

Cite this: *Org. Chem. Res.* **2022**, Vol. 8, 74-88.

DOI: 10.22036/org.chem.2023.413023.1293

The Latest Developments of *N*-Heterocyclic Carbenes (NHCs) Complexes in Cross-Coupling Reactions

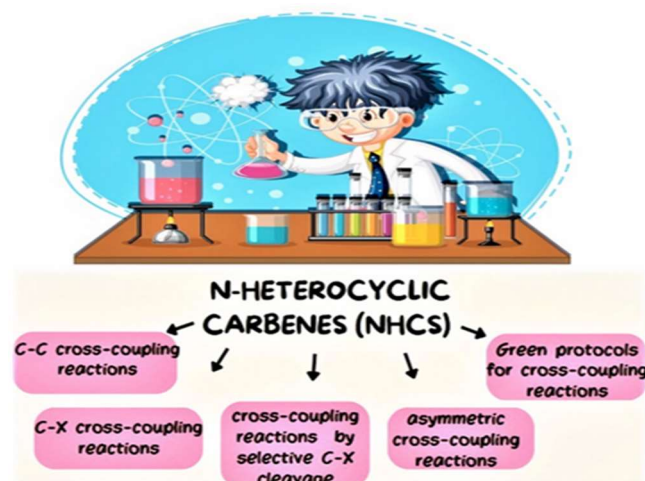
Fatemeh Pirani , Hossein Eshghi *

Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, Mashhad 91775-1436, Iran. E-mail: heshghi@um.ac.ir

Received: August 23, 2023; Accepted: October 25, 2023

Abstract: The advancements in cross-coupling chemistry are a considerably powerful tool for the synthesis of pharmaceutical molecules. The formation of catalytic carbon-heteroatom (C-X) and carbon-carbon (C-C) bonds is one of the important reactions in organic synthesis, which plays a key role in the synthesis of biologically active molecules, natural products, heterocycles, and useful compounds. Recently, there has been a significant increase in the development and advancement of environmentally friendly catalysts that serve as a suitable alternative to conventional metal-based catalysts. On the other hand, *N*-heterocyclic carbenes (NHCs)-metal-based catalysts became suitable for performing a wide range of chemical transformations due to their unique spatial and electronic properties. The NHCs have received much attention as ligands due to their important properties. The present review aimed to discuss the recent advances in the application of NHCs in cross-coupling chemistry in the last six years. The present study focused on the catalytic application of NHCs in various cross-coupling reactions, such as Suzuki, Heck, Sonogashira, Hiyama, Kumada, Buchwald-Hartwig, Ullmann, and Chan. Moreover, some cross-coupling reactions by selective C-X cleavage catalyzed by NHCs with high catalytic activity were discussed. In addition, several chiral NHCs capable of catalyzing asymmetric cross-coupling reactions were reported. Finally, numerous green protocols for cross-coupling reactions catalyzed by functional and biocompatible NHCs under mild conditions were investigated. These protocols had advantages such as high-yield products, short time, cost-effectiveness, and high catalytic activity.

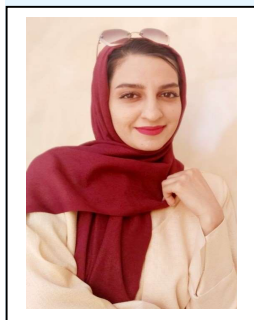
Keywords: *N*-Heterocyclic carbenes, Cross-coupling reactions, Catalysis, Selective C-X cleavage, Asymmetric cross-coupling reactions



1. Introduction

During the last few decades, *N*-heterocyclic carbenes (NHCs) have been used as a new class of ligands with unique and multifunctional properties in transition metal catalysis.¹⁻⁴ The advantages of these ligands include high stability in air and moisture and strong sigma electron-donating properties, which makes it possible to establish strong NHC-metal bonds with several transition metals. The transition metals chelated with NHCs have been used in various types of homogeneous and heterogeneous catalytic reactions, such as carbon-carbon coupling and carbon-heteroatom bond formation.⁵⁻¹² Transition metals chelated with NHCs contain ligands and expensive heavy metals. The heterogeneous metal-NHCs compounds are very popular in preventing product contamination with heavy metals and allowing reuse. The NHCs have received much attention due to their unique properties, such as high activity and low toxicity.¹³⁻¹⁷ Some

studies indicated that supported NHCs catalysts in organic reactions carried out in a homogeneous system may have similar or higher selectivity and catalytic activity than that of the original homogeneous catalytic system. Due to the adjustable electronic effects and strong donating capabilities of NHCs, they have become the best ligands in organometallic chemistry. Moreover, NHCs are suitable precursors for catalysis in aqueous reactions because their transition metal compounds are usually resistant to air, moisture, and heat.¹⁸⁻²¹ The need for innovative carbon-carbon bond-forming reactions as an ongoing process is an important issue in organic chemistry. The developed methods have to include the following principles: (1) The raw materials should be available, (2) the catalysts should be non-toxic, (3) the reactants should be non-toxic, and (4) the reaction conditions should be mild.²²⁻²⁷ The development of these ideal methods has always been discussed and challenged. The C-C coupling



Fatemeh Pirani obtained her BS degree in chemistry from University of Zabol, Iran, in 2013, where she also received her MSc degree, in 2016. She is currently an organic chemistry PhD student at Ferdowsi University of Mashhad (FUM), Iran. Her research activities lie in the area of developing nanotechnology in organic chemistry reactions through new synthetic *N*-Heterocyclic carbenes (NHCs) complexes, nanoclay and heterogeneous catalysis.

Hossein Eshghi received his BS degree in Chemistry from Arak University, Arak, Iran, in 1988, and MS and PhD degrees in organic chemistry from Shiraz University, Shiraz, Iran, in 1991 and 1995, respectively.

He has published extensively in the areas of synthesis and application of macrocyclic crown ethers and also in the introduction of some new catalysts in methodology. He has been studying nanotechnology and nanoscience in medicine and chemistry since early 2005. His current interests include gold nanoparticles for targeted cancer therapy, metal-organic framework (MOF), CO₂ transformations. He has published more than 350 scientific papers in international journals. He is presently a professor of chemistry at Ferdowsi University of Mashhad (FUM), Iran.



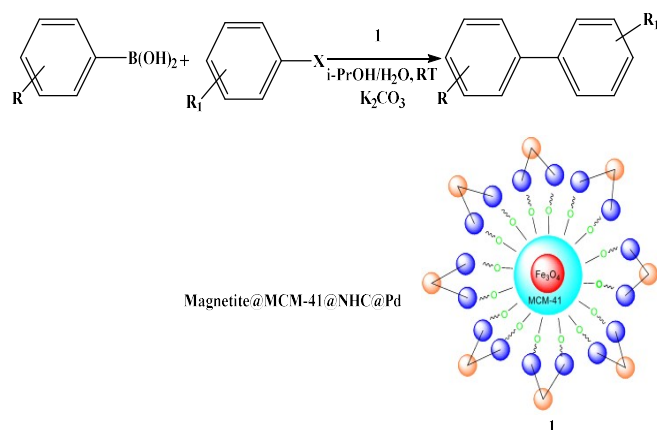
reactions, such as Suzuki, Hiyama, Sonogashira, Mizoroki-Heck, played a key role in a robust synthetic protocol for the production of new heterocycles, biologically active molecules, natural products, nanostructures, etc.²⁸⁻³⁶

The purpose of the present investigation is to highlight and focus on the recent advances in NHC-catalyzed cross-coupling reactions and related green processes reported in the last six years.

2. Applications of NHC complexes in cross-coupling reactions

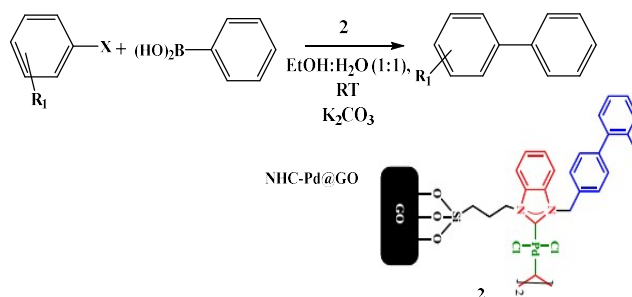
C-C cross-coupling reactions

Suzuki coupling reactions. In 2021, Akkoç and co-workers effectively prepared Magnetite@MCM-41@NHC@Pd catalyst. Subsequently, they investigated the catalytic activity of the Magnetite@MCM-41@NHC@Pd in the Suzuki coupling reactions. The coupling reaction products provided excellent efficiencies and up to 408404 (TOF). h⁻¹ in the presence of 2 mg of catalyst in 2-propanol/H₂O (1:2) as solvent at room temperature (Scheme 1).³⁷



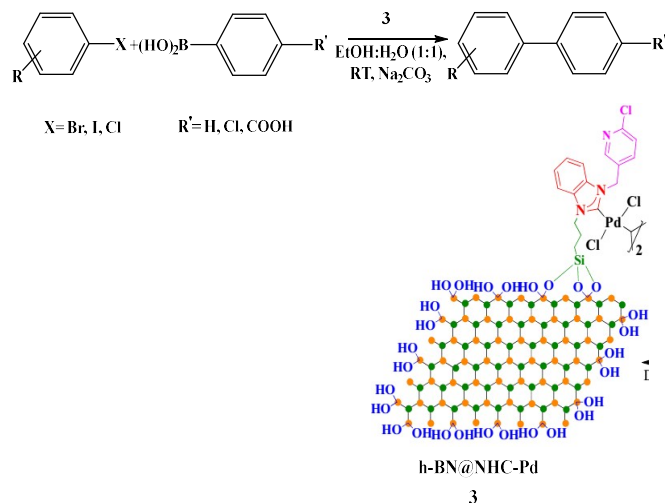
Scheme 1. Suzuki coupling using Magnetite@MCM-41@NHC@Pd

In 2020, Kandathil *et al.*, employed a novel and efficient *N*-heterocyclic carbene (NHC)-palladium (II) complex immobilized on graphene oxide for the Suzuki coupling of aryl halides and phenylboronic acids in EtOH:H₂O (1:1) at room temperature. NHC-Pd@GO heterogeneous catalyst showed good catalytic activity for the Suzuki cross-coupling reaction. Some of the important advantages of this catalyst are its compatibility with the environment, the ability to applied the recycled catalyst without significant loss of catalytic activity in Suzuki-Miyaura cross-coupling reactions, and its simple design (Scheme 2).³⁸



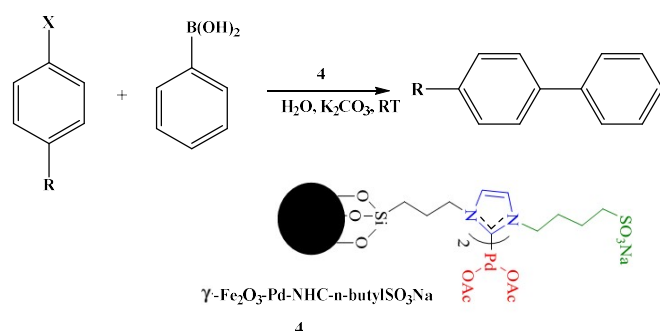
Scheme 2. Suzuki coupling using NHC-Pd@GO

Antony *et al.*, reported the preparation of the hexagonal boron nitride supported *N*-heterocyclic carbene-palladium(II) complex (h-BN@NHC-Pd) for the first time. Then, the catalytic activity of heterogeneous catalyst was investigated in Suzuki cross-coupling reactions between aryl boronic acids and aryl halides, at room temperature in aqueous medium. The h-BN@NHC-Pd heterogeneous catalyst shows significant advantages such as high stability without leaching, excellent yield of products, short reaction time, and heterogeneous nature. The recyclability of this catalyst shows its application in commercial-scale production (Scheme 3).³⁹



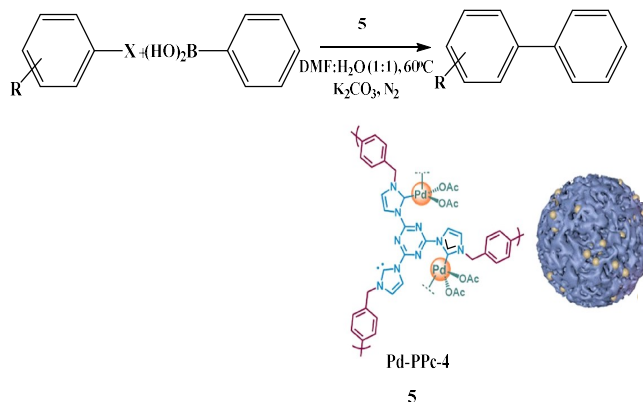
Scheme 3. Suzuki coupling using h-BN@NHC-Pd

Chahkamali *et al.*, described the synthesis of new water-dispersible Pd-*N*-heterocyclic carbene complex immobilized on magnetic nanoparticles (γ -Fe₂O₃-Pd-NHC-*n*-butyl-SO₃Na). The possibility of carrying out the reaction in water as a green environment, and the absence of any auxiliary additives or solvents, have made this method an environmentally friendly protocol for biaryl synthesis (Scheme 4).⁴⁰



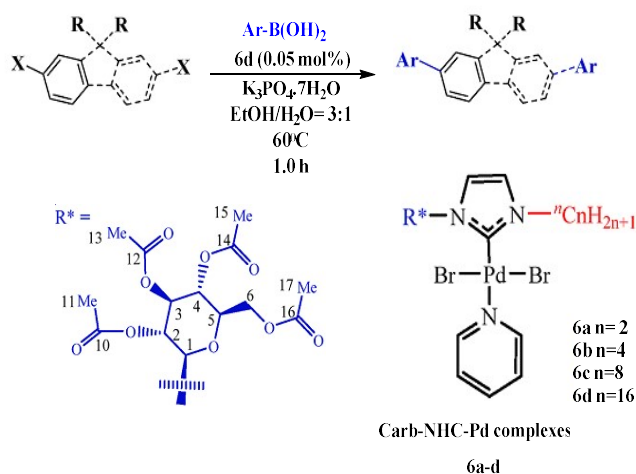
Scheme 4. Suzuki coupling using γ -Fe₂O₃-Pd-NHC-*n*-butyl-SO₃Na

N-heterocyclic-carbene based polymers with plentiful active sites was employed by Li *et al.*, compared to small molecular catalysts, (Pd-PPc-4) as a heterogeneous catalyst showed higher catalytic activity under milder reaction conditions. Besides, exceptionally high recyclability was demonstrated, benefiting from the strong coordination bond between the metal and the polycarbonate. The Suzuki-Miyaura cross-coupling reactions was carried out with high efficiency between aryl halides and phenyl boronic acid reaction in the presence of Pd-PPc-4 heterogeneous catalyst and K₂CO₃ as base in DMF:H₂O (1:1) as the reaction medium under N₂ gas (Scheme 5).⁴¹



Scheme 5. Suzuki coupling using Pd-PPc-4

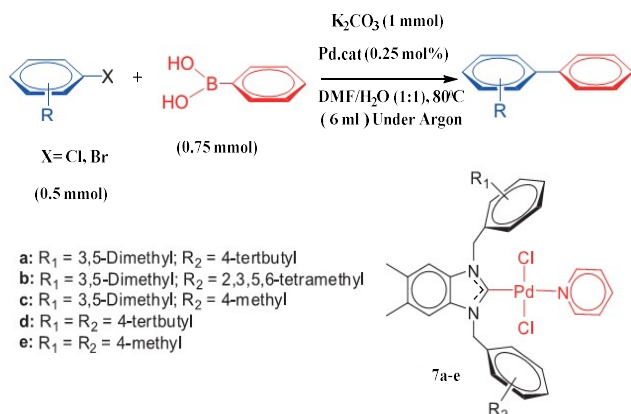
Four new Carb-NHC-Pd complexes **6a-d** were prepared by Xie *et al.*, their catalytic activities for Suzuki-Miyaura reaction were considered. The Carb-NHC-Pd complex behaves as a general surfactant, forming a temporary oil-in-water contact interface and promoting the Suzuki-Miyaura reaction. Complex **6d** showed the highest catalytic reaction among the other four complexes. The key to the success of the aqueous Suzuki-Miyaura reaction was the development and application of **6d** complex surfactants with highly hydrophobic alkyl chains (Scheme 6).⁴²



Scheme 6. Suzuki coupling using Carb-NHC-Pd complex

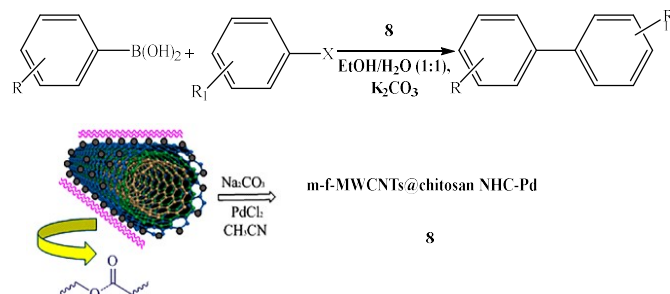
Pd-PEPPSI-NHC complexes **7a-e** were designed in good yields by Boubakri *et al.*, the catalytic activities of complexes **7a-e** in the Suzuki-Miyaura cross-coupling reactions were investigated. The reaction was carried out in DMF:H₂O (1:1) mixtures using aryl bromides, chlorides, phenylboronic acid, and K₂CO₃ as base at 80 °C (Scheme 7).⁴³

Sedghi *et al.*, described the synthesis of multi-walled carbon nanotubes@chitosan *N*-heterocyclic carbene-palladium. The m-f-MWCNTs@chitosan-NHC-Pd catalyst showed high catalytic activity in the Suzuki-Miyaura reactions of aryl chlorides in aqueous media. In addition, this catalyst can be



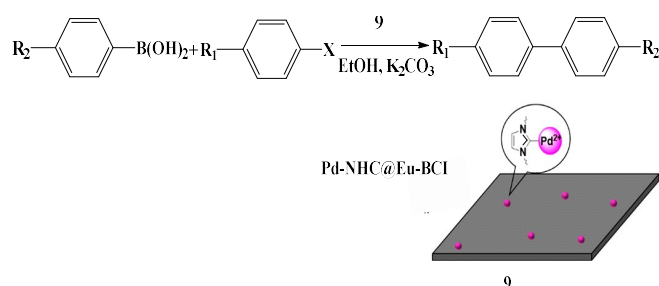
Scheme 7. Suzuki coupling using Pd-PEPPSI-NHC complexes

easily recycled by an external magnetic field. High TOF and TON show their usefulness in other reactions related to m-f-MWCNTs@chitosan-NHC-Pd catalysts. The Suzuki-Miyaura cross-coupling reactions was carried out in the presence of potassium carbonate as base and EtOH/H₂O (1:1) solvent system with high yields (Scheme 8).⁴⁴



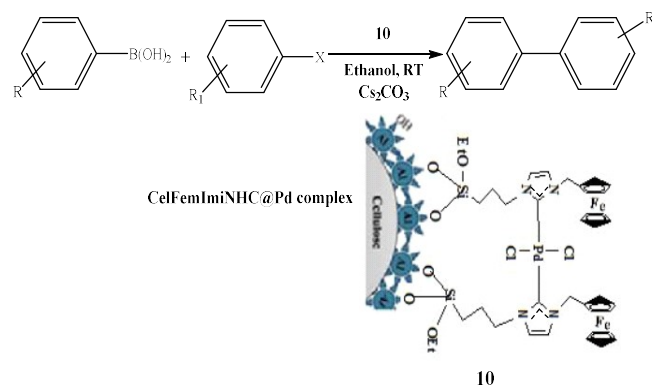
Scheme 8. Suzuki coupling using M-f-MWCNTs@chitosan-NHC-Pd

The study by You and co-workers in 2023 was the first ever report on *N*-heterocyclic carbene-Palladium Functionalized Coordination Polymer (Pd-NHC@Eu-BCI) catalysts in Suzuki cross-coupling reactions. The catalytic activity of Pd-NHC@Eu-BCI was investigated for the Suzuki-Miyaura cross-coupling reactions. This catalyst maintained its catalytic activity and initial structure after five cycles. The reaction was carried out in the presence of K₂CO₃ as base in ethanol with high yields (Scheme 9).⁴⁵



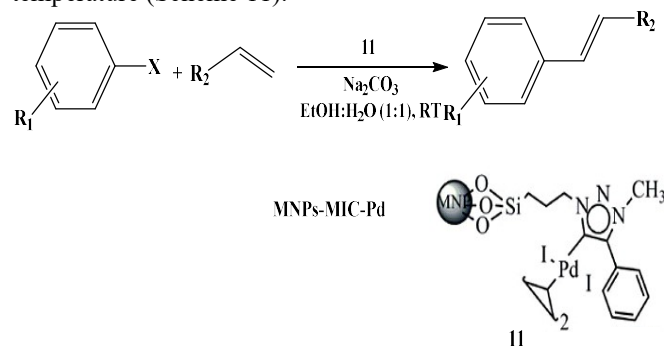
Scheme 9. Suzuki coupling using Pd-NHC@Eu-BCI

Kale *et al.*, reported the preparation of the ferrocene tethered *N*-heterocyclic carbene-Pd complex anchored on cellulose (CeIFemImiNHC@Pd complex) as efficient heterogeneous catalyst for the Suzuki-Miyaura coupling. Good efficiency catalyst with a high yield of products, large-scale synthesis, high TON and TOF, and easy recycling of this catalyst are among the significant features of the reported method (Scheme 10).⁴⁶



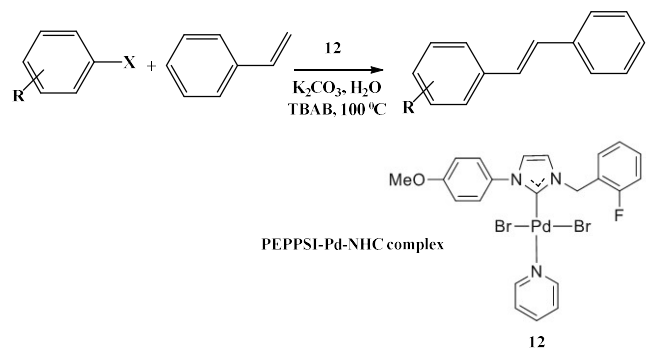
Scheme 10. Suzuki coupling using CeIFemImiNHC@Pd complex

Heck coupling reactions. A simplistic multistep method for fabrication of magnetic nanoparticles tethered mesoionic carbene palladium (II) complex and their application in the Heck coupling reaction was introduced by Kempasiddhaiah *et al.* The MNPs-MIC-Pd heterogeneous catalyst showed excellent catalytic activity toward the Heck reaction. Ease of recovery, environment comparability, and cost-effectiveness are among the main advantages of nanomagnetic catalysts. In addition, the recovered MNPs-MIC-Pd nanomagnetic catalyst can be used at least five times in the Heck reaction. The reaction was performed well in the presence of sodium carbonate base in the EtOH:H₂O (1:1) solvent system at room temperature (Scheme 11).⁴⁷



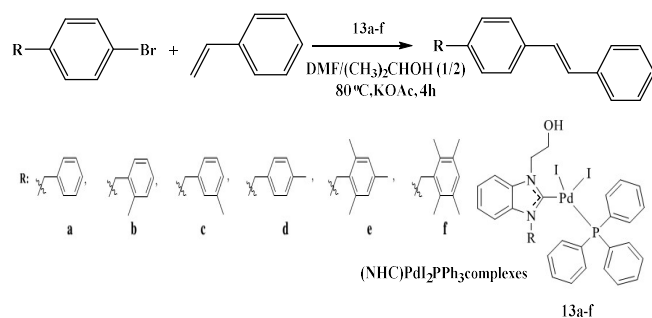
Scheme 11. Heck coupling reaction using MNPs-MIC-Pd

Borah group showed that Pd-PEPPSI NHCs is air and moisture-stable complexes. They were applied the PEPPSI-Pd-NHC complex, for the first time, for Heck reactions in an aqueous medium. The reaction yields reported from good to excellent (Scheme 12).⁴⁸



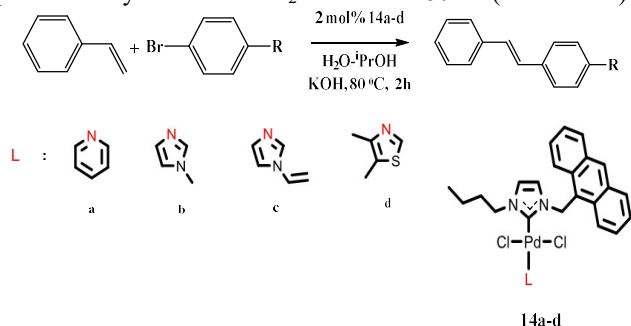
Scheme 12. Heck coupling reaction using Pd-PEPPSI nanoparticles

Recently, Erdemir *et al.*, presented six new Pd-based complexes containing a mixture of *N*-heterocyclic carbene (NHC) and triphenylphosphine (PPh₃) ligands synthesized from the reaction of PPh₃ with (NHC)PdI₂(pyridine). The produced (NHC)PdI₂(PPh₃) complexes was used for the Heck coupling reaction from the reaction of styrene and aryl bromides in the presence of ligands **13a-f** and KOAc as a base in DMF/(CH₃)₂CHOH (1/2) at 80 °C. The authors achieved between 80 and 100% catalytic conversion of the complexes from the reaction of styrene and aryl bromides (Scheme 13).⁴⁹



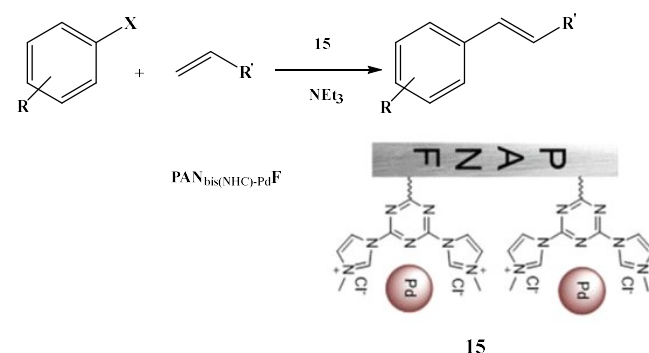
Scheme 13. Heck coupling reaction using (NHC)PdI₂(PPh₃) complexes

In 2020, Karataş *et al.*, reported the synthesis of four novel imidazole-based palladium *N*-heterocyclic carbene complexes **14a-d**. The catalytic activity of these complexes was investigated for Heck reactions. The authors believe that complex **14d** showed the best catalytic activity for the Heck reaction. The reaction was carried out in the presence of potassium hydroxide and H₂O-*i*-PrOH at 80 °C (Scheme 14).⁵⁰



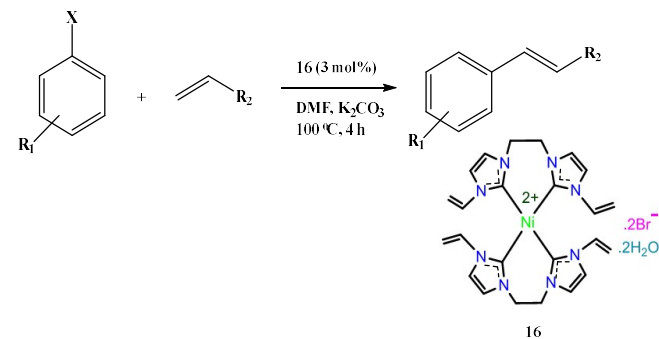
Scheme 14. Heck coupling reaction using imidazole-based palladium *N*-heterocyclic carbene complexes

Zhang *et al.*, reported the synthesis study of a new functionalized fiber with bis (*N*-heterocyclic carbene) structure made using polyacrylonitrile fiber (PANF). This functionalized fiber was used for the effective catalysis of the Heck reaction with high catalytic activity. The Heck reaction was carried out from the reaction between aryl halides and alkenes in the presence of NEt₃ as a base and PAN_{bis}(NHC)-PdF catalyst (Scheme 15).⁵¹



Scheme 15. Heck coupling reaction using PAN_{bis}(NHC)-PdF

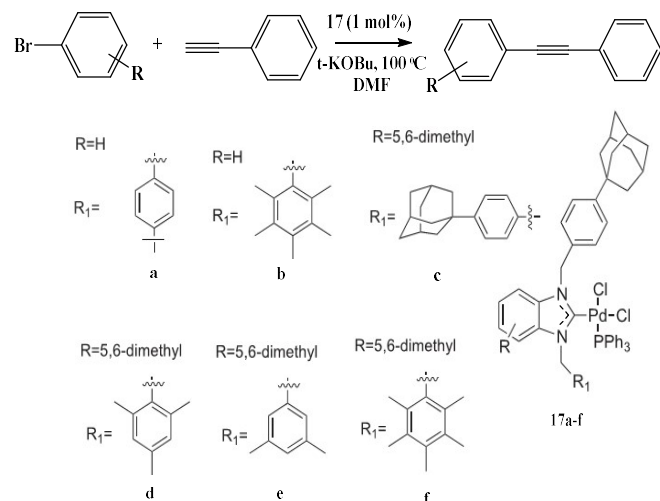
Nirmala *et al.*, synthesized a new homoleptic nickel(II) bis-carbene complex. This complex **16** showed excellent catalytic activities with only 3% catalyst loading for Heck reactions. The reaction was carried out in the presence of K₂CO₃ as a base in DMF at 100 °C (Scheme 16).⁵²



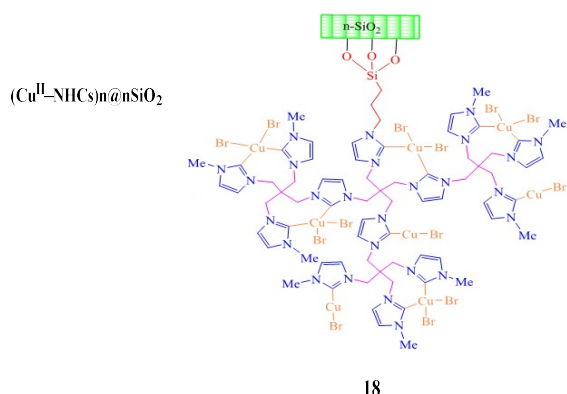
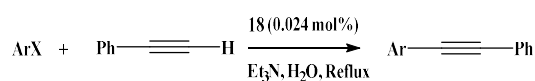
Scheme 16. Heck coupling reaction using nickel(II) bis-carbene complex

Sonogashira coupling reactions. In 2018, Dehimat *et al.*, presented complexes **17a-f** as the catalysts for the Sonogashira reaction in aerobic and copper-free conditions. Sonogashira reaction between phenylacetylene and aryl bromides was carried out in DMF solvent. Low catalyst loading and high catalytic activity in the Sonogashira reaction are among the advantages of these catalysts (Scheme 17).³¹

In 2019, Khajehzadeh *et al.*, introduced complex **18** (poly(*N*-heterocyclic carbene Cu complex) immobilized on nano-silica). The catalytic activity of this new catalyst was studied in the Sonogashira cross-coupling reactions. The (Cu^{II}-NHCs)_n@nSiO₂ heterogeneous catalyst showed advantages such as high reusability, good to excellent yield, short reaction time, and easy isolation (Scheme 18).⁵³



Scheme 17. Sonogashira reaction using Pd-NHC



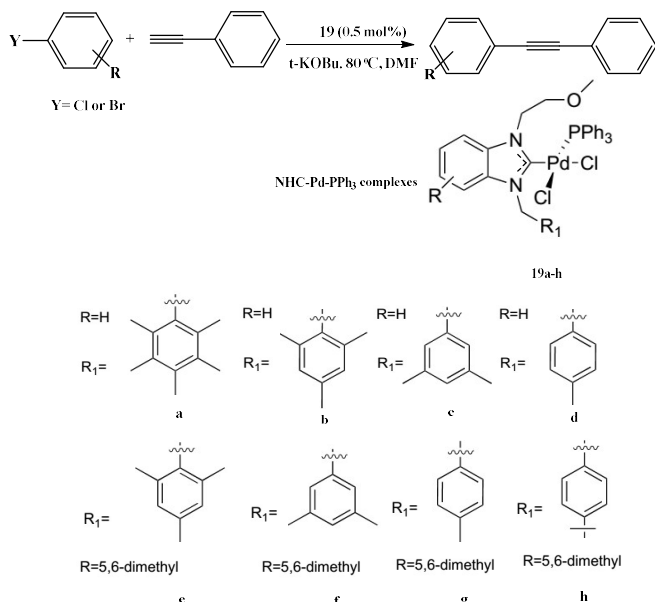
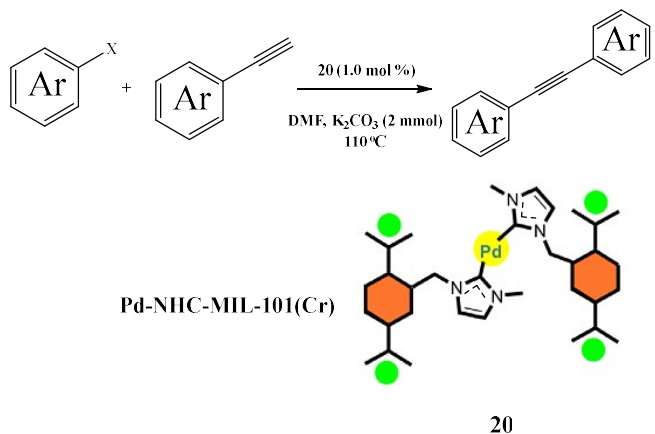
18

Scheme 18. Sonogashira reaction using $(\text{Cu}^{\text{II}}\text{-NHC})_n@n\text{SiO}_2$

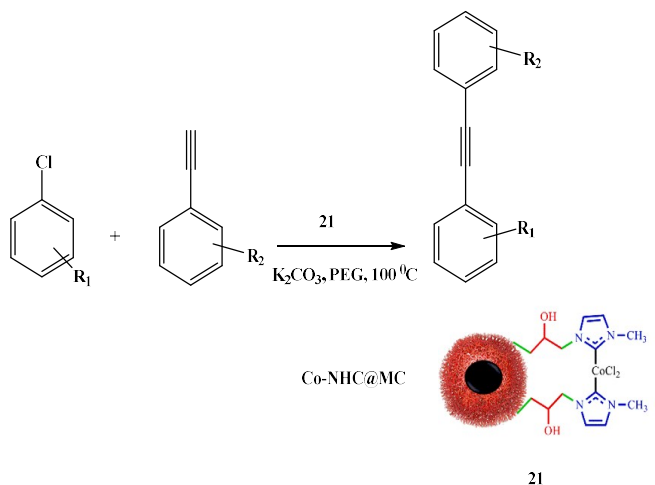
Touj *et al.*, presented complexes **19a-h**. These complexes were used for Sonogashira cross-coupling reactions between phenylacetylene and aryl bromides in DMF at 80 °C. Palladium complexes showed high catalytic activity. The high stability of catalysts and low catalyst loading were among the other advantages of this method (Scheme 19).⁵⁴

Niknam *et al.*, introduced Immobilized Pd on a NHC-functionalized metal-organic framework MIL-101(Cr) catalyst for Cu-free Sonogashira reaction. The reaction was carried out in the presence of MIL-101(Cr)-NHC as a catalyst and K_2CO_3 as a base in DMF as solvent at 110 °C with high efficiency⁵⁵ (Scheme 20).

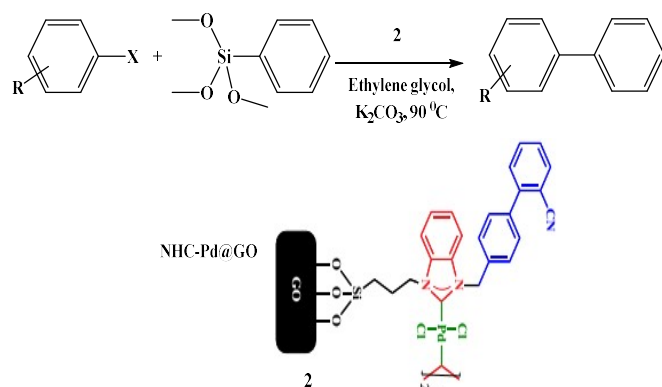
Hajipour *et al.*, synthesized cobalt-NHC (*N*-Heterocyclic carbene) complex **21**. It was found that the synthesized catalyst is efficient in this field. Sonogashira coupling showed high activity and recyclability in polyethylene glycol (PEG) as a green reaction medium. The reaction was carried out in PEG and the presence of K_2CO_3 as base using **21** as catalyst at 100 °C (Scheme 21).⁵⁶

Scheme 19. Sonogashira reaction using NHC-Pd-PPh₃

Scheme 20. Sonogashira reaction using MIL-101(Cr)-NHC

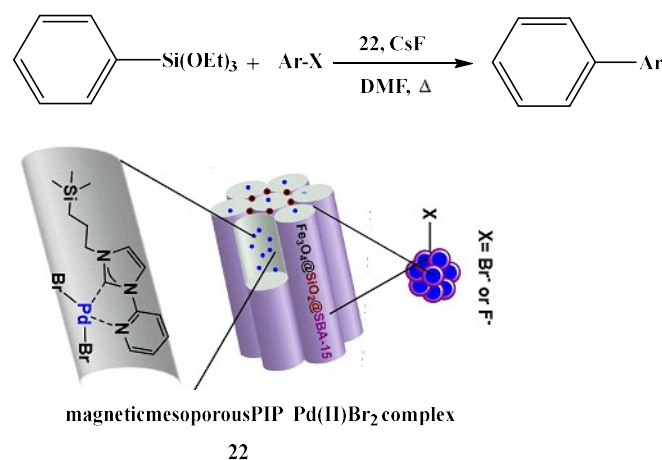
Scheme 21. Sonogashira reaction using Cobalt-NHC (*N*-Heterocyclic carbene) complex

Hiyama coupling reactions. Kandathil *et al.*, reported the catalytic efficiency of complex **2** (*N*-heterocyclic carbene (NHC)-palladium(II) complex) for the Hiyama coupling reactions. Complex **2** efficiently catalyzed Hiyama coupling reactions. The high yield of products, low-cost reagents, greener reaction conditions, and high recyclability of catalyst **2** have turned it into an environmentally friendly catalyst system. The Hiyama coupling reaction was performed from the reaction between aryl halides and trimethoxyphenylsilane in the presence of K_2CO_3 as a base in ethylene glycol as a green medium at 90 °C (Scheme 22).⁵⁷



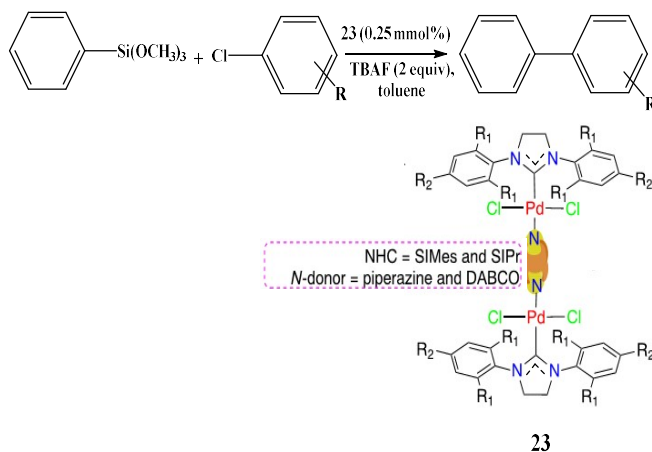
Scheme 22. Hiyama coupling using *N*-heterocyclic carbene (NHC)-palladium(II) complex

Nuri *et al.*, designed a highly efficient and recoverable magnetic SBA-15 functionalized with a NHC-Pd(II) catalyst. This catalyst was successfully used for the reaction of triethoxyphenylsilane and aryl halides (Scheme 23).⁵⁸



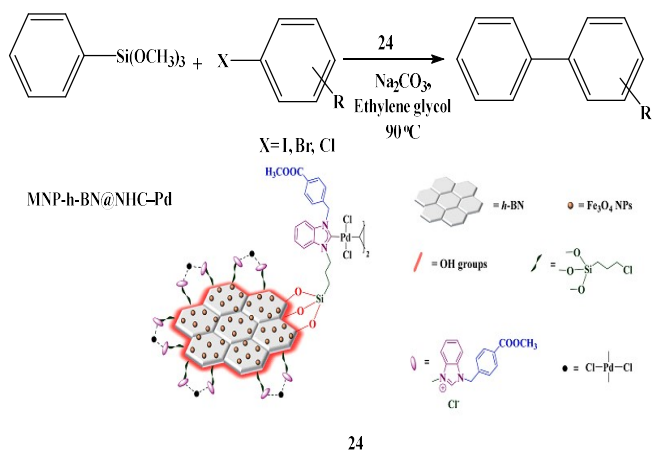
Scheme 23. Hiyama coupling using NHC-Pd

Wang *et al.*, prepared complex **23**. These complexes act as catalysts for the coupling of aryl chlorides with phenyltrimethoxysilane to produce biaryl products. It has been reported that these complexes have shown good catalytic activity and resilience to different chemical functions (Scheme 24).⁵⁹



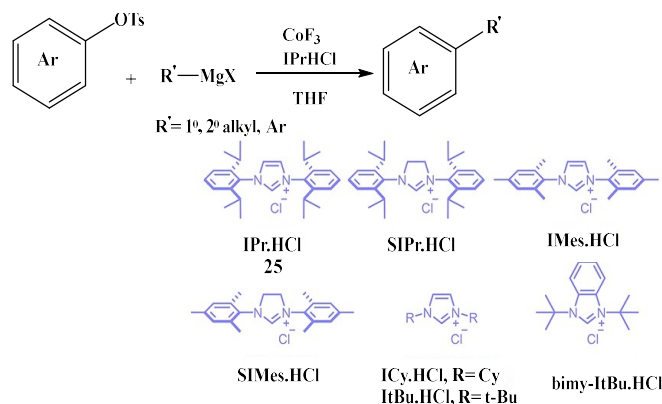
Scheme 24. Hiyama coupling using NHC-Pd

Antony *et al.*, designed an efficient, effective, and heterogeneous magnetic catalyst. The synthesized catalyst **24** was investigated for its catalytic ability in a fluoride-free Hiyama cross-coupling reaction, and it was recycled for up to six cycles without significant loss of activity (Scheme 25).⁶⁰

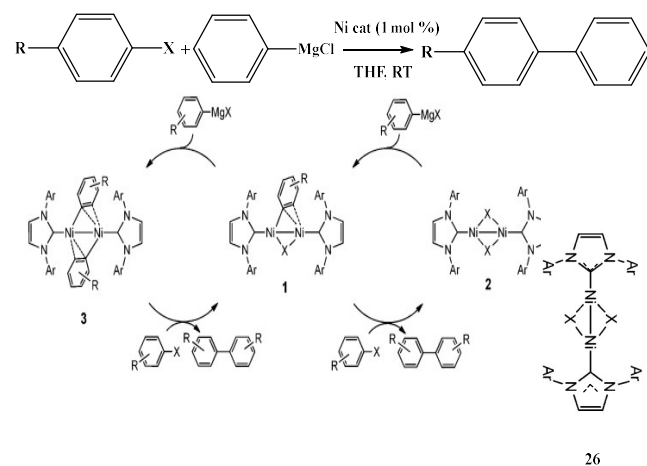


Scheme 25. Hiyama coupling using MNP-h-BN@NHC-Pd

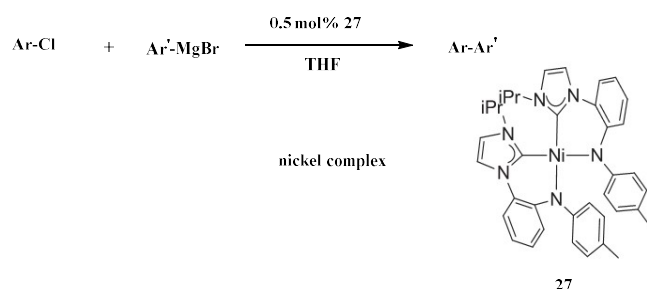
Kumada coupling reactions. Piontek *et al.*, reported the first cobalt-catalyzed cross-coupling of aryl tosylates with alkyl and aryl Grignard reagents. This reaction was carried out through highly selective C-O bond activation, which produced the corresponding products in high yield (Scheme 26).⁶¹ Matsubara *et al.*, showed that highly active nickel (I) complexes **26** play an effective role in the catalytic cycle of the Kumada cross-coupling reaction of aryl halides. Komada reaction of aryl halides was carried out by nickel complexes in the presence of THF at ambient temperature (Scheme 27).⁶² Zhang *et al.*, synthesized three nickel complexes. The catalytic ability of three nickel complexes was tested in the Kumada coupling reaction. Complex **27** showed the best catalytic activity. The coupling of aryl chlorides with Grignard reagents showed good yields with only 0.5% of complex **27** (Scheme 28).⁶³



Scheme 26. Kumada coupling reactions



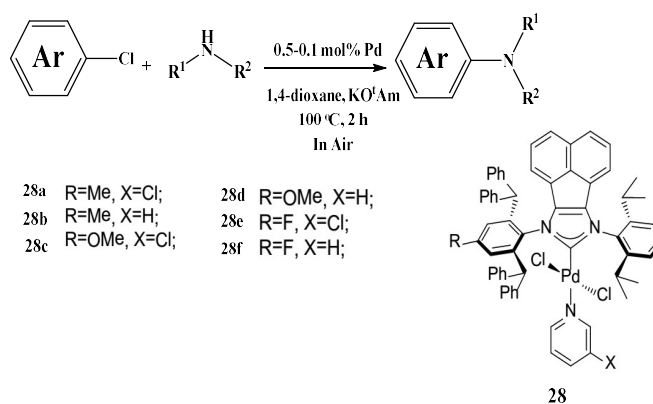
Scheme 27. Kumada coupling reactions using nickel (I) complexes



Scheme 28. Kumada coupling reactions using nickel complexes

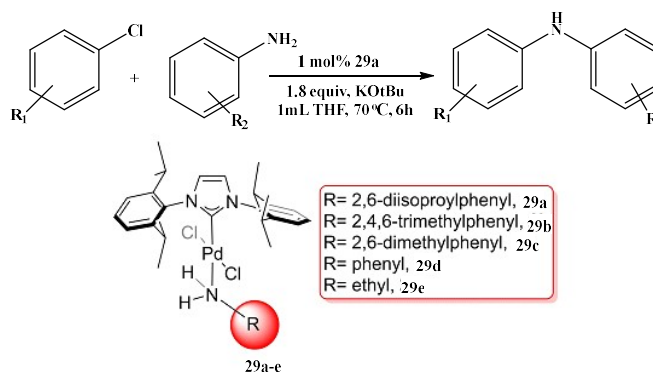
C-X cross-coupling reactions

Buchwald-Hartwig coupling reactions. Lan *et al.*, introduced complexes **28a-f** as excellent pre-catalysts for Hartwig amination of aryl chlorides with the existing amines in the air. They indicated that the coupling products are obtained in excellent yield in the presence of 0.5–0.1 mol% loading of palladium. The evaluation of the pre-catalysts confirmed that the flexible steric bulky and strong σ -donating nature are necessary to secure high catalytic activity (Scheme 29).⁶⁴



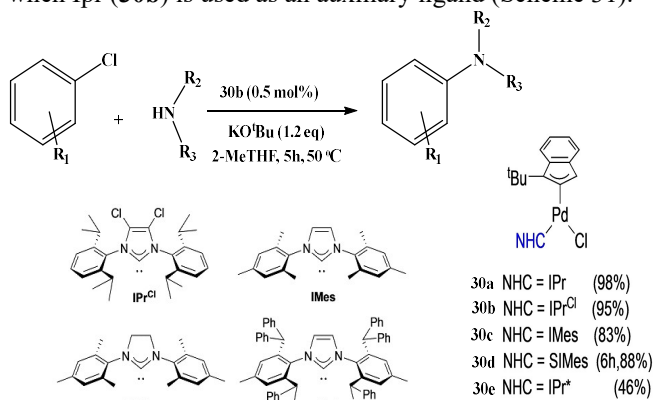
Scheme 29. Buchwald-Hartwig coupling reactions using NHC-Pd

Hsu *et al.*, investigated complexes **29a-e** for the Buchwald reaction. These complexes showed good catalytic activities for the Buchwald-Hartwig reaction of aryl chlorides to prepare arylated anilines under mild conditions. All reactions were performed in the air and desired coupling products were obtained in moderate to high yields under optimal conditions (Scheme 30).⁶⁵



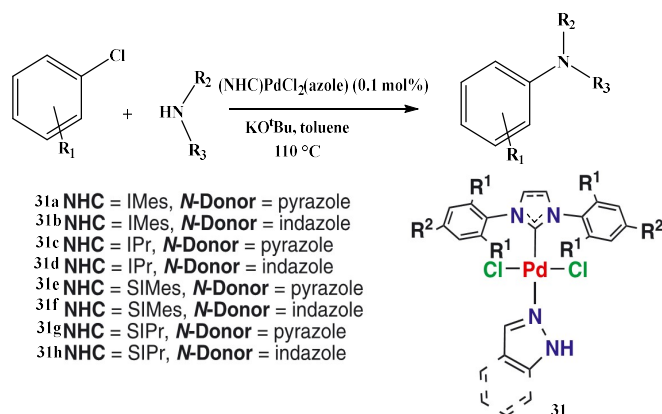
Scheme 30. Buchwald-Hartwig coupling reactions using NHC-Pd

Liu *et al.*, presented the easy synthesis of pre-catalysts **30a-e**. These synthesized pre-catalysts showed excellent catalytic activity in classical Buchwald-Hartwig reactions, especially when Ipr (**30b**) is used as an auxiliary ligand (Scheme 31).⁶⁶



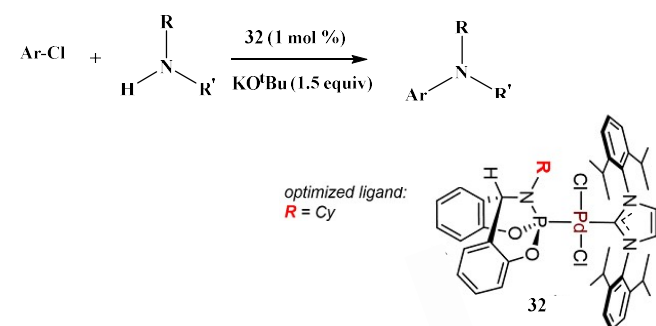
Scheme 31. Buchwald-Hartwig coupling reactions using NHC-Pd

Yang introduced complexes **31a-h**. These complexes showed good catalytic activities in Buchwald-Hartwig amination for aryl chlorides (Scheme 32).⁶⁷



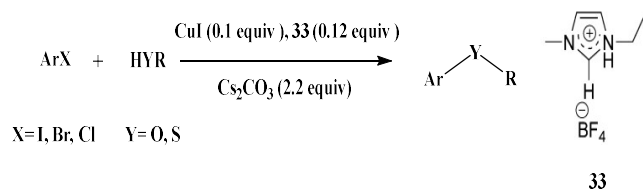
Scheme 32. Buchwald-Hartwig coupling reactions using NHC-Pd

Kim *et al.*, investigated a synergistic effect of *N*-heterocyclic carbene and phosphorus ligands in palladium-catalyzed Buchwald-Hartwig amination reactions. They argued that catalyst **32** is a highly efficient pre-catalyst for coupling primary or secondary amines with aryl chlorides in high yield under mild reaction conditions (Scheme 33).⁶⁸



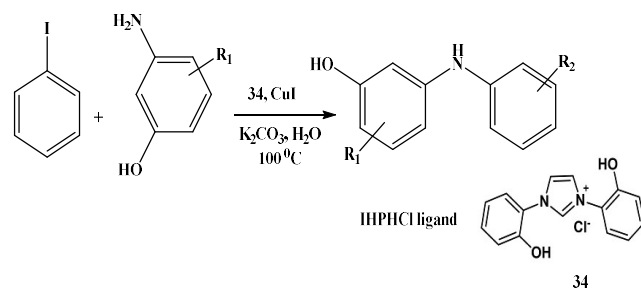
Scheme 33. Buchwald-Hartwig coupling reactions using NHC-Pd

Ullmann-type reaction. In 2016, Wu *et al.*, introduced simple *N*-heterocyclic compound **33** as a very efficient ligand in the Ullmann coupling reaction. The resulting products included ethers and thioethers. They stated that the ligand precursors are low-cost and readily available, and the process is simple to implement. They are also more economical and less toxic alternatives to heavy metal-based catalysts for Ullmann-type cross-coupling reactions (Scheme 34).⁶⁹



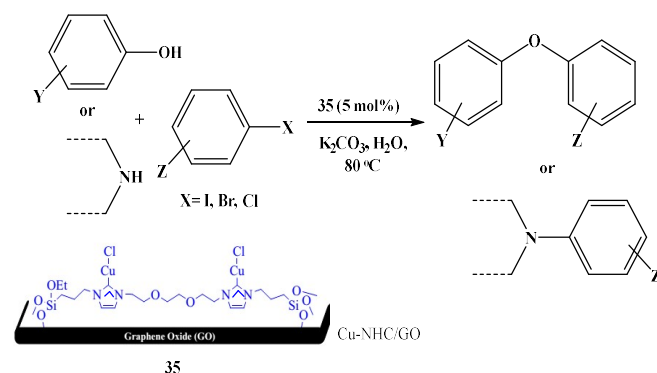
Scheme 34. Ullmann-type reaction using CuI and ligand **33**

Paul *et al.*, presented a simple and green method for the selective *N*-arylation of 3-aminophenols with a good substrate range and efficiency (60-88%). They believed that the presence of chelating group (OH) on **34** (IHPHCl (1,3-bis-[2-hydroxyphenyl] imidazolium chloride)) increases *N*-selectivity⁷⁰ (Scheme 35).



Scheme 35. Ullmann-type reaction using CuI and ligand **34**

Imanpour *et al.*, studied highly active and stable *N*-Heterocyclic Carbene **35** for *O*-arylation and *N*-arylation reactions in water. They noted that when the ionic liquid was attached to the graphene surface, thermal stability increased. The Cu catalyst was active in the *O*-arylation of phenols with aryl halides and the *O*-arylation of azoles with aryl halides in water as the reaction medium. They reported a high yield of products with this catalytic system (Scheme 36).⁷¹

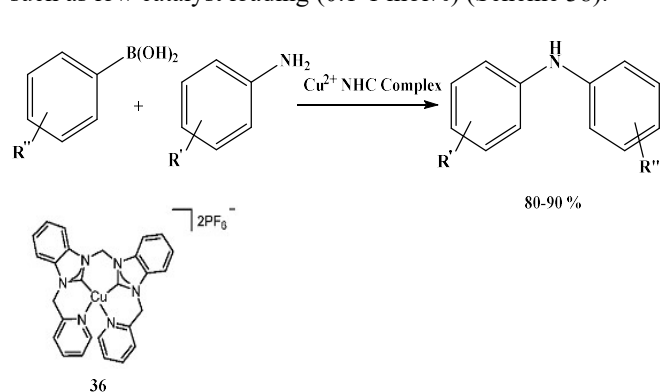


Scheme 36. Ullmann-type reaction using Cu-NHC/GO

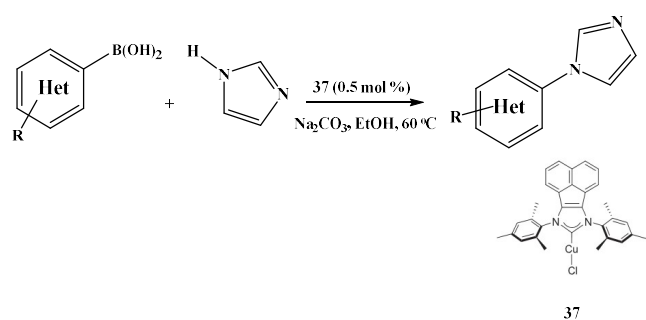
Chan-Lam coupling reaction. Cope *et al.*, synthesized complex **36**. They investigated this complex for the Chan coupling reaction. The simple synthesis of this framework and the use of cheap metals in this system make copper (II) complex **36** significantly applicable as a catalyst for cross-coupling reactions (Scheme 37).⁷²

Guo *et al.*, developed an efficient protocol for Chan-Evans-Lam reactions involving aryl boronic acids and azole and amine derivatives based on a series of *N*-heterocyclic complexes **37** as pre-catalysts. They also investigated the relationship between the structure of the catalyst and the catalytic properties. The results showed that modification of the *N*-heterocyclic carbene backbone with the acenaphthyl group can have a significant beneficial effect on placenta

efficiency. The advantages of this protocol include mild reaction conditions of non-toxic solvent and oxidation by air, such as low catalyst loading (0.1-1 mol%) (Scheme 38).⁷³



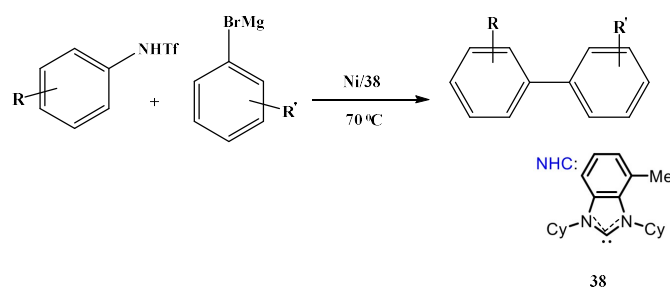
Scheme 37. Chan coupling using copper (II) complex



Scheme 38. Chan coupling using Cu-NHC

Cross-coupling reactions by selective C-X cleavage

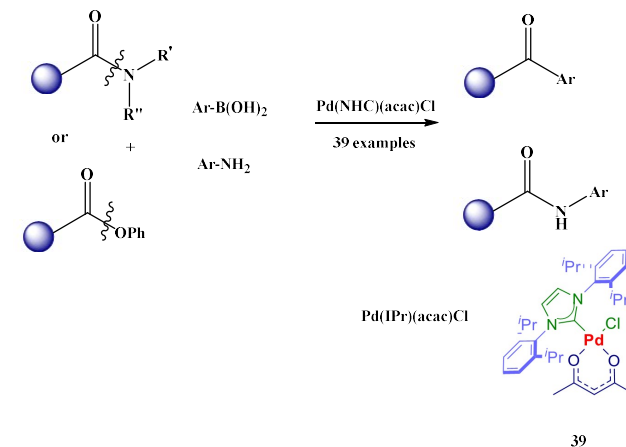
Zhang *et al.*, introduced the new *N*-heterocyclic carbene **38**. This *N*-heterocyclic carbene had high reactivity for C-N cleavage and C-C cross-coupling reaction. They noted that an ortho-directing group is not required to break the C-N bond of sulfonyl-protected anilines, which is not limited to π -expanded anilines, and sulfamidomagnesium salt is the main coupling agent (Scheme 39).⁷⁴



Scheme 39. Cross-coupling reactions by selective C-N cleavage

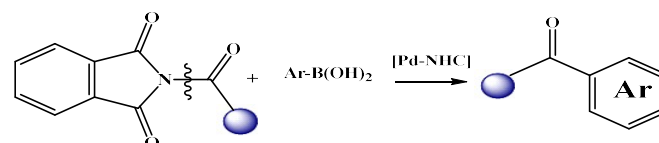
Zhou *et al.*, investigated Pd(II)-NHC pre-catalysts for Suzuki, and Buchwald-Hartwig cross-coupling by selective N-C or O-C cleavage. These pre-catalysts are air-stable and readily available. The study showed that [Pd(NHC)(acac)Cl] should be routinely included during the development of new coupling

methods because these pre-catalysts are highly active and easier to synthesize (Scheme 40).⁷⁵



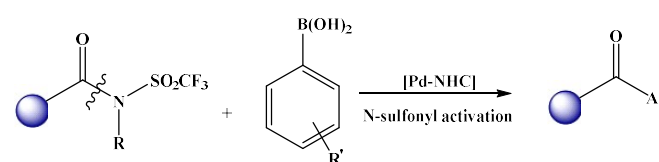
Scheme 40. Buchwald-Hartwig cross-coupling by selective N-C or O-C cleavage

Rahman *et al.*, reported a highly selective method for Suzuki-Miyaura cross-coupling of *N*-acylphthalimides through N-C(O) acyl cleavage catalyzed by Pd-NHC pre-catalysts. They stated that pre-catalysts supported by a sterically demanding IPr (1,3-Bis-(2,6-diisopropylphenyl)imidazol-2-ylidene) subligand, provide high yields in this reaction (Scheme 41).⁷⁶



Scheme 41. Suzuki-Miyaura cross-coupling of *N*-acylphthalimides through N-C(O) acyl cleavage

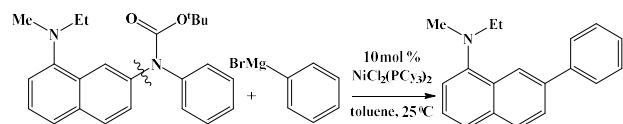
Shi *et al.*, reported direct and highly chemically selective Suzuki-Miyaura cross-coupling of trifluoromethane sulfonamides by N-C(O) selective amide bond cleavage. They believe that mechanistic studies support spin inversion, electronic activation, and selective insertion under mild conditions. They suggest that triflamides should routinely be considered as precursors in amide bond cross-coupling (Scheme 42).⁷⁷



Scheme 42. Suzuki-Miyaura cross-coupling by N-C(O) selective amide bond cleavage

Zhang *et al.*, studied a nickel-catalyzed Kumada coupling of aniline derivatives with selective cleavage of aryl C-N bonds under mild reaction conditions. They noted that the Boc-protected aromatic amines coupling with aryl Grignard

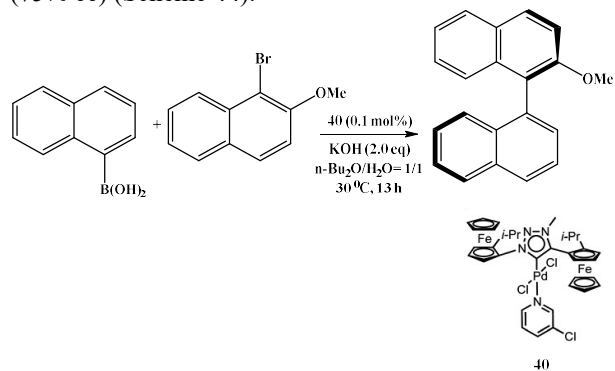
reagents results in asymmetric biaryls without pre-installation of an ortho-directing group on the anilines (Scheme 43).⁷⁸



Scheme 43. Kumada coupling with selective cleavage of aryl C-N bonds

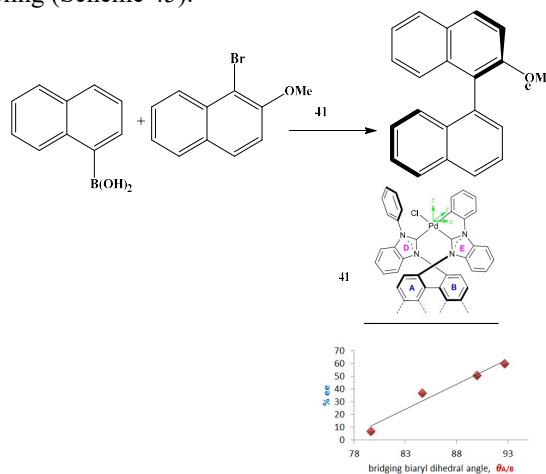
Asymmetric cross-coupling reactions

Haraguchi *et al.*, prepared chiral **40** pre-catalyst and used it in the asymmetric Suzuki-Miyaura cross-coupling reaction. They examined the electronic and spatial nature of this complex and demonstrated its powerful ability to donate electrons and its high spatial volume. The complex with such unique properties exhibited a very high catalytic activity of TON= 420 for the asymmetric Suzuki-Miyaura cross-coupling. The coupling product had good enantioselectivity (75% ee) (Scheme 44).⁷⁹



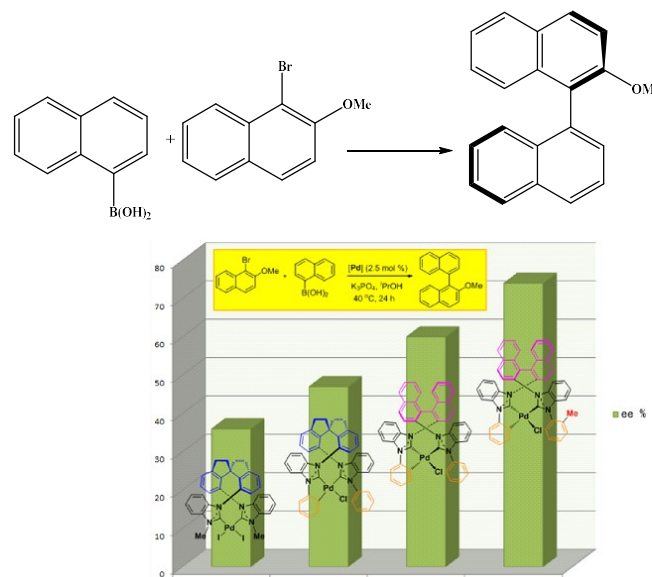
Scheme 44. The asymmetric Suzuki-Miyaura cross-coupling reaction

Zhang's group synthesized a series of complexes **41** and investigated their use in asymmetric Suzuki couplings of aryl halide and aryl boronic acid. They believed in the existence of a linear correlation between the dihedral angle in these palladium complexes and reported selectivity of cross-coupling (Scheme 45).⁸⁰



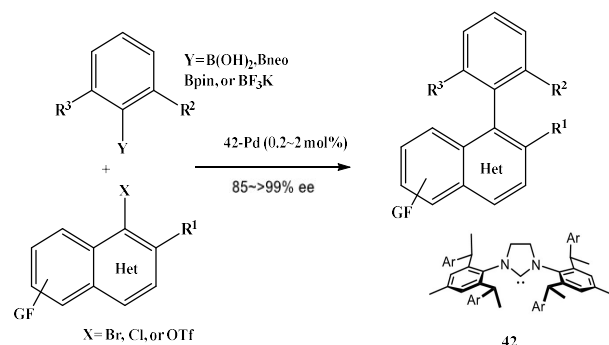
Scheme 45. The asymmetric Suzuki couplings

Zhang's group investigated the asymmetric Suzuki-Miyaura cross-coupling reactions. They noted that the enantioselectivity of biaryl products has been greatly improved (up to 74% ee). According to the results for this type of palladium catalyst, the structural features of chiral scaffolds play a decisive role in the enantioselectivity of cross-coupling reactions (Scheme 46).⁸¹



Scheme 46. The asymmetric Suzuki-Miyaura cross-coupling reactions

Shen's group studied highly enantioselective Suzuki-Miyaura cross-coupling reactions. They reported that this protocol provided general and efficient access to various atropisomeric biaryls and heterobiaryls in excellent enantioselectivity (up to 99% ee) without the need to use bulky ortho-substituted substrates and it was useful to synthesize tetra-ortho-substituted biaryls (Scheme 47).⁸²

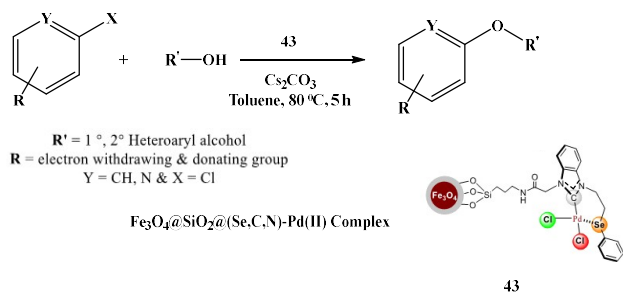


Scheme 47. Enantioselective Suzuki-Miyaura cross-coupling reactions

Green protocols for cross-coupling reactions

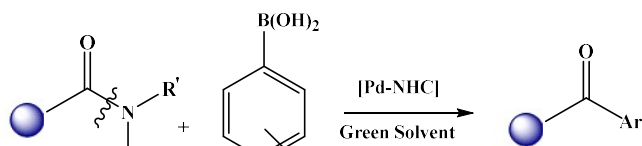
Khandaka *et al.*, used an environmentally friendly heterogeneous catalyst **43** for the cross-coupling of alcohols and chloroarenes. They reported that the synthesized catalyst is efficient for C-O cross-coupling reactions and can be easily

separated from the reaction medium by an external magnet. The novel dual separation strategy with negligible palladium leaching from complex **43** makes it an environmentally friendly and economical catalyst in terms of activity and recyclability (Scheme 48).⁸³



Scheme 48. An environmentally friendly heterogeneous catalyst **43** for the cross-coupling

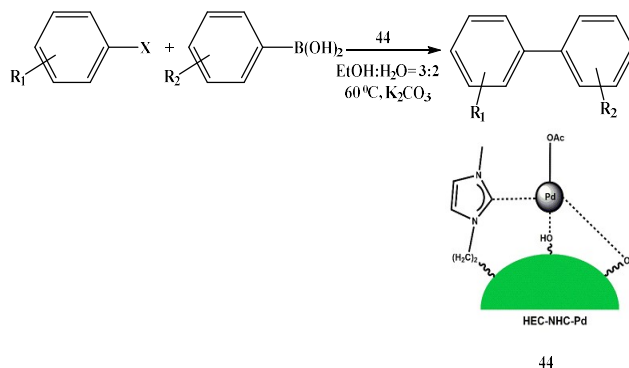
Lei *et al.*, developed an effective, practical, and environmentally friendly protocol for Suzuki-Miyaura coupling. They evaluated a range of environmentally friendly solvents in Suzuki-Miyaura coupling of amides in an attempt to provide the first solvent selection guide for potent C-C coupling by amide bond cleavage. They considered 14 solvents and 10 Pd-catalysts and introduced *i*-PrOAc as a recommended and environmentally friendly solvent for coupling (Scheme 49).⁸⁴



Scheme 49. Practical, and environmentally friendly protocol for Suzuki-Miyaura coupling

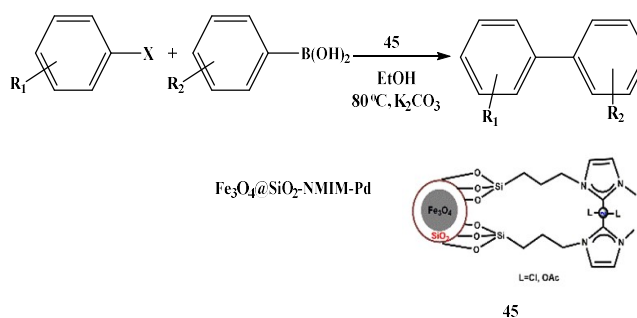
Dong *et al.*, developed a new approach to Suzuki reaction in an environmentally friendly and green process by using **44** as an efficient catalyst. They used environmentally friendly catalysts effectively in the Suzuki reaction in ethanol aqueous solution (Scheme 50).⁸⁵

Dong *et al.*, showed an environmentally friendly and suitable method for Suzuki cross-coupling reaction. They designed and prepared the environmentally friendly catalyst **45**. The resulting catalyst showed excellent catalytic activity towards the Suzuki cross-coupling reaction for the synthesis of the corresponding biaryls in good to excellent yields (up to 96%) under aerobic conditions. This catalyst can be easily recovered through magnetic separation in several cycles. The synthesized palladium complex showed advantages such as



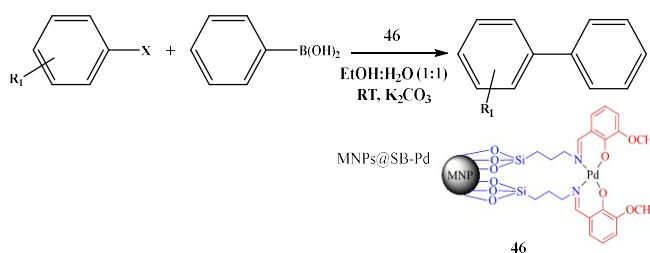
Scheme 50. New approach to Suzuki reaction in an environmentally friendly and green process

low toxicity, high thermal stability, and insensitivity to oxygen in coupling reactions (Scheme 51).⁸⁶



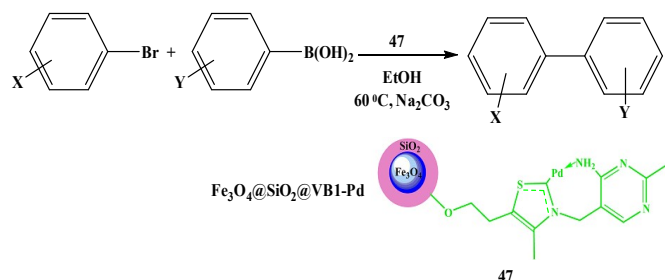
Scheme 51. An environmentally friendly and suitable method for Suzuki cross-coupling reaction

Kandathil *et al.*, described a green and environmentally friendly method for Suzuki-Miyaura cross-coupling using catalysis **46**. They used synthesized Pd nanomagnetic catalysts with air and moisture stability in C-C bond formation through Suzuki-Miyaura cross-coupling reactions. The major advantages of the proposed method include the use of a green environment, environmental compatibility, efficient preparation which leads to high yields of products. Besides, the nanomagnetic Pd-catalyst was easily separated from the reaction mixture with the help of an external magnetic field and performed well for five consecutive cycles in the Suzuki-Miyaura cross-coupling without significant loss of catalytic activity (Scheme 52).⁸⁷



Scheme 52. A green and environmentally friendly method for Suzuki-Miyaura cross-coupling

Rafiee *et al.*, reported a green approach for C–C Coupling at 60 °C using **47** as an efficient catalyst in ethanol solvent. The synthesized catalyst was a separable and highly active magnetic catalyst for the Suzuki coupling reactions of various aryl halides with substituted phenylboronic acids. The desired products were obtained with excellent yields in short reaction times (Scheme 53).⁸⁸



Scheme 53. Green approach for C–C Coupling

Conclusion and future scope

Considering the importance of cross-coupling reaction chemistry in the synthesis of pharmaceutical molecules, the present review investigated the performance of NHC complexes as efficient catalysts with high activity and selectivity in various types of cross-coupling reactions. Various types of carbon-carbon and carbon-heteroatom cross-couplings, catalyzed by NHCs reactions efficiently, were reviewed. Moreover, the catalytic performance of NHCs in some cross-coupling reactions of selective C–X cleavage, asymmetric cross-couplings by chiral NHCs, and green methods catalyzed by NHCs for cross-coupling reactions was also covered. According to the *literature* review, it was observed that NHCs had high catalytic activity, selectivity, stability against moisture and air, as well as low toxicity. Products with high yields were obtained economically in a short time under green and environment-friendly conditions. We hope that this review will attract interest from researchers and encourage further research on the application of NHCs in key cross-coupling reactions.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

Fatemeh Pirani: Investigation, Writing-Original draft preparation, Visualization.

Hossein Eshghi: Supervision, Conceptualization, Writing-Reviewing and Editing.

Author(s) ID

Hossein Eshghi: <https://orcid.org/0000-0002-8417-220X>

Fatemeh Pirani: <https://orcid.org/0009-0000-8251-7502>

References

1. E. Peris, *Chem. Rev.*, **2017**, *118*, 9988-10031.
2. J. Liu, X. -N. Xing, J. -H. Huang, L. -Q. Lu, W. -J. Xiao, *Chem. Sci.*, **2020**, *11*, 10605-10613.
3. S. Singha, E. Serrano, S. Mondal, C. G. Daniliuc, F. Glorius, *Nat. Catal.*, **2020**, *3*, 48-54.
4. H. Ohmiya, *ACS Catal.*, **2020**, *10*, 6862-6869.
5. Q. Deng, Y. Shen, H. Zhu, T. Tu, *Chem. Comm.*, **2017**, *53*, 13063-13066.
6. K. Matsubara, Y. Fukahori, T. Inatomi, S. Tazaki, Y. Yamada, Y. Koga, S. Kanegawa, T. Nakamura, *Organometallics.*, **2016**, *35*, 3281-3287.
7. I. Kim, H. Im, H. Lee, S. Hong, *Chem. Sci.*, **2020**, *11*, 3192-3197.
8. X. Wang, R. Yang, B. Zhu, Y. Liu, H. Song, J. Dong, Q. Wang, *Nat. Commun.*, **2023**, *14*, 2951.
9. S. Barik, S. Shee, A. T. Biju, *Org. Lett.*, **2022**, *24*, 6066-6071.
10. A. Mnasri, A. S. Al-Ayed, İ. Özdemir, N. Gürbüz, H. Naceur, *J. Mol. Struct.*, **2021**, *1234*, 130204.
11. M. M. Heravi, S. Asadi, S. M. Hoseini Chopani, E. Jaderi, *Appl. Organomet. Chem.*, **2020**, *34*, e5805.
12. L. Aloui, R. Abidi, M. J. Chetcuti, *Inorganica Chim. Acta.*, **2020**, *505*, 119494.
13. M. Kaloğlu, N. Kaloğlu, S. Günal, İ. Özdemir, *J. Coord. Chem.*, **2022**, *74*, 3031-3047.
14. F. Prencipe, A. Zanfardino, M. Di Napoli, F. Rossi, S. D'errico, G. Piccialli, G. F. Mangiatordi, M. Saviano, L. Ronga, M. Varcamonti, *Int. J. Mol. Sci.*, **2021**, *22*, 2497.
15. S. Şahin-Bölükbaşı, P. Cantürk-Kılıçkaya, O. Kılıçkaya, *Drug Dev. Res.*, **2021**, *82*, 907-926.
16. W. Liu, R. Gust, *Coord. Chem. Rev.*, **2016**, *329*, 191-213.
17. D. Bensalah, N. Gurbuz, I. Özdemir, R. Gatri, L. Mansour, N. Hamdi, *Bioinorg Chem Appl.*, **2023**, *2023*.
18. M. Bahadori, S. Tangestaninejad, M. Moghadam, V. Mirkhani, A. Mechler, I. Mohammadpoor-Baltork, F. Zadehahmadi, *Microporous Mesoporous Mater.*, **2017**, *253*, 102-111.
19. A. Aktaş, Ü. Keleştemur, Y. Gök, S. Balcıoğlu, B. Ateş, M. Aygün, *J. Iran. Chem. Soc.*, **2018**, *15*, 131-139.
20. S. Thanneeru, K. M. Ayers, M. Anuganti, L. Zhang, C. V. Kumar, G. Ung, J. He, *J. Mater. Chem. C.*, **2020**, *8*, 2280-2288.
21. P. V. G. Reddy, M. V. K. Reddy, R. R. Kakarla, K. V. Ranganath, T. M. Aminabhavi, *Environ. Res.*, **2023**, *115515*.
22. M. S. Ahmad, Y. Nishina, *Nanoscale.*, **2020**, *12*, 12210-12227.
23. J. A. Milligan, J. P. Phelan, S. O. Badir, G. A. Molander, *Angew. Chem., Int. Ed.*, **2019**, *58*, 6152-6163.
24. B. Kim, Y. Kim, S. Y. Lee, *J. Am. Chem. Soc.*, **2020**, *143*, 73-79.

25. H. Y. Bae, D. Höfler, P. S. Kaib, P. Kasaplar, C. K. De, A. Döhning, S. Lee, K. Kaupmees, I. Leito, B. List, *Nat. Chem.*, **2018**, *10*, 888-894.
26. S. Azad, B. B. F. Mirjalili, A. Bamoniri, *Org. Chem. Res.*, **2021**, *7*, 23-31.
27. A. Danesh, M. Aghazadeh, M. Jalilzadeh Hedayati, *Org. Chem. Res.*, **2019**, *5*, 112-116.
28. M. Nasrollahzadeh, Z. Issaabadi, M. M. Tohidi, S. Mohammad Sajadi, *Chem. Rec.*, **2018**, *18*, 165-229.
29. I. Kanwal, A. Mujahid, N. Rasool, K. Rizwan, A. Malik, G. Ahmad, S. A. A. Shah, U. Rashid, N. M. Nasir, *Catalysts*, **2020**, *10*, 443.
30. M. M. Dutta, P. Phukan, *Catal. Commun.*, **2018**, *109*, 38-42.
31. Z. I. Dehimat, S. Yaşar, D. Tebbani, İ. Özdemir, *Inorganica Chim. Acta.*, **2018**, *469*, 325-334.
32. P. Devendar, R. -Y. Qu, W. -M. Kang, B. He, G. -F. Yang, *J. Agric. Food Chem.*, **2018**, *66*, 8914-8934.
33. M. Tarahomi, H. Alinezhad, B. Maleki, *Appl. Organomet. Chem.*, **2019**, *33*, e5203.
34. B. Maleki, R. Nejat, Z. Vahdani, *Polycycl. Aromat. Compd.*, **2022**, *42*, 3638-3650.
35. M. Daryanavard, B. Mohammadi, S. Nadri, M. Joshaghani, *Org. Chem. Res.*, **2021**, *7*, 77-85.
36. N. Attaran, H. Eshghi, *Org. Chem. Res.*, **2021**, *7*, 1-11.
37. M. Akkoc, N. Buğday, S. Altın, S. Yaşar, *Appl. Organomet. Chem.*, **2021**, *35*, e6233.
38. V. Kandathil, B. Kulkarni, A. Siddiqa, M. Kempasiddaiah, B. Sasidhar, S. A. Patil, S. A. Patil, *Catal. Lett.*, **2020**, *150*, 384-403.
39. A.M. Antony, V. Kandathil, M. Kempasiddaiah, B. Sasidhar, S. A. Patil, S. A. Patil, *Catal.*, **2021**, *151*, 1293-1308.
40. F. O. Chahkamali, S. Sobhani, J. M. Sansano, *Catal. Lett.*, **2022**, *152*, 2650-2668.
41. X. Li, X. Yu, W. Zhang, C. Pan, J. Tang, G. Yu, *J. Porous Mater.*, **2022**, *29*, 601-608.
42. Q. Xie, J. Li, X. Wen, Y. Huang, Y. Hu, Q. Huang, G. Xu, Y. Xie, Z. Zhou, *Carbohydr. Res.*, **2022**, *512*, 108516.
43. L. Boubakri, K. Dridi, A. S. Al-Ayed, İ. Özdemir, S. Yasar, N. Hamdi, *J. Coord. Chem.*, **2019**, *72*, 516-527.
44. R. Sedghi, B. Heidari, H. Shahmohamadi, P. Zarshenas, R. S. Varma, *Molecules*, **2019**, *24*, 3048.
45. L. You, R. Tan, X. Wang, J. Hao, S. Xie, G. Xiong, F. Ding, A. S. Potapov, Y. Sun, *Crystals*, **2023**, *13*, 341.
46. D. Kale, G. Rashinkar, A. Kumbhar, R. Salunkhe, *React. Funct. Polym.*, **2017**, *116*, 9-16.
47. M. Kempasiddhaiah, V. Kandathil, R. B. Dateer, B. S. Sasidhar, S. A. Patil, S. A. Patil, *Appl. Organomet. Chem.*, **2019**, *33*, e4846.
48. D. Borah, B. Saha, B. Sarma, P. Das, *J. Chem. Sci.*, **2020**, *132*, 1-10.
49. F. Erdemir, A. Aktaş, D. Barut Celepci, Y. Gök, *Chem. Pap.*, **2020**, *74*, 99-112.
50. M. O. Karataş, N. Özdemir, B. Alici, İ. Özdemir, *Polyhedron*, **2020**, *176*, 114271.
51. H. Zhang, W. Liang, J. Xiao, J. Zhao, *J. Chem. Eng.*, **2023**, *455*, 140592.
52. M. Nirmala, S. Arruri, M. Vaddamanu, R. Karupnaswamy, M. Mannarsamy, M. Adinarayana, P. Ganesan, *Polyhedron*, **2019**, *158*, 125-134.
53. M. Khajehzadeh, M. Moghadam, S. Jamehbozorgi, *Inorganica Chim. Acta.*, **2019**, *485*, 173-189.
54. N. Touj, S. Yaşar, N. Özdemir, N. Hamdi, İ. Özdemir, *J. Organomet. Chem.*, **2018**, *860*, 59-71.
55. E. Niknam, F. Panahi, A. Khalafi-Nezhad, *J. Organomet. Chem.*, **2021**, *935*, 121676.
56. A. R. Hajipour, S. S. Malek, *Mol. Catal.*, **2021**, *508*, 111573.
57. V. Kandathil, A. Siddiqa, A. Patra, B. Kulkarni, M. Kempasiddaiah, B. Sasidhar, S. A. Patil, C. S. Rout, S. A. Patil, *Appl. Organomet. Chem.*, **2020**, *34*, e5924.
58. A. Nuri, Y. Mansoori, A. Bezaatpour, A. Shchukarev, J. P. Mikkola, *ChemistrySelect*, **2019**, *4*, 1820-1829.
59. H. Wang, J. Yang, *Appl. Organomet. Chem.*, **2017**, *31*, e3543.
60. A. M. Antony, V. Kandathil, M. Kempasiddaiah, R. B. Dateer, S. A. Patil, *J. Phys. Chem. Solids*, **2023**, *177*, 111283.
61. A. Piontek, W. Ochędzan-Siodłak, E. Bisz, M. Szostak, *ChemCatChem*, **2021**, *13*, 202-206.
62. K. Matsubara, H. Yamamoto, S. Miyazaki, T. Inatomi, K. Nonaka, Y. Koga, Y. Yamada, L. F. Veiros, K. Kirchner, *Organometallics*, **2017**, *36*, 255-265.
63. S. Zhang, X. Li, H. Sun, O. Fuhr, D. Fenske, *J. Organomet. Chem.*, **2016**, *820*, 41-45.
64. X. -B. Lan, Y. Li, Y. -F. Li, D. -S. Shen, Z. Ke, F. -S. Liu, *J. Org. Chem.*, **2017**, *82*, 2914-2925.
65. Y. C. Hsu, M. T. Chen, *Eur. J. Inorg. Chem.*, **2022**, *2022*, e202100828.
66. Y. Liu, T. Scattolin, A. Gobbo, M. Beliš, K. Van Hecke, S. P. Nolan, C. S. Cazin, *Eur. J. Inorg. Chem.*, **2022**, *2022*, e202100840.
67. J. Yang, *Appl. Organomet. Chem.*, **2017**, *31*, e3734.
68. M. Kim, T. Shin, A. Lee, H. Kim, *Organometallics*, **2018**, *37*, 3253-3258.
69. J. P. Wu, A. K. Saha, N. Haddad, C. A. Busacca, J. C. Lorenz, H. Lee, C. H. Senanayake, *Adv. Synth. Catal.*, **2016**, *358*, 1924-1928.
70. S. Paul, B. P. Joy, G. Sasikala, A. G. Raghuthaman, V. B. Gudimetla, *ChemistrySelect*, **2020**, *5*, 15004-15009.
71. M. Imanpour, K. Lamei, H. Eshghi, *Catal. Lett.*, **2023**, *153*, 1390-1409.
72. J. D. Cope, P. E. Sheridan, C. J. Galloway, R. F. Awoyemi, S. L. Stokes, J. P. Emerson, *Organometallics*, **2020**, *39*, 4457-4464.
73. M. Guo, B. Chen, K. Chen, S. Guo, F. -S. Liu, C. Xu, H. -G. Yao, *Tetrahedron Lett.*, **2022**, *107*, 154074.
74. Z. -B. Zhang, J. -B. Xia, *Org. Lett.*, **2020**, *22*, 9609-9613.

75. T. Zhou, G. Li, S. P. Nolan, M. Szostak, *Org. Lett.*, **2019**, *21*, 3304-3309.
76. M. M. Rahman, J. Buchspies, M. Szostak, *Catalysts.*, **2019**, *9*, 129.
77. S. Shi, R. Lalancette, R. Szostak, M. Szostak, *Org. Lett.*, **2019**, *21*, 1253-1257.
78. Z. -B. Zhang, C. -L. Ji, C. Yang, J. Chen, X. Hong, J. -B. Xia, *Org. Lett.*, **2019**, *21*, 1226-1231.
79. R. Haraguchi, S. Hoshino, T. Yamazaki, S. -I. Fukuzawa, *Chem. Comm.*, **2018**, *54*, 2110-2113.
80. D. Zhang, J. Yu, *Organometallics.*, **2022**, *41*, 811-819.
81. D. Zhang, J. Yu, *Organometallics.*, **2020**, *39*, 1269-1280.
82. D. Shen, Y. Xu, S. -L. Shi, *J. Am. Chem. Soc.*, **2019**, *141*, 14938-14945.
83. H. Khandaka, R. K. Joshi, *Tetrahedron Lett.*, **2022**, *111*, 154163.
84. P. Lei, Y. Mu, Y. Wang, Y. Wang, Z. Ma, J. Feng, X. Liu, M. Szostak, *ACS Sustain. Chem. Eng.*, **2020**, *98*, 552-559
85. Y. Dong, J. Bi, S. Zhang, D. Zhu, D. Meng, S. Ming, K. Qin, Q. Liu, L. Guo, T. Li, *Appl. Surf. Sci.*, **2020**, *531*, 147392.
86. Y. Dong, F. Xue, Y. Wei, *J. Phys. Chem. Solids.*, **2021**, *153*, 110007.
87. V. Kandathil, T. S. Koley, K. Manjunatha, R. B. Dateer, R. S. Keri, B. Sasidhar, S. A. Patil, S. A. Patil, *Inorganica Chim. Acta.*, **2018**, *478*, 195-210.
88. F. Rafiee, N. Mehdizadeh, *Catal. Lett.*, **2018**, *148*, 1345-1354.