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Palladium-NHC catalysed biaryl ether formation

Paladyum-NHC katalizli biaril eter oluşumu

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Palladium-NHC Catalysed Biaryl Ether Formation

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Önemli noktalar (Highlights)

- *Biaryl ether synthesis via in situ palladium catalysis.*
- *Successful evaluation of catalytic activity in various phenol derivatives.*
- *High-efficiency transformation of challenging substrates.*

Grafik Özet (Graphical Abstract)

This manuscript describes the synthesis of three novel benzimidazolium bromide salts and their catalytic performance in ether formation using in situ generated Pd-NHC complexes.

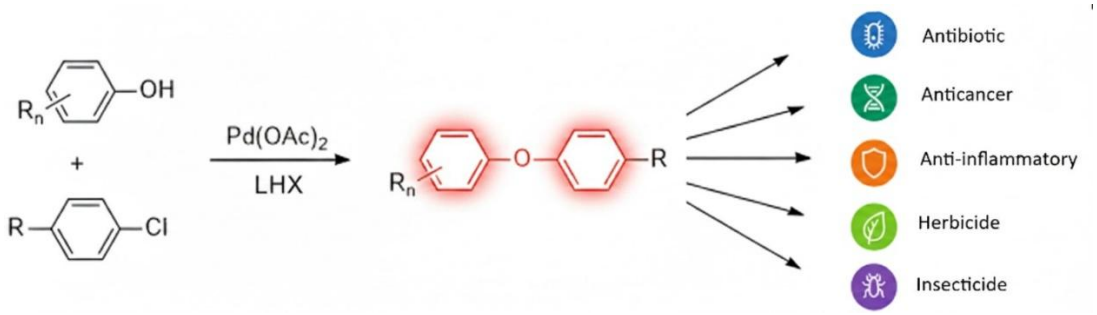

Figure. Biaryl ether formation

Aim

The present report highlights for the first time, synthesis of three new benzimidazolium bromide salts and their catalytic performance as ligand precursors for insitu- generated Pd-NHC complexes. In particular, here the performance of these catalytic systems is studied in the C-O cross-coupling reaction for biaryl ether formation between different phenol derivatives and aryl compounds.

Design & Methodology

Three new benzimidazolium bromide salts were created and applied to $Pd(OAc)_2$ as ligand precursors to evaluate their catalytic efficiency. The in-situ produced complexes were applied in the C-O cross-linking of various phenols and aryl substrates to synthesize biaryl ethers.

Originality

This study introduces three novel benzimidazolium salts not previously reported in the literature. Their originality lies in demonstrating their potential as highly effective ligand precursors in in situ Pd-NHC-catalyzed C-O cross-linking reactions for synthesizing biaryl ethers under optimized conditions..

Findings

The catalytic evaluation of Pd-NHC complexes (1a-c) in C-O cross-coupling revealed exceptional efficiency, with yields reaching 98%. Ligand 1a demonstrated perfect performance across diverse substrates. The system exhibited powerful tolerance for electron-withdrawing groups (e.g., nitro-phenols) and successfully accommodated sterically hindered phenols. These results highlight the protocol's versatility and the ligands' ability to stabilize active palladium species during challenging transformations.

Conclusion

This study reports the synthesis of novel benzimidazolium salts (1a-c) as effective Pd-NHC precursors for C-O cross-coupling. The methoxyethyl-substituted ligand (1a) demonstrated perfect catalytic activity, likely due to hemilabile oxygen stabilization. Achieving yields up to 98%, this powerful methodology offers broad substrate tolerance for synthesizing biologically important biaryl ethers.

Declaration of Ethical Standards

The authors state that there is neither the approval of the ethics committee nor a special legal license for the data and methods used in this study.

Palladium-NHC Catalysed Biaryl Ether Formation

Araştırma Makalesi / Research Article

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ABSTRACT

In the search for efficient and stable catalyst systems for organic reactions, N-heterocyclic carbene (NHC) precursors have played an important role in modern organometallic chemistry. Three new benzimidazolium bromide salts were prepared by alkylation of benzimidazole derivatives in this work. The chemical structures of the newly formed ligand precursors were fully characterized and verified by ^{1}H, ^{13}C-NMR, elemental analysis and FT-IR methods. After determining the process, the catalytic behavior of this material was tested in a palladium-catalyzed C-O bond formation reaction, which is an important method for producing biaryloxy. The catalytically active Pd-NHC complexes were synthesized in situ from $Pd(OAc)_2$ as the metal donor. The results showed that this new benzimidazolium salt exhibits high catalytic activity and supports the synthesis of various phenolic derivatives with aryl halides, affording the corresponding biaryl ethers in high yields and purity. This study not only demonstrates the powerful ability of Pd-NHC catalysts in complex C-O bonding, but also contributes to the advancement of synthetic methods for biological products. Overall, these results provide an important basis for the design, development, and application of catalytic processes in biosynthesis.

Keywords: Benzimidazole-2-yliden, *in-situ*, Pd-NHC, C-O bond forming.

Paladyum-NHC Katalizli Biaril Eter Oluşumu

ÖZ

Organik dönüşümler için verimli ve kararlı katalitik sistemler geliştirme arayışında, N-heterosiklik karben (NHC) öncüleri modern organometalik kimyada güçlü araçlar olarak öne çıkmıştır. Bu çalışmada, üç yeni benzimidazolyum bromür tuzu, benzimidazol türevlerinin alkilasyonu yoluyla başarılı bir şekilde sentezlenmiştir. Yeni sentezlenen bu ligand öncülerinin kimyasal yapıları; ^{1}H and, ^{13}C-NMR, elementel analiz ve FT-IR analiz yöntemleri kullanılarak kapsamlı bir şekilde karakterize edilmiş ve doğrulanmıştır. Yapısal aydınlatmanın ardından, bu bileşiklerin katalitik etkinliği, biaril eterlerin inşası için kritik bir yol olan paladyum katalizli C-O çapraz kenetlenme reaksiyonlarında değerlendirilmiştir. Aktif Pd-NHC kompleksleri, metal kaynağı olarak $Pd(OAc)_2$ kullanılarak in situ oluşturulmuştur. Elde edilen sonuçlar, bu yeni benzimidazolyum tuzlarının yüksek katalitik aktivite sergilediğini ve çeşitli fenol türevlerinin aril halojenürlerle kenetlenmesini sağlayarak ilgili biaril eterleri yüksek verimlilik ve saflıkta oluşturduğunu göstermiştir. Bu çalışma, yalnızca zorlu C-O bağ oluşum reaksiyonlarında Pd-NHC katalizörlerinin güçlü potansiyelini vurgulamakla kalmayıp, aynı zamanda biyolojik olarak aktif bileşiklerin sentetik süreçlerinin ilerlemesine de önemli ölçüde katkıda bulunmaktadır. Sonuç olarak bu bulgular, sürdürülebilir organik sentezde yeni nesil katalitik sistemlerin tasarımı, geliştirilmesi ve uygulanması için önemli bir temel oluşturmaktadır.

Anahtar Kelimeler: Benzimidazol-2-iliden, in situ, Pd-NHC, C-O bağ oluşumu.

1. INTRODUCTION

Biaryl ether groups are the main structure underlying many bioactive compounds, drugs, pesticides and functional agents [1-3]. These specific aryl ether bonds are often included in the molecular structure of important compounds, such as the antibiotic vancomycin, as well as many other effective antibiotics and insecticides [4-6]. Therefore, the development of efficient and effective methods to form CO bonds has become an intense research topic in the field of modern organic synthesis. While traditional methods such as Ullmann condensation often require large and stoichiometric amounts of copper, recent advances have demonstrated the potential of palladium-catalyzed cross-coupling supported by palladium-N-heterocyclic carbene (Pd-NHC) catalysts [7]. Pd-NHC catalysts are a unique subclass and highly effective transition metal NHC complexes. *N*-heterocyclic carbenes (NHC) are neutral two-electron donor ligands in which the carbene carbon is stabilized by adjacent nitrogen atoms in the heterocycle. These various ligands have excellent σ-donating properties, allowing them to form strong bonds with metals such as palladium, but their stability is generally greater than phosphine ligands [8]. The thermal protection prevents the release of the ligand from the metal center, preventing the formation of inactive "palladium black" and extending the lifetime of the catalyst. Due to their good thermal stability, oxidation stability and high catalytic conversion, Pd-NHC catalysts have emerged as a powerful alternative to conventional systems. In the specific context of CO cross-coupling, these catalysts show higher activity compared to conventional phosphine-based methods [9]. Their unique electronic and steric profiles are important for the catalytic cycle.

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The free energy potential of NHC is oxidizing Addition of complexing reagents such as aryl chloride and promotes internal elimination steps to reduce steric hindrance, leading to higher yields of the marketer product. In addition, the reliability of the Pd-NHC complex makes it useful in a heterogeneous process or two-step environment, reducing operational errors and reducing overall operational costs [10]. Perhaps the most attractive feature of Pd-NHC catalysts is their excellent tunability [11]. By manipulating the nitrogen atom or NHC nucleus, scientists can measure the negative and electronic environment around the metal. This level of control provides excellent possibilities for coordinating CO reactions and opens up the possibility of coupling between sterically hindered or electronically deactivated molecules. Considerable efforts are currently being made to optimize the production of electron-rich NHC ligands to increase their practical applications in commercial synthesis [8]. In addition, the stability of the catalysts usually allows the reaction to be carried out at higher temperatures. Pd-NHC catalysts have been shown to be reliable with many cofactors [7]. It retains strong activity with a variety of phenolic and aryl halides, including electron-poor or electron-rich reagents that often lead to external reactions such as hydrohalogenation. This versatility makes it very attractive for the synthesis of various diaryls with specific pharmacological properties. Despite these advances, some problems remain [12]. Issues related to palladium cost, efforts to reduce catalyst loading, and the transition to reactive catalysts are still in the research field. Researchers are now focusing on developing cheaper, more stable and more accessible Pd-NHC precursors. The advent of Pd-NHC catalysts has changed the landscape of synthetic chemistry, providing efficient and flexible results. Tools for Diaryl Ether Synthesis [13] The unique properties, optimization, structural design and broad synthesis of the substrate complexes offer a good way to overcome the limitations of conventional ester synthesis [14]. Continued innovation in the development of benzimidazolium salts will lead to further progress in this field. In this study, the catalytic performance of our newly synthesized benzimidazolium chloride salts was evaluated in situ in a $Pd(OAc)_2$ catalyst. By testing six different phenol derivatives on two different aryl halide substrates, these new salts were shown to have high catalytic activity. These efficiently facilitate the coupling of various phenols with aryl aryls to produce the corresponding biaryl ethers in high yield and purity. This study demonstrates the potential of Pd-NHC catalysts in complex CO bond-forming reactions and contributes to the development of synthetic methods for biological compounds. Overall, these results provide an important basis for the development and application of the next catalyst in biosynthesis.

2. MATERIAL and METHOD

All tests are conducted in a vacuum because certain chemicals are sensitive to oxygen and moisture in the atmosphere. After being heated in a vacuum to eliminate moisture and air, the glass utilized in the process was filled with inert gas. The techniques outlined in the literature were employed to dry and wash the solvents and reagents. [15-20]. The NMR and FT-IR spectra of the synthesized salts are provided in the Supporting Information file.

2.1. General Synthesis of Benzimidazolium Salts

1-(Cyclohexylmethyl)benzimidazole (1 mol) was eliminated in anhydrous dimethyformamide (15 ml) then the inclusion of the corresponding alkyl halide (1 mol). A white precipitate developed during the course of stirring the reaction mixture at room temperature for the entire night. After that, the mixture was heated for 2 h at 120°C. Diethyl ether (Et_2O) (15 ml) was added once The resulting solid was filtered once the mixture had cooled to room temperature. After reconstituting the crude product from an EtOH/Et_2O mixture, it was cleaned with three rounds of ten milliliters of Et_2O and vacuum-dried. [15-20].

***1-(Cyclohexylmethyl)-3-(methoxyethyl)benzimidazolium chloride,* 1a**

2-Methoxyethyl chloride (1.04 g; 11 mmol) was gradually added to a solution of 1-(cyclohexylmethyl)benzimidazole (2.15 g; 10 mmol) in DMF (5 ml). Under an inert environment, the reaction proceeded for 12 h at 70°C. Following the completion of the reaction, DMF was extracted under vacuum and crystallized in a combination of Et_2O and ethanol. To create a white compound **1a**, the resulting white crystals were cleaned with Et_2O and vacuum-dried. Yield: 91 % (2.91 g), $\nu_{(CN)}$= 1559 cm^{-1}, m.p.: 166 °C, ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.20 [6H, pent., *J*= 20.0 Hz, $CH_2C_6\mathbf{H}_6$], 1.66 [4H, d, *J*= 6.0 Hz, $CH_2C_6\mathbf{H}_4$], 2.04 [1H, s, $CH_2C_6\mathbf{H}_1$], 3.36 [3H, s, $CH_2CH_2O_2C\mathbf{H}_3$], 3.96 [3H, *J*= 4.0 Hz, t, $CH_2C\mathbf{H}_2O_2CH_3$], 4.46 [2H, d, *J* = 4.0 Hz, $C\mathbf{H}_2C_6H_{11}$], 4.91 [2H, t, *J*= 6.0 Hz, $C\mathbf{H}_2CH_2O_2CH_3$], 7.64-7.91 [4H, m, $C_6\mathbf{H}_4$], 11.05 [1H, s, NCHN]. ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 25.3, 25.8, 30.3, 37.8, [$CH_2\mathbf{C}_6H_{11}$], 47.7 [$\mathbf{C}H_2C_6H_{11}$], 53.4 [$\mathbf{C}H_2CH_2O_2CH_3$], 59.1 [$CH_2CH_2O_2\mathbf{C}H_3$], 70.3 [$CH_2\mathbf{C}H_2O_2CH_3$], 112.9, 114.2, 127.1, 131.4, 132.0 [$\mathbf{C}_6H_4$], 143.0 [N**C**HN], Anal. Calcd. for $C_{17}H_{25}N_2OCl$ (%): Calculated H: 8.16, C: 66.11, N: 9.07; found H: 8.24, C: 66.39, N: 8.99.

***1-(Cyclohexylmethyl)-3-(ethoxyethyl)benzimidazolium chloride*, 1b**

2-Ethoxyethyl chloride (1.20 g; 11 mmol) was gradually added to a solution of 1-(cyclohexylmethyl)benzimidazole (2.15 g; 10 mmol) in DMF (5 ml) and synthesized similarly to **1a**. Yield: 89 % (2.89 g), $\nu_{(CN)}$= 1566 cm^{-1}, m.p.: 188.5°C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.07 [3H, s, $CH_2CH_2O_2CH_2C\mathbf{H}_3$], 1.15 [6H, d, *J* = 22.0 Hz, $CH_2C_6\mathbf{H}_6$], 1.65 [4H, d, *J* = 6.0 Hz, $CH_2C_6\mathbf{H}_4$], 2.00 [1H, s, $CH_2C_6\mathbf{H}_1$], 3.50 [2H, s, $CH_2CH_2O_2C\mathbf{H}_2CH_3$], 3.97 [2H, s, $CH_2C\mathbf{H}_2O_2CH_2CH_3$], 4.44 [2H, t, *J*=4.0 Hz, $C\mathbf{H}_2C_6H_{11}$], 4.88 [2H, t, *J*= 4.0 Hz, $C\mathbf{H}_2CH_2O_2CH_2CH_3$], 7.60-7.90 [4H, m, $C_6\mathbf{H}_4$],

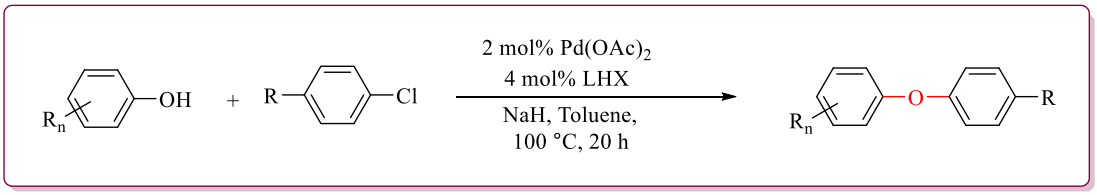
11.08 [1H, s, NCHN]. ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 15.0 [$CH_2CH_2O_2CH_2\mathbf{C}H_3$], 25.3, 25.7, 30.3, 37.8 [$CH_2\mathbf{C}_6H_{11}$], 47.9 [$\mathbf{C}H_2C_6H_{11}$], 53.3 [$\mathbf{C}H_2CH_2O_2CH_2CH_3$], 66.8 [$CH_2\mathbf{C}H_2O_2CH_2CH_3$], 68.1 [$CH_2CH_2O_2\mathbf{C}H_2CH_3$], 112.8, 114.3, 126.9, 127.0, 131.3, 132.0 [$\mathbf{C}_6H_4$], 143.0 [N**C**HN], Anal. Calcd. for $C_{18}H_{27}N_2OCl$ (%): Calculated H: 8.43, C: 66.96, N: 8.68; found H: 8.51, C: 66.87, N: 8.73.

*1-(*Cyclohexylmethyl*)-3-(2,4,6-trimethylbenzyl)benzimidazolium chloride*, 1c

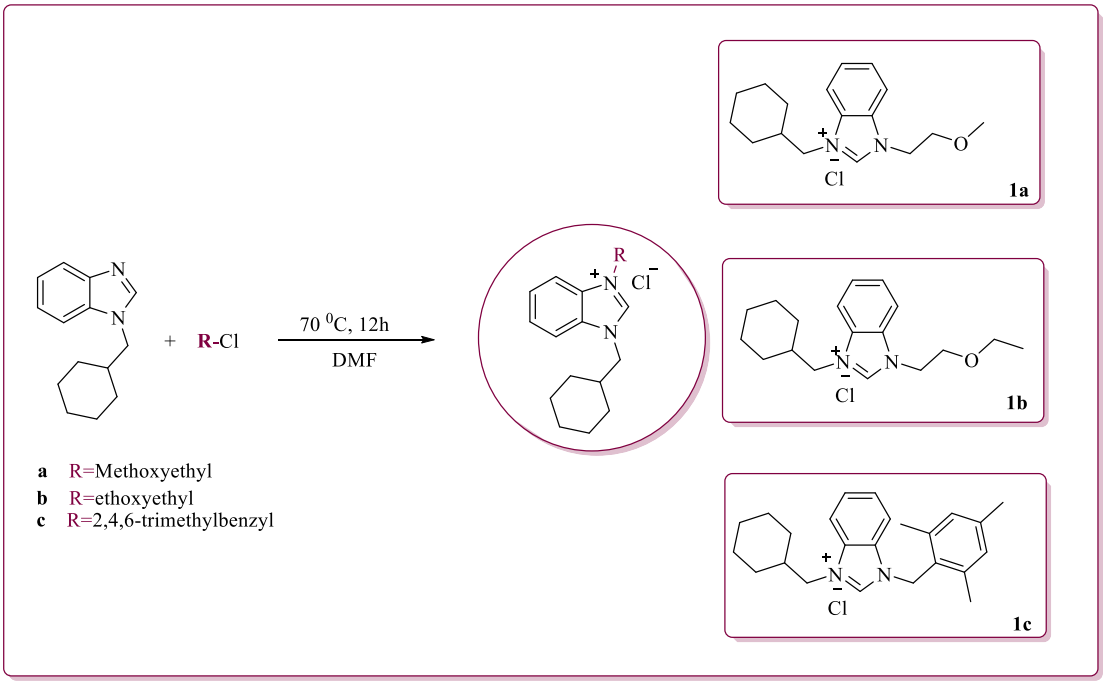
2,4,6-Trimethylbenzyl chloride (2.85 g; 11 mmol) was gradually added to a mixture of 1-(cyclohexylmethyl)benzimidazole (2.15 g; 10 mmol) in DMF (5 ml) and synthesized similarly to **1a**. Yield: 90 % (3.60 g), $\nu_{(CN)}$= 1552 cm^{-1}, m.p.: 234 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 1.18 [6H, pent., *J* = 18.0 Hz, $CH_2C_6\mathbf{H}_6$], 1.67 [4H, d, *J* = 6.0 Hz, $CH_2C_6\mathbf{H}_4$], 2.00 [1H, s, $CH_2C_6\mathbf{H}_1$], 2.30 [3H, s, $CH_2C_6H_2$-($C\mathbf{H}_3$)-4], 2.33 [6H, s, $CH_2C_6H_2$-($C\mathbf{H}_3$)$_2$-2,6], 4.48 [2H, d, *J*= 4.0 Hz, $C\mathbf{H}_2C_6H_{11}$], 5.94 [2H, s, $C\mathbf{H}_2C_6H_2$-$(CH_3)_3$-2,4,6], 6.93 [2H, s, $CH_2C_6\mathbf{H}_2$-$(CH_3)_3$-2,4,6], 7.12-7.68 [4H, m, $C_6\mathbf{H}_4$], 11.67 [1H, s, NCHN]. ^{13}C-NMR (100 MHz, $CDCl_3$): δ= 20.3 [$CH_2C_6H_2$-($\mathbf{C}H_3$)$_2$-2,6], 21.8 [$CH_2C_6H_2$-($\mathbf{C}H_3$)-4], 25.3, 25.7, 30.3, 37.4 [$CH_2\mathbf{C}_6H_{11}$], 47.5 [$\mathbf{C}H_2C_6H_{11}$], 53.3 [$\mathbf{C}H_2C_6H_2$-$(CH_3)_3$-2,4,6], 113.1, 114.0, 126.8, 127.0, 133.9 [$\mathbf{C}_6H_4$], 125.2, 130.2, 131.3, 131.9, 139.6 [$CH_2\mathbf{C}_6H_3$-$(CH_3)_2$-3,5], 144.3 [N**C**HN] ppm. Anal. Calcd. for $C_{24}H_{31}ClN_2$ (%): Calculated H: 8.40, C: 75.07, N: 7.30; found H: 8.51, C: 75.17, N: 7.23.

2.2. In Situ Pd-NHC Catalyzed Diaryl Ether Formation

A dry Schlenk tube was used to add phenol derivative (1 mmol), aryl halide derivative (1.05 mmol), $Pd(OAc)_2$ (2 mol %), **1a-c** (4 mol%), toluene (3 ml), and NaH (1 mmol). Heat for 20 h at 100°C. Allow the mixture to come to room temperature. Silica gel was used to purify the product. GC and GC-MS were used to examine the product (**Scheme 1**).



Scheme 1. Catalytic etherification reaction.



Scheme 2. Synthesis of benzimidazolium salts.

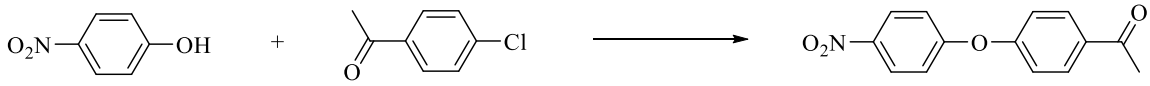
3. FINDINGS

3.1. General Preparation of Benzimidazolium Salts

Using the Schlenk method against ambient moisture and oxygen, all salts were created in an inert atmosphere. Methylcyclohexyl was attached to the nitrogen atom in one position of benzimidazolium. After obtaining 1-methylcyclohexylbenzimidazole, benzimidazolium salts were synthesized by reacting with methoxyethyl chloride, ethoxyethyl chloride and 2,4,6-trimethylbenzyl chloride at 80 °C for 12 h. Scheme 2 displays the structures of the 89-91 % conjugated salts (**1a-c**). In

general, all salts are stable and resistant to humidity in the air and oxygen. NMR, FT-IR, elemental analysis and melting point measurement were used to describe the benzimidazolium salts, which was produced in good yield. In the ^{13}C-NMR spectrum, the characteristic NCHN carbon peaks are 143.0, 143.0, and 144.3 ppm, respectively. Within the ^{1}H-NMR spectrum, the characteristic hydrogen peaks of NCHN were found at 11.05, 11.08 and 11.67 ppm single signal, respectively. The corresponding -C = N- structure in the heterocyclic carbene structure was discovered at **1a-c** 1559, 1566, and 1552 cm^{-1}, respectively, when FT-IR spectra were analyzed. These findings are in line with the literature and our earlier research [7-9].

Table 1. Determination of reaction conditions.



Entry	Pd(OAc)$_2$/LHX (% / %)	Base	Solvent	Time (h)	Temp. (ºC)	Yield (%)
1	2/4	NaOH	Toluen	20	100	71
2	2/4	NaH	Toluen	20	100	98
3	2/4	Na_2CO_3	Toluen	20	100	59
4	2/4	KOH	Toluen	20	100	84
5	2/4	K_2CO_3	Toluen	20	100	65
6	2/4	Cs_2CO_3	Toluen	20	100	70
7	2/4	NaH	Dioxane	20	100	74
8	2/4	NaH	DMF	20	100	83
9	2/4	NaH	Toluen	24	100	98
10	2/4	NaH	Toluen	16	100	76
11	2/4	NaH	Toluen	12	100	53
12	1/1	NaH	Toluen	20	100	51
13	1/2	NaH	Toluen	20	100	55
14	1/3	NaH	Toluen	20	100	55
15	1/4	NaH	Toluen	20	100	55
16	2/1	NaH	Toluen	20	100	52
17	2/2	NaH	Toluen	20	100	67
18	2/3	NaH	Toluen	20	100	81
19	3/6	NaH	Toluen	20	100	98
20	2/4	NaH	Toluen	20	120	98
21	2/4	NaH	Toluen	20	80	65

3.2. Diaryl Ether Formation

To improve the chemical reaction during catalytic etherification, bases such as NaH, Cs_2CO_3 and K_3PO_4, with toluene as solvent, were used. The best results were obtained at 100°C using NaH in toluene (**Table 1**) [21].

The catalytic activity of synthetic benzimidazolium salts during ether formation was investigated. Sodium hydride (NaH, 1.4 mmol) was placed in a dry Schlenk tube. 1.1 mmol phenol and 3 ml toluene were added and the mixture was stirred under argon for 30 min at 100°C (**Scheme 1**). The reaction mixture cooled to room temperature, then 2.0 % Pd(OAc)$_2$, 4.0 mol % 1,3-dialkylbenzimidazolium salt and 1.0 mmol aryl chloride were added. The reaction is then heated at 100°C for 20 h. The cooled mixture was extracted using Et_2O and filtered through silica gel once the reaction was finished. Following the concentration of the filtrate under vacuum, flash chromatography was used to purify it. The yield was computed in relation to the aryl chloride. The reactions and results determined relative to aryl chlorides are shown in **Table 2**.

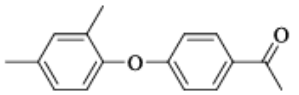
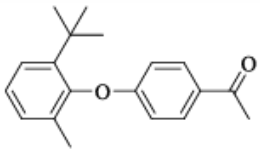
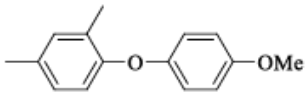
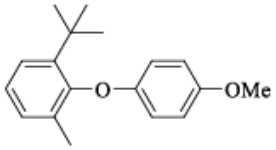
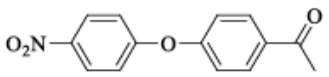
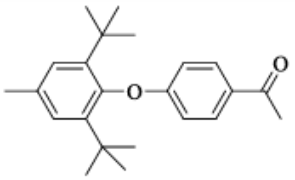
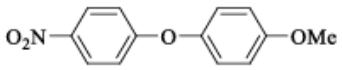
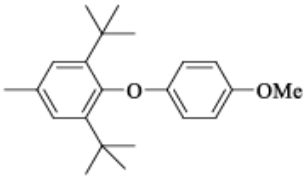
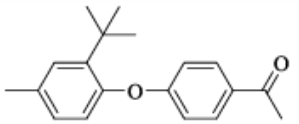
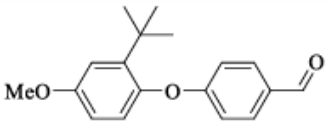
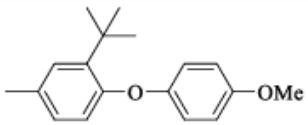
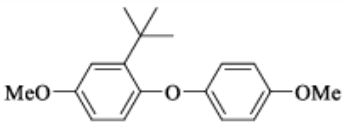
3.3. Evaluation of Catalytic Activity and Substrate Scope in Pd-NHC Catalyzed C-O Cross-Coupling

The experiments were optimized using toluene as solvent and NaH as base at 100°C for 20 h. The catalyst load was kept at a ratio of 4.0 mol % related 1,3-dialkylbenzimidazolium salt and, 2.0 mol % Pd(OAc)$_2$. After processing, the products are separated by flash chromatography and strictly use GC-MS to ensure the integrity of the sample and calculate the value of aryl chloride [21]. In summary, the Pd-NHC system derived from salts 1a-c provides a powerful and practical tool for

the synthesis of various biaryl ethers. The results show that the manipulation of NHC side chains, especially the introduction of hemilabile groups as in 1a, is a powerful strategy for fine-tuning catalytic activity for complex organic transformations.

The synthesized benzimidazolium salts (**1a-c**) act as *N*-heterocyclic carbene (NHC) precursors, characterized by an *N*-cyclohexylmethyl moiety and different N-moieties that dictate catalytic activity. Ligand 1a (Methoxyethyl): This derivative consistently shows the best activity in all reagents tested, reaching up to 98 % yield. This better performance is due to the potential inhibitory coordination of the ether oxygen to the palladium center, making the species more robust throughout the catalytic cycle. Ligand **1b** (Ethoxyethyl): Although the mechanism was similar to **1a**, the ethoxyethyl variant showed a slight decrease, suggesting that the increased carbon length has little effect on the coordination. Ligand **1c** (2,4,6-Trimethylbenzyl): Despite frequent substitutions, this ligand is still very useful, although it is generally obtained in lower yields compared to 1a, especially with related phenols [22-27].

Table 2. Biarylether products.

		LHX			LHX
1		**1a:** 91 % **1b:** 85 % **1c:** 83 %	7		**1a:** 91 % **1b:** 84 % **1c:** 88 %
2		**1a:** 85 % **1b:** 80 % **1c:** 74 %	8		**1a:** 84 % **1b:** 81 % **1c:** 79 %
3		**1a:** 98 % **1b:** 95 % **1c:** 95 %	9		**1a:** 89 % **1b:** 85 % **1c:** 84 %
4		**1a:** 97 % **1b:** 90 % **1c:** 91 %	10		**1a:** 79 % **1b:** 76 % **1c:** 74 %
5		**1a:** 91 % **1b:** 90 % **1c:** 88 %	11		**1a:** 94 % **1b:** 90 % **1c:** 90 %
6		**1a:** 88 % **1b:** 83 % **1c:** 78 %	12		**1a:** 85 % **1b:** 87 % **1c:** 83 %

Reaction Conditions: Reaction Conditions: 1.1 mmol phenol, 1.0 mmol aryl chloride, 2.0 mol % $Pd(OAc)_2$, 1.4 mmol NaH, 4.0 mol % LHX, 3 ml toluene, 100 °C, 20 h. Aryl chloride served as the basis for the results, and GC was used to track every reaction.

The catalytic system showed the best performance, avoiding multiple electronic components and the transformation of the two interfaces. Electronic effect (phenol): The process is very good for phenols bearing strong electron withdrawing groups. For example, 4-nitrophenol reacted with 4-chloroacetophenone and 4-chloroanisole to form ethers 3 and 4 in 98 % and 97 % yields, respectively. This may be due to the increased acidity of nitro-substituted phenols, which facilitates the formation of the intermediate phenoxide and improves the efficiency of transmetalation. Electrolytic effect (aryl halides): Active aryl halides, such as 4-chloroacetophenone, are often more effective than inactive ones such as 4-chloroanisole. This structure

follows a cross-coupling mechanism in which the electron-deficient aryl chloride more readily undergoes oxidative addition to the Pd(0) center. Steric hindrance: An important feature of this system is its strong resistance to steric bulk. Detailed claims, including 2,6-di-tert-butyl-4-methylphenol, were successfully combined to produce products 9 and 10 in yields of 74 % and 89 %. This shows that the NHC coordinate system is flexible enough to accommodate changing states.

When the mechanism of the reaction in question is examined, the most widely accepted mechanism for Ullmann C-O cross-linking involves the formation of organopalladium halide by oxidative addition of an organic halide to a palladium catalyst. This step is usually the rate-determining step of the catalytic cycle. Subsequently, a diorganopalladium complex is obtained by transmetalation with phenol under basic conditions, and after a reductive elimination, the linkage product is formed (**Scheme 3**) [28]. The base used in the catalytic reaction lowers the oxidation state of the Pd complex in the initial step, while also enhancing product formation by neutralizing the acid generated in the reaction medium.

4. CONCLUSION

In conclusion, this study describes the design, synthesis, and overall characterization of three novel *N*-cyclohexylmethyl functionalized benzimidazolium salts (**1a-c**) bearing methoxyethyl, ethoxyethyl, and 2,4,6-trimethylbenzyl substituents, respectively. These new compounds were evaluated as ligand precursors for Pd-NHC complex formation, which proved to be excellent catalysts for C-O bond formation by cross-coupling different phenols with aryl chlorides. Catalytic studies have shown that the nature of the *N*-member of the benzimidazole backbone plays an important role in the catalytic determination. The methoxyethyl-substituted salt (**1a**) consistently exhibited superior activity compared to its ethoxyethyl (**1b**) and sterically bulky 2,4,6-trimethylbenzyl (**1c**) counterparts. The enhanced performance of 1a is attributed to the subtle steric profile of the methoxy group, which facilitates a more effective and less hindered hemilabile coordination of the ether oxygen to the palladium center than the bulkier ethoxy group in **1b**. This optimized coordination ensures better stabilization of the active catalytic species throughout the cycle. While the significant steric bulk of 1c generally restricted substrate access to the palladium surface, the system remained robust, accommodating a wide range of electronic and steric variations. The protocol successfully produced biaryl ethers with high yields (74-98%), even for challenging, sterically hindered substrates like 2,6-di-tert-butyl-4-methylphenol. Overall, this work provides an efficient and effective method for the synthesis of biaryl ether scaffolds. These results demonstrate the ability to control the NHC side chain for efficient catalytic activity, providing insight into the future design of Pd-NHC systems intended for competitive organic transformation in pharmaceutical and pharmaceutical applications.

AUTHORS' CONTRIBUTIONS

Emine Özge KARACA: Write the manuscript and analysis the results.

Mitat AKKOÇ: Write the manuscript and analysis the results.

Nevin GÜRBÜZ: Write the manuscript and analysis the results.

İsmail ÖZDEMİR: Write the manuscript and analysis the results.

CONFLICT OF INTEREST

There is no conflict interest in this study.

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