-Methoxyethyl-3-(4-methylbenzyl)-5,6-dimethylbenzimidazolium chloride (4h). Rdt: 87%, $C_{20}H_{25}N_2\text{OBr}$, $M = 389.3 \text{ g mol}^{-1}$, p.f. 256.8°C , $\nu(\text{CN}) = 1559.72 \text{ cm}^{-1}$. $^1\text{H NMR}$ (CDCl_3 , 400 MHz, δ , ppm): 2.32 (s, 3H, $\text{CH}_3(c)$), 2.37 (s, 3H, $\text{CH}_3(a)$), 2.41 (s, 3H, $\text{CH}_3(b)$), 3.36 (s, 3H, $\text{CH}_3(4')$), 3.95 (t, 2H, H_2'), 4.78 (t, 2H, H_1'), 5.72 (s, 2H, H_1''), 7.18 (d, 2H, $\text{H}_3'',7''$), 7.36 (d, 1H, H_7), 7.31 (d, 2H, $\text{H}_4'',6''$), 7.53 (s, 1H, H_4), 11.23 (s, 1H, H_2). $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz, δ , ppm): 20.6 ($\text{C}(a)$), 20.7 ($\text{C}(b)$), 21.2 ($\text{C}(c)$), 40.2 (C_1'), 51.0 (C_1''), 59.2 (C_4'), 70.3 (C_2'), 113.0 (C_7), 113.5 (C_4), 128.2 ($\text{C}_8,9$), 130.0 ($\text{C}_3'',4'',6'',7''$), 130.8 (C_2''), 137.2 (C_5''), 139.1 ($\text{C}_5,6$), 141.8 (C_2).



1-Methoxyethyl-3-(4-*tert*-butylbenzyl)-5,6-dimethylbenzimidazolium chloride (4i). Rdt: 74%, $C_{23}H_{31}N_2OBr$, $M = 431.4$ g mol⁻¹, p.f 255.4 °C. $\nu(CN) = 1559.06$ cm⁻¹. ¹H NMR (CDCl₃, 400 MHz, δ , ppm): 1.29 (s, 9H, CH₃(c,d,e)), 2.40 (s, 3H, CH₃(a)) 2.43 (s, 3H, CH₃(b)), 3.38 (s, 3H, CH₃(4')), 3.98 (t, 2H, H2'), 4.79 (t, 2H, H1'), 5.73 (s, 2H, H1''), 7.34 (s, 1H, H7), 7.53 (s, 1H, H4), 7.42 (s, 4H, H3'', 5'', 6'', 7''), 11.27 (s, 1H, H₂). ¹³C NMR (CDCl₃, 100 MHz, δ , ppm): 20.6 (Ca), 20.7 (Cb), 31.2 (Cc,d,e), 47.5 (C1'), 50.9 (C1''), 59.2 (C4'), 70.3 (C2'), 112.9 (C7), 113.5 (C4), 126.3 (C4'', 6''), 128.0 (C3'', 7''), 129.5 (C8) et 129.8 (C9), 130.8 (C2''), 137.2 (C5,6), 141.8 (C2), 152.3 5 (C5'').

6.4 General procedure for carbonylative coupling

A stainless steel autoclave equipped with a magnetic stirring bar was charged with benzimidazolium salt (0.05 mmol), K₂CO₃ (2 mmol) and Pd(OAc)₂ (0.025 mmol). After flushing the atmosphere with N₂, a solution of 2-bromopyridine (1 mmol) in 5 mL of dry THF was added under N₂. The reaction mixture was stirred for 1 h at 80 °C. After this time, the autoclave was cooled down to room temperature and a solution of boronic acid (1.1 mmol) in 5 mL of dry THF was added under N₂. The autoclave was flushed with CO, pressurized to 20 bar and heated to 120 °C. At the end of the reaction and after cooling down to room temperature, the solution was filtered and the solvent was removed under vacuum. The residue was purified by silica gel chromatography (EtOAc/hexane) to give pure product.

The cytotoxic activity was assessed according to the literature.^{44,45}

Conflicts of interest

There are no conflicts to declare.

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References

- X. J. Wang, L. Zhang, X. F. Sun, Y. B. Xu, D. Krishnamurthy and C. H. Senanayake, *Org. Lett.*, 2005, **7**, 5593.
- B. Hatano, J. Kadokawa and H. Tagaya, *Tetrahedron Lett.*, 2002, **43**, 5859.
- S. Gmouh, H. L. Yang and M. Vaultier, *Org. Lett.*, 2003, **5**, 2219.
- T. Yamamoto, T. Kohara and A. Yamamoto, *Chem. Lett.*, 1976, **11**, 1217.
- Y. Hatanaka, S. Fukushima and T. Hiyama, *Tetrahedron*, 1992, **48**, 2113.
- J. J. Brunet and R. Chauvin, *Chem. Soc. Rev.*, 1995, **24**, 89.
- E. Fillion, D. Fishlock, A. Wilsily and J. M. Goll, *J. Org. Chem.*, 2005, **70**, 1316.
- D. O. Jang, K. S. Moon, D. H. Cho and J. G. Kim, *Tetrahedron Lett.*, 2006, **47**, 6063.
- T. Ishiyama, H. Kizaki, N. Miyaura and A. Suzuki, *Tetrahedron Lett.*, 1993, **34**, 7595.
- T. Ishiyama, H. Kizaki, T. Hayashi, A. Suzuki and N. Miyaura, *J. Org. Chem.*, 1998, **63**, 4726.
- M. V. Khedkar, T. Sasaki and B. M. Bhanage, *RSC Adv.*, 2013, **3**, 7791.
- J. R. Niu, M. M. Liu, P. Wang, Y. Long, M. Xie, R. Li and J. T. Ma, *New J. Chem.*, 2014, **38**, 1471.
- (a) F. S. Yates, *Comprehensive Heterocyclic Chemistry*, ed. A. J. Boulton and A. McKillop, Pergamon, Oxford, 1984, vol. 2, ch. 2.08; (b) M. Balasubramanian and J. G. Keay, *Comprehensive Heterocyclic Chemistry II*, ed. A. McKillop, Pergamon, Oxford, 1995, vol. 5, ch. 5.06.
- (a) D. J. Hlasta and J. J. Court, *Tetrahedron Lett.*, 1989, **30**, 1773–1776; (b) C. K. Herrmann, Y. P. Sachdeva and J. F. Wolfe, *J. Heterocycl. Chem.*, 1987, **24**, 1061–1065; (c) T. Sakamoto, Y. Kondo, N. Murata and H. Yamanaka, *Tetrahedron*, 1993, **49**, 9713–9720; (d) Y. Yamamoto, H. Ouchi and T. Tanaka, *Chem. Pharm. Bull.*, 1995, **43**, 1028–1030; (e) F. Trécourt, G. Breton, V. Bonnet, F. Mongin, F. Marsais and G. Queguiner, *Tetrahedron Lett.*, 1999, **40**, 4339–4342.
- Samuel COUVE-BONNAIRE, Synthesis of functionalized pyridine derivatives-ketones, ketoamides and ketoesters-by carbonylation reaction of halogenated precursors, PhD thesis, thesis no. 3015, Université de Lille, 1, 2001.
- (a) S. Couve-Bonnaire, J.-F. Carpentier, A. Mortreux and Y. Castanet, *Tetrahedron Lett.*, 2001, **42**, 3689–3691; (b) S. Couve-Bonnaire, J.-F. Carpentier, A. Mortreux and Y. Castanet, *Tetrahedron*, 2003, **59**, 2793–2799.
- (a) A. J. Arduengo, R. L. Harlow and M. Kline, *J. Am. Chem. Soc.*, 1991, **113**, 361–363; (b) G. C. Fortman and S. P. Nolan, *Chem. Soc. Rev.*, 2011, **40**, 5151–5169; (c) H. Clavier and S. P. Nolan, *Chem. Commun.*, 2010, **46**, 841–861.
- W. A. Herrmann, M. Elison, J. Fisher, C. Köcher and G. R. Artus, *Angew. Chem., Int. Ed.*, 1995, **34**, 2371.
- N. M. Scott and S. P. Nolan, *Eur. J. Inorg. Chem.*, 2005, 1815.
- H. W. Wanzlick and E. Schikora, *Angew. Chem.*, 1960, **72**, 494.
- D. Bourissou, O. Guerret, F. P. Gabbaï and G. Bertrand, *Chem. Rev.*, 2000, **100**, 39.
- S. Díez-González and S. P. Nolan, *Coord. Chem. Rev.*, 2007, **251**, 874.
- W. A. Herrmann, *Angew. Chem., Int. Ed.*, 2002, **41**, 1290.
- G. A. Grasa, M. S. Viciu, J. Huang, C. Zhang, M. L. Trudell and P. Nolan, *Organometallics*, 2002, **21**, 2866.
- G. A. Grasa, M. S. Viciu, J. Huang, C. Zhang, M. L. Trudell and S. P. Nolan, *Organometallics*, 2002, **21**(14), 2866–2873.
- (a) S. Díez-González, N. Marion and S. P. Nolan, *Chem. Rev.*, 2009, **109**, 3612–3676; (b) *N-Heterocyclic Carbenes in Transition Metal Catalysis*, ed. F. Glorius, Springer, Berlin Heidelberg, 2007; (c) *N-Heterocyclic Carbenes From Laboratory Curiosities to Efficient Synthetic Tools*, ed. S. Díez-González, RSC Publishing, Cambridge, UK, 2011; (d) E. L. Kolychev, A. F. Asachenko, P. B. Dzhevakov, A. A. Bush, V. V. Shuntikov, V. N. Khurstalev and



- M. S. Nechaev, *Dalton Trans.*, 2013, **42**, 6859–6866; (e) A. R. Leverett, A. I. McKay and M. L. Cole, *Dalton Trans.*, 2015, **44**, 498–500.
- 27 (a) G. C. Vougioukalakis and R. H. Grubbs, *Chem. Rev.*, 2010, **110**, 1746–1787; (b) E. Colacino, J. Martinez and F. Lamaty, *Coord. Chem. Rev.*, 2007, **251**, 726–764; (c) C. Samojlowicz, M. Bieniek and K. Grela, *Chem. Rev.*, 2009, **109**, 3708–3742; (d) M. Yus and I. M. Pastor, *Chem. Lett.*, 2013, **42**, 94–108; (e) L. A. Schaper, S. J. Hock, W. A. Herrmann and F. E. Kuhn, *Angew. Chem., Int. Ed.*, 2013, **52**, 270–289; (f) M. J. Ingleson and R. A. Layfield, *Chem. Commun.*, 2012, 3579–3589; (g) N. Marion and S. P. Nolan, *Acc. Chem. Res.*, 2008, **41**, 1440–1449; (h) S. Çekirdek, S. Yaşar and İ. Özdemir, *Appl. Organomet. Chem.*, 2014, **28**, 423–431; (i) S. Yaşar, K. J. Cavell, B. D. Ward and B. Kariuki, *Appl. Organomet. Chem.*, 2011, **25**, 374–382; (j) S. Yaşar, S. Çekirdek and İ. Özdemir, *J. Coord. Chem.*, 2014, **67**, 1236–1248; (k) E. Ö. Karaca, M. Akkoç, E. Öz, S. Altin, V. Dorcet, T. Roisnel, N. Gürbüz, Ö. Çelik, A. Bayri, C. Bruneau, S. Yaşar and I. Özdemir, *J. Coord. Chem.*, 2017, **70**, 1270–1284; (l) S. Yaşar, E. Ö. Karaca, Ç. Şahin, İ. Özdemir, O. Şahin and O. Büyükgüngör, *J. Organomet. Chem.*, 2015, **789–790**, 1–7.
- 28 (a) H. Ren, Y. Xu, E. Jeanneau, I. Bonnamour, T. Tu and U. Darbos, *Tetrahedron*, 2014, **70**, 2829–2837; (b) R. Zhong, A. Pothig, Y. Feng, K. Riener, W. A. Herrmann and F. E. Kuhn, *Green Chem.*, 2014, **16**, 4955–4962; (c) H. Turkmen, L. Gok, I. Kani and B. Cetinkaya, *Turk. J. Chem.*, 2013, **37**, 633–642; (d) M. Teci, E. Brenner, D. Matt, C. Gourlaouen and L. Toupet, *Dalton Trans.*, 2014, **43**, 1251–1262; (e) M. Teci, E. Brenner, D. Matt and L. Toupet, *Eur. J. Inorg. Chem.*, 2013, 2841–2848; (f) R. L. Sutar, V. K. Kumar, R. D. Shingare, S. Thorat, R. Gonnade and D. S. Reddy, *Eur. J. Org. Chem.*, 2014, 4482–4486.
- 29 (a) H. Valdes, M. Poyatos, G. Ujaque and E. Peris, *Chem.–Eur. J.*, 2014, **20**, 1–12; (b) Y. Li, L. Yang, Q. Chen, C. Cao, P. Guan, G. Pang and Y. Z. Shi, *Z. Anorg. Allg. Chem.*, 2013, **639**, 575–581; (c) Y. C. Lin, H. H. Hsueh, S. Kanne, L. K. Chang, F. C. Liu, I. J. B. Lin, G. H. Lee and S. M. Peng, *Organometallics*, 2013, **32**, 3859–3869.
- 30 (a) R. A. Batey, M. Shen and J. Lough, *Org. Lett.*, 2002, **4**, 1411–1414; (b) L. Ray, S. Barman, M. M. Shaikh and P. Ghosh, *Chem.–Eur. J.*, 2008, **14**, 6646–6655; (c) F. T. Luo and H. K. Lo, *J. Organomet. Chem.*, 2011, **696**, 1262–1265.
- 31 (a) H. V. Huynh and C. S. Lee, *Dalton Trans.*, 2013, **42**, 6803–6809; (b) L. Yang, Y. Li, Q. Chen, Y. Du, C. Cao, Y. Shi and G. Pang, *Tetrahedron*, 2013, **69**, 5178–5184; (c) A. Biffis, M. Cipani, E. Bressan, C. Tubaro, C. Graiff and A. Venzo, *Organometallics*, 2014, **33**, 2182–2188; (d) H. Lu, L. Wang, F. Yang, R. Wu and W. Shen, *RSC Adv.*, 2014, **4**, 30447–30452.
- 32 R. Miri, O. Firuzi, P. Peymani, Z. Nazarian and A. Shafiee, *Synthesis and Cytotoxicity Study of New Cyclopenta [b] quinoline-1,8-dione Derivatives*, *Iran. J. Pharm. Res.*, 2011, **10**, 489–496.
- 33 R. Miri, K. Javidnia, Z. Amirghofran, S. H. Salimi, Z. Sabetghadam, S. Meilia and A. R. Mehdipour, *Cytotoxic Effect of Some 1,4-Dihydropyridine Derivatives Containing Nitroimidazole Moiety*, *Iran. J. Pharm. Res.*, 2011, **10**, 497–503.
- 34 M. Vosooghi, H. Yahyavi, K. Divsalar, H. Shamsa, A. Kheirollahi, M. Safavi, S. K. Ardestani, S. Sadeghi-Neshat, N. Mohammadhosseini, N. Edraki, M. Khoshneviszadeh, A. Shafiee and A. Foroumadi, *Synthesis and in vitro cytotoxic activity evaluation of (E)-16-(substituted benzylidene) derivatives of dehydroepiandrosterone*, *Daru, J. Pharm. Sci.*, 2013, **21**, 34.
- 35 B. Lamia, A. Chakchouk-Mtibaa, B. Hallouma, S. Yasser, I. Ozdemir, L. Mansour, L. Mellouli and N. Hamdi, *Molecules*, 2017, **22**(3), 420.
- 36 N. Touj, A. Chakchouk-Mtibaa, L. Mansour, A. H. Harrath, J. H. Al-Tamimi, I. Özdemir, L. Mellouli, S. Yaşar and N. Hamdi, *J. Organomet. Chem.*, 2017, **853**, 49–63.
- 37 N. Touj, I. Özdemir, S. Yasar and N. Hamdi, *Inorganica Chim. Acta*, 2017, **467**, 21–32.
- 38 N. Touj, N. Gürbüz, N. Hamdi, S. Yaşar and İ. Özdemir, *Palladium PEPPSI complexes: Synthesis and catalytic activity on the Suzuki-Miyaura coupling reactions for aryl bromides at room temperature in aqueous media*, *Inorganica Chim. Acta*, 2018, **478**, 187–194.
- 39 L. Boubakri, L. Mansour, A. H. Harrath, I. Özdemir, S. Yaşar and N. Hamdi, *N-heterocyclic carbene-Pd (II)-PPh₃ complexes a new highly efficient catalyst system for the Sonogashira cross-coupling reaction: Synthesis, characterization and biological activities*, *J. Coord. Chem.*, 2018, **71**, 183–199.
- 40 E. Maerten, M. Sauthier, A. Mortreux and Y. Castanet, *Tetrahedron*, 2007, **63**, 682–689.
- 41 A. Brennfürher, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2009, **48**, 4114–4133.
- 42 D.-J. Chen, Z.-Y. Zhou, Q. Wang, D.-M. Xiang, N. Tian and S.-G. Sun, *Chem. Commun.*, 2010, **46**, 4252–4254.
- 43 D. S. McGuinness and K. J. Cavell, *Organometallics*, 2000, **19**, 741.
- 44 T. Mosmann, *Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays*, *J. Immunol. Methods*, 1983, **65**, 55–63.
- 45 A. Zonouzi, R. Mirzazadeh, M. Safavi, S. Kabudanian Ardestani, S. Emami and A. Foroumadi, *Iran. J. Pharm. Res.*, 2013, **12**(4), 679–685.

