

Effects of Solvent Polarity in the Sonogashira Coupling: A Brief Overview

Biswajit Panda

Department of Chemistry, City College, Kolkata, West Bengal, India

Corresponding Author's Email: biswajitchem@citycollegekolkata.org

Abstract

The Sonogashira cross-coupling reaction is a powerful and widely utilized synthetic method for the formation of carbon-carbon bonds. Over the years, extensive research has been conducted to explore the influence of different solvents on the reaction efficiency and selectivity. The solvent choice in Sonogashira cross-coupling reactions greatly affects the reaction rate and yield. A diverse range of solvents, including polar protic, polar aprotic, and nonpolar solvents, have been investigated. This chapter examines the impact of solvent polarity, dielectric constant, hydrogen-bonding ability, and solubility on the reaction outcome. Furthermore, solvent effects on the reactivity of the reactants as well as the stability of intermediates and catalysts are also discussed. The understanding and manipulation of solvent parameters in this reaction provide valuable insights for the development of improved protocols and the design of new catalytic systems. This chapter provides a comprehensive overview of the various facets of solvent effects in the Sonogashira cross-coupling, highlighting the significant role played by solvents in this transformation. This article aims to stimulate further research in the field, facilitating the advancement of the Sonogashira cross-coupling methodology towards more efficient and sustainable synthetic processes. Overall, the findings highlight the crucial influence of solvent polarity on the efficiency and selectivity of Sonogashira coupling, offering valuable insights for optimizing reaction conditions in synthetic organic chemistry.

Keywords: *Alkynylation; Carbon-Carbon Bond Formation; Catalysis; Solvent Effects; Sonogashira Cross-Coupling*

Introduction

Transition-metal-catalyzed carbon-carbon (C-C) bond-forming reactions have emerged as transformative processes in the realm of organic synthesis, playing a pivotal role in modern chemical methodologies. The utilization of transition metals as catalysts imparts unique reactivity, selectivity, and efficiency to these transformations, enabling the formation of C-C bonds under milder conditions compared to traditional methods (Docherty *et al.*, 2023). Within this array, the palladium-catalyzed sp^2 - sp coupling reaction, employing aryl or alkenyl halides or triflates with terminal alkynes, emerges

Sustainable Chemical Insight in Biological Exploration

as an important method for synthesizing arylalkynes and conjugated enynes. These compounds serve as key precursors for natural products (Tabassum *et al.*, 2022), pharmaceuticals (Cruz, Mateus & Peterson, 2021), and molecular organic materials (Gao *et al.*, 2022). Alkynes are pivotal in synthesizing carbocycles and heterocycles via metal catalysis, where they undergo diverse cyclization reactions. Alkynes are versatile intermediates in metal catalyzed cyclization reactions like cycloisomerization (Chan *et al.*, 2020), benzannulation (Amin *et al.*, 2024), etc. Additionally, under organocatalytic conditions, alkynes participate in cyclization processes facilitated by organic catalysts, enabling efficient formation of complex molecular structures (Zhang *et al.*, 2024). The inception of this reaction can be traced back to independent reports in 1975 by Heck and Cassar. Heck's approach relied on the Mizoroki-Heck reaction, utilizing a phosphane-palladium complex as a catalyst, triethylamine or piperidine as a base, and a corresponding solvent (Dieck & Heck, 1975). Cassar's method involved a phosphane-palladium catalyst with sodium methoxide as a base and DMF as the solvent, with both methods typically requiring high temperatures, up to 100°C (Cassar, 1975).

In the same year, Sonogashira, Tohda and Hagihara (1975) introduced a pivotal observation, noting that the addition of a catalytic amount of copper(I) iodide significantly accelerated the reaction (figure 1). This innovation allowed for performing the alkynylation at room temperature, marking a significant advancement. The Sonogashira-Hagihara protocol, commonly known as the Sonogashira coupling, rapidly became the preferred choice for alkynylation reactions involving aryl or alkenyl halides. Notably, even primary and secondary alkyl bromides have been successfully alkynylated using this protocol, although the exploration of sp³-sp coupling in this context is relatively recent.

However, the inclusion of copper salts as co-catalysts in Sonogashira cross-coupling reactions present certain drawbacks. This addition introduces another environmentally unfriendly reagent that is challenging to recover. The in-situ generation of copper acetylides during the reaction conditions can lead to undesired side reactions, such as the Glaser coupling, particularly when the terminal acetylene is scarce or costly. Over the years, various alternatives to the copper(I) co-catalyst have been explored to address issues arising from competitive homocoupling to the diyne. These alternatives include the use of stoichiometric amounts of silver oxide or tetrabutylammonium salts as activators, as well as the exploration of palladium-only procedures. This versatile and robust reaction has greatly contributed to the advancement of modern synthetic chemistry and continues to be an active area of research and development.

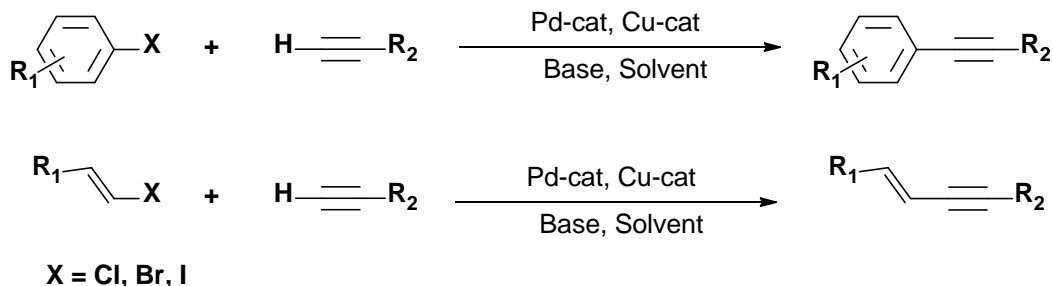


Figure 1: The Sonogashira Coupling

While the Sonogashira cross-coupling reaction has witnessed significant advancements in recent years, the choice of solvent plays a crucial role in influencing the reaction outcomes (Choy, Gan & Kwong, 2023). Solvents are not merely inert reaction media but actively participate in the reaction by influencing reaction rates, selectivity, and catalyst stability. By stabilising the ionic intermediates of the catalytic cycle, the solvents' polarity and hydrogen bonding ability help to accelerate the reaction, while steric bulk reduces this ability. These findings are consistent with the mechanistic investigations into the Cu-free version of the Sonogashira reaction (Ljungdahl *et al.*, 2006). The selection of an appropriate solvent can enhance the efficiency and control of the cross-coupling process. Table 1 shows the polarity of various commonly used protic and aprotic solvents along with their boiling points.

Table 1: Boiling points and dielectric constants of commonly used solvents

Solvent	Boiling Point (°C)	Dielectric constant (ϵ)	Protic/Aprotic
Water	100	80.4	Protic
Methanol	65	32.6	Protic
Ethanol	78	24.3	Protic
Acetonitrile	82	37.5	Protic
Ethylene glycol	197	37.0	Protic
Acetone	56	20.7	Protic
N, N-Dimethyl formamide	153	36.7	Aprotic
N, N-Dimethyl acetamide	165	37.8	Aprotic
Dimethyl sulfoxide	189	45.0	Aprotic
Tetrahydrofuran	66	7.6	Aprotic
Diethyl ether	35	4.3	Aprotic
Chloroform	61	4.8	Aprotic
Dichloromethane	40	8.9	Aprotic
Dichloroethane	84	10.4	Aprotic
Benzene	80	2.3	Aprotic
Toluene	111	2.4	Aprotic
o-Xylene	144	2.6	Aprotic
n-Hexane	69	1.9	Aprotic

The importance of solvent choice in the Sonogashira cross-coupling reaction arises from its influence on several key aspects. Firstly, solvents can affect the reaction rates by modulating the accessibility of reactants to the catalyst and the kinetic barriers

involved in the reaction steps. Secondly, solvents play a vital role in determining the selectivity of the cross-coupling process, influencing regioselectivity and stereoselectivity. Solvent effects can also impact the stability and activity of the catalyst, which are crucial for achieving high yields and prolonged catalyst lifetimes. The purpose of this chapter is to explore the role of solvents in the Sonogashira cross-coupling reaction, with a specific focus on their impact on reaction rates, selectivity, and catalyst stability.

Methodology

Various solvents are applicable for cross-coupling reactions, with particular significance in palladium-catalyzed processes, akin to most solution-based chemical transformations. The chosen solvent profoundly influences reaction kinetics, selectivity, and equilibrium. It regulates product partitioning, facilitating by-product removal or clean product separation, while also impacting catalyst stability through coordination effects and modulating the activity of acids and bases via complementary functionalities. Proper solvent selection enhances catalyst lifespan, acid-base activity, and process benefits, serving as a heat sink for temperature control and allowing substances to be pumped as solutions. This article is designed in such a way that the readers can get the idea about the effect of the solvent in Sonogashira cross-coupling reaction. How the solvent polarity affects the overall outcome of the coupling process by influencing both the reactivity and selectivity of the reaction. In some cases, solvent molecules are not innocent, they also participated in the catalytic cycle by coordinating the metal centre and influencing the ligand etc.

Results and Discussion

Understanding solvent interactions is crucial for comprehending their impact on cross-coupling reactions. Among intermolecular forces, the most prevalent are weak, spontaneously induced dipoles (dispersion forces), inherent in all solvents due to organic molecule polarizability. Solvents with high polarizability, like aromatic and chlorinated solvents such as toluene, can stabilize induced and permanent dipoles in other molecules. Those with strong permanent dipoles are termed polar or dipolar, while cyclic solvents, with restricted conformations favoring higher dipole moments, exhibit greater polarity compared to equivalent acyclic counterparts (e.g., tetrahydrofuran over diethyl ether). Additionally, hydrogen bonding, a potent force with specific directionality, distinguishes solvents as hydrogen bond donors (e.g., alcohols) and/or acceptors (e.g., ethers), while those lacking hydrogen donors are termed aprotic.

The Sonogashira coupling reaction presents a challenge for solvent selection due to the diverse nature of its components. The solvent must effectively dissolve a range of solutes, including lipophilic aryl halides, copper acetylide organometallics, inorganic

palladium complexes, and sometimes salts like bases and additives. A suitable choice for this purpose is a dipolar aprotic solvent, with N, N-Dimethylformamide (DMF) serving as a classic example. DMF, a polar and aprotic solvent, is cost-effective, capable of coordinating in metal complexes, and dissolves most organic compounds and many inorganic salts to varying extents. With a boiling point of 153 °C, DMF enhances reaction rates and can be easily recovered via distillation, making it a common solvent choice for the Sonogashira coupling. It is hypothesized that DMF's high electron-donating capacity facilitates alkyne deprotonation by coordinating with the Pd metal center and promoting product dissociation at the catalytic cycle's conclusion (Sherwood *et al.*, 2019). However, DMF's reproductive toxicity necessitates its substitution. Yet, alternative polar solvents like DMSO and 1,4-dioxane present challenges due to their stability and toxicity concerns in the Sonogashira reaction (Gao *et al.*, 2020).

Solvent polarity and nucleophilicity

Solvent polarity refers to the distribution of charge within a solvent molecule, with polar solvents having a separation of positive and negative charges. Nucleophilicity, on the other

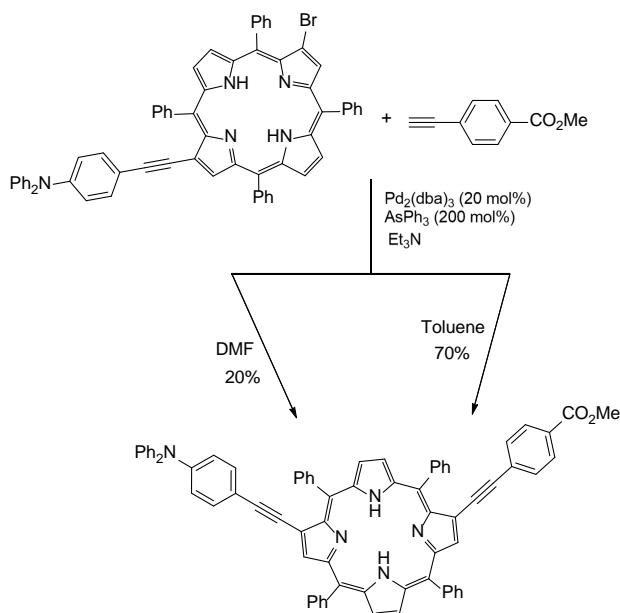


Figure 2: Sonogashira coupling of β -bromoporphyrin

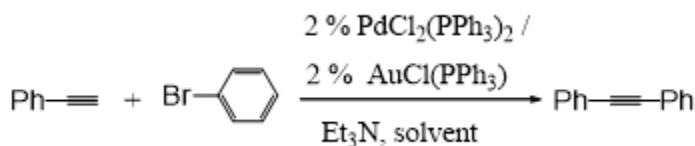
hand, refers to the ability of a solvent molecule to donate an electron pair. These properties are closely related and can affect the reaction kinetics and reactivity of the cross-coupling partners. Solvent polarity and nucleophilicity are critical factors to consider when screening solvents for Sonogashira cross-coupling reactions. Zhou and

co-workers (2014) reported a protocol for the copper-free Sonogashira coupling of β -bromoporphyrin using the $\text{Pd}_2(\text{dba})_3/\text{AsPh}_3$ system as the catalyst. They found that a better yield was obtained when the reaction was performed in toluene solvent (70%) compared to DMF (20%) (Figure 2). The authors indicated that DMF may have slowed the reaction by displacing the AsPh_3 ligands from the active palladium complex. Therefore, a solvent screening approach should include solvents with a range of polarities to evaluate their effects on the reaction outcome.

Influence of polar solvents on reaction rates and yields

Polar solvents, such as acetonitrile, dimethylformamide (DMF), and dimethyl sulfoxide (DMSO), can enhance the reaction rates in Sonogashira coupling reactions. The polar nature of these solvents allows for effective solvation of the reactants and catalyst, increasing their accessibility and promoting favorable interactions. The solvation of the reactants can also facilitate the deprotonation step, promoting the activation of the acetylenic or aryl halide coupling partners. The enhanced solvation of the intermediates and transition states can stabilize the reactive species, resulting in improved yields. For example, palladium and gold dual catalytic sonogashira coupling of aryl halides were found to be most effective in polar solvents like DMF and DMA (96% yield) compared to non-polar solvent toluene (33%) (Table 2 & Figure 3) (Panda & Sarkar, 2010a). Here $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ and $\text{AuCl}(\text{PPh}_3)$ were used as effective synergistic catalytic systems. The generality of this protocol was proved through the application of a wide range of aryl halides under this condition (Panda & Sarkar, 2013). Aryl halides containing various functional groups were coupled nicely with alkynes effectively and provided the desired coupled products in good to excellent yields. Similarly, the Pd-Au dual catalytic Sonogashira coupling of arene diazonium salts also

Table 2: Solvent optimization of Pd-Au dual catalytic Sonogashira Coupling



Entry	Solvent	Yield (%)
1	THF	81
2	H ₂ O	40
3	Et ₃ N	67
4	Toluene	33
5	MeCN	84
6	DMSO	89
7	DMF	96
8	DMA	96

Source: Panda & Sarkar, 2010a

Panda
Effects of Solvent Polarity in the Sonogashira Coupling

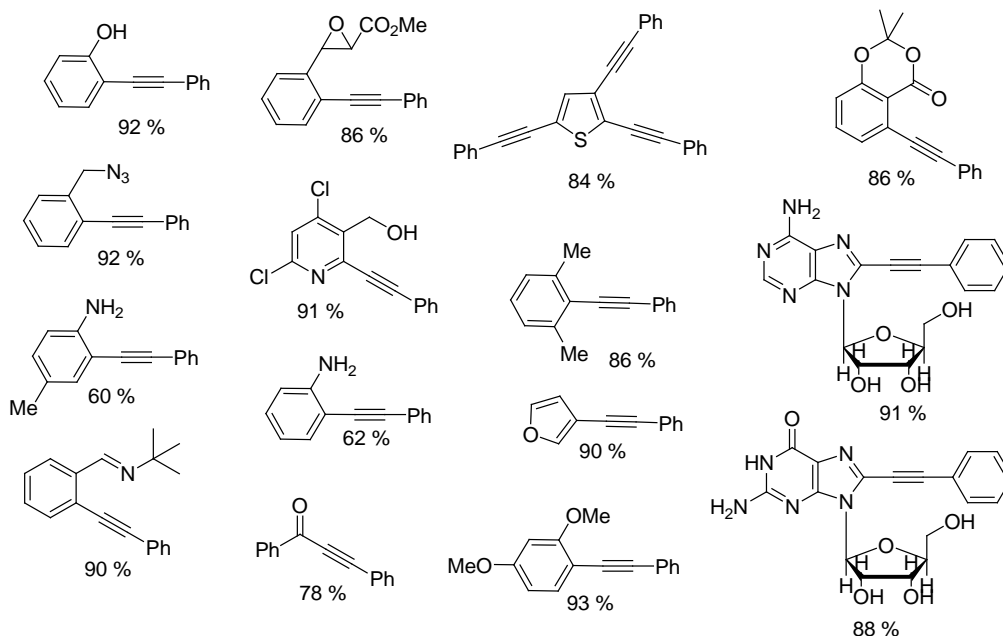
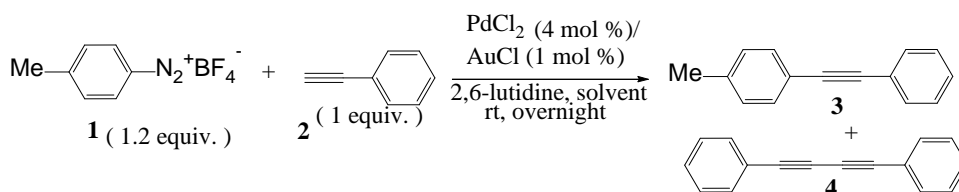


Figure 3: Pd-Au dual catalytic Sonogashira coupling

Table 3: Sonogashira Coupling of Arenediazonium Salts under Various Conditions



Entry	Solvent	Yield(%) of 3	Yield(%) of 4
1	THF	62	8
2	1,4-dioxane	74	5
3	H ₂ O	62	14
4	MeCN-H ₂ O(1:1)	76	9
5	MeCN	74	0
6	Toluene	11	27

Source: Panda & Sarkar, 2010b

provides the best yield in acetonitrile solvent (Table 3 & Figure 4) (Panda & Sarkar, 2010b). Arenediazonium salts, derived from inexpensive anilines, serve as readily available and highly reactive aryl surrogates, demonstrating superior reactivity compared to aryl halides and triflates in diverse cross-coupling reactions (Panda, 2021).

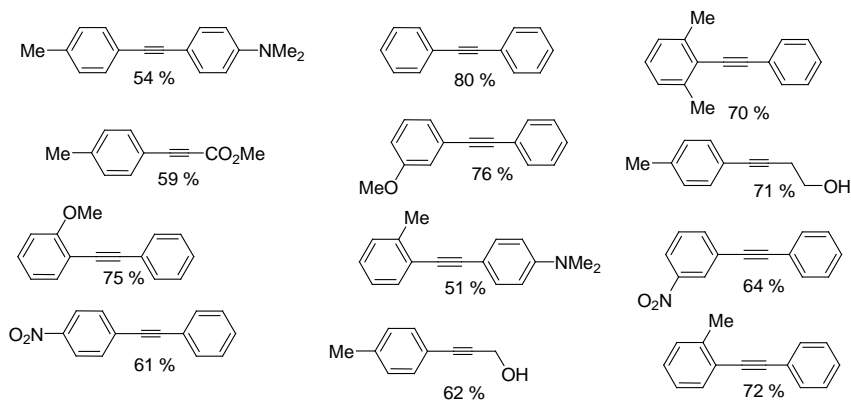
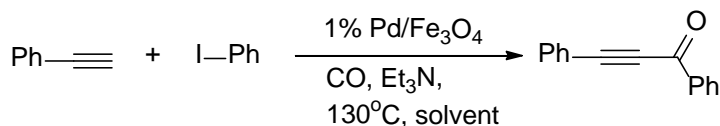


Figure 4: Pd-Au dual catalytic Sonogashira Coupling of Arenediazonium salts

Impact of Nonpolar Solvents on Reaction-on-Reaction Kinetics

Nonpolar solvents, such as benzene, toluene, and xylene, are often employed in Sonogashira coupling reactions. These solvents have low polarity and reduced nucleophilicity compared to polar solvents. While nonpolar solvents may decrease the solubility of polar reactants and catalysts, they can still play a crucial role in the reaction kinetics. In nonpolar solvents, the reactants and catalysts may have reduced solvation and experience decreased steric hindrance. This can lead to increased collision frequency between reactant molecules, promoting faster reaction kinetics. Additionally, nonpolar solvents can also influence the regioselectivity of the cross-coupling reaction by reducing competing side reactions, resulting in improved selectivity. In 2008, Liu and co-workers reported a carbonylative Sonogashira coupling

Table 4: Solvent optimization of Pd/Fe₃O₄ catalytic Sonogashira Coupling



Entry	Solvent	Yield (%)
1	THF	63
2	Toluene	93
3	MeCN	64
4	DME	49
5	1,4-dioxane	51

Source: Liu et al., 2008

of aryl iodides in the presence of a magnetically separable palladium catalyst under copper and phosphene-free conditions. Optimization studies revealed that, non-polar solvent toluene was found to be the best solvent compared to polar solvents like DME, THF, 1,4-dioxane and CH₃CN (Table 4). In their method, various functionalized aryl iodides were coupled successfully with alkynes to produce internal alkynes in high

yields. It is important to note that the choice of solvent in Sonogashira coupling is a delicate balance between the desired reactivity and selectivity. While polar solvents generally enhance reaction rates and yields, they may also lead to undesired side reactions or catalyst deactivation. Conversely, nonpolar solvents can promote faster reaction kinetics but may result in reduced solubility and limited reaction control.

Influence of solvent polarity on regioselectivity of cross-coupling reactions

Solvent polarity can have a profound impact on the regioselectivity of Sonogashira coupling reactions. The orientation of the reactants, particularly the terminal alkyne and the aryl or vinyl halide, is influenced by the solvation and electrostatic interactions within the reaction medium. Polar solvents, such as DMF or DMSO, can enhance regioselectivity by solvating and stabilizing charged or polar intermediates. The solvation effects can promote the formation of the desired regio-isomer in Heck and Hiyama reactions by reducing steric hindrance or providing specific interactions. A nice review by Fairlamb and co-workers (2006) lucidly described the regioselective cross-coupling reactions.

Li and co-workers reported the Sonogashira reaction of multifunctional 2-iodophenyl-acetylenes, aimed at generating cyclic products, exhibits favorable outcomes in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF₄]) (Figure 5) (Li *et al.*, 2005). However, when attempted in organic solvents (DMF, THF) under identical conditions, the reaction proves less effective. Copper(I) iodide, employed to facilitate the coupling, leads to undesirable homocoupling emerging as the major reaction pathway in organic solvents, even in the presence of an inert atmosphere. In contrast, the use of the ionic liquid allows for a significant reduction in the amount of CuI required (1 mol%), thereby enhancing the selectivity of the reaction.

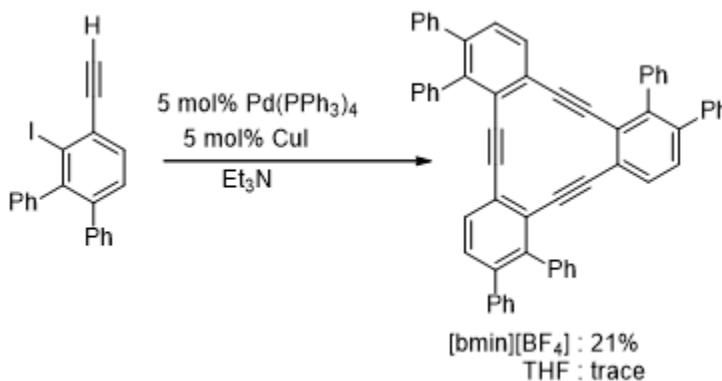


Figure 5: Sonogashira reaction of multifunctional 2-iodophenyl-acetylenes

In 2020, Al-zoubi and co-workers have revealed that solvent has a strong influence in regioselectivity of the Sonogashira coupling. According to their studies, when 1,2,3-tri-

iodobenzene coupled with phenylacetylene in a polar aprotic solvent, DMF provides an inseparable mixture of alkynylated product mixture, thus showing poor regioselectivity (Figure 6). On the other hand, using anhydrous toluene as solvent, the Sonogashira coupling produced mono-alkynylated products selectively. During the optimization studies in the regioselective Sonogashira coupling reaction, Al-zoubi and co-workers also observed that in DMF solvent, full consumption of the starting material needs 12 hours, whereas in toluene solvent it needs 24 hours. This indicates that the rate of the reaction is higher in DMF compared to non-polar solvent toluene. High reactivity and low selectivity in DMF solvent and reverse effect in toluene were observed. Under these optimized reaction conditions, various highly functionalized tri-iodobenzenes were coupled efficiently with terminal alkynes and provided the desired products in moderate to good yields (Figure 7).

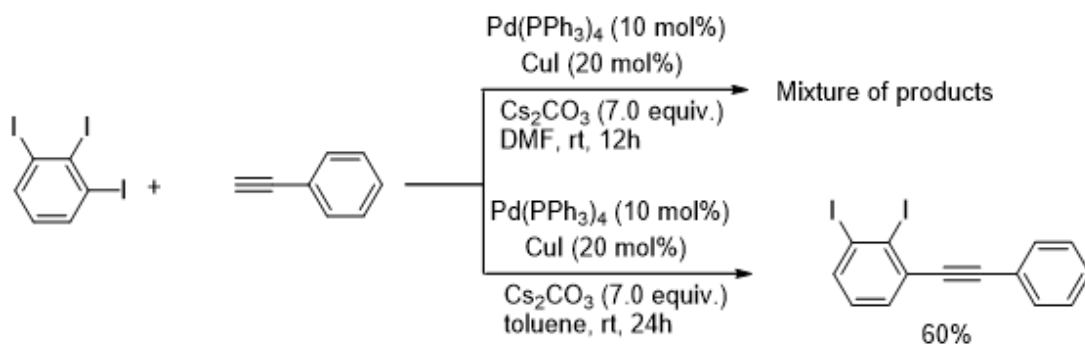


Figure 6: Solvent dependent selective Sonogashira coupling

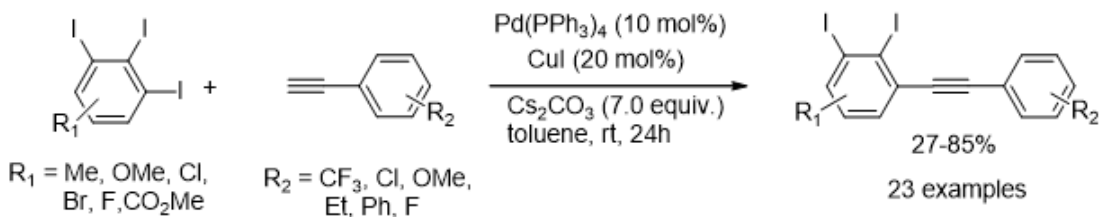


Figure 7: Selective Sonogashira coupling of functionalized tri-iodobenzenes

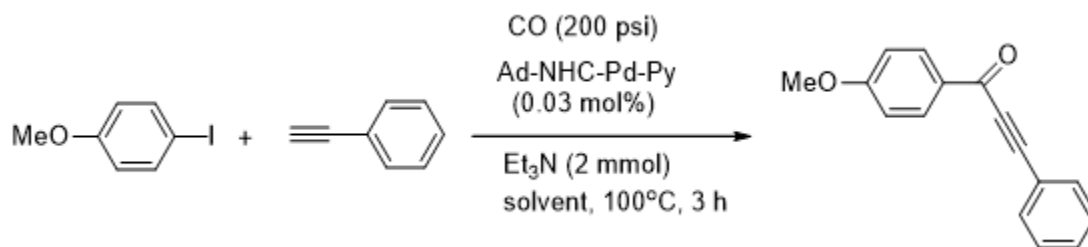
Solvent-induced effects on steric interactions and selectivity

Solvents can also influence the selectivity of Sonogashira coupling reactions by modulating steric interactions between the reactants and the catalyst. The choice of solvent can affect the accessibility of reactive sites, the relative orientation of reactants, and the efficiency of sterically demanding cross-coupling partners. Nonpolar solvents, such as toluene or hexane, can minimize steric hindrance and improve selectivity by reducing the interaction between bulky substituents.

Mansour and co-workers (2020) used isopropyl, benzyl, and adamantyl N-substituted (NHC) ligand-based palladium(II) complexes for the carbonylative Sonogashira coupling for the synthesis of ynones (Table 5). From their studies, they have found that adamantyl N-substituted N-heterocyclic carbene ligand-based palladium(II) complex was found to be most efficient in toluene solvent. Solvent screening reveals that polar solvents like THF, DMF, and MeCN are found to be less effective. The adamantyl-NHC-Pd complex is the softest species in this complex series, according to the frontier orbital quantum mechanical descriptors obtained through DFT analysis. This may be due to the unique steric and electronic properties of the adamantyl group relative to the isopropyl and benzyl groups. This observation is consistent with the complex's frequently observed maximum catalytic activity towards soft substrates.

It is important to note that the solvent-induced selectivity in Sonogashira coupling reactions can be complex and dependent on a variety of factors, including the nature of the reactants, catalyst, and reaction conditions. The understanding of solvent effects on selectivity is an active area of research, and further investigations are necessary to uncover the underlying mechanisms and develop strategies for controlling selectivity through solvent choice.

Table 5: Carbonylative Sonogashira Coupling



Entry	Solvent	Yield (%)
1	THF	61
2	DMF	73
3	MeCN	84
4	Toluene	97

Source: Mansour et al., 2020

Application of green and sustainable solvents

In the realm of Sonogashira coupling, the quest for green and sustainable solvent choices has gained significant traction. Researchers are increasingly focused on identifying solvents that not only promote efficient reaction outcomes but also minimize environmental impact. One promising avenue lies in the utilization of renewable and non-toxic solvents such as ethanol, water, or supercritical carbon dioxide. These solvents offer distinct advantages, including low toxicity, biodegradability, and reduced energy consumption during purification processes. Additionally, the implementation of

solvent-free or solvent-minimized conditions has emerged as an attractive strategy, further enhancing the sustainability profile of Sonogashira coupling reactions. Through innovative solvent selection and process optimization, chemists aim to achieve greener synthetic pathways without compromising reaction efficiency or product yields.

Moreover, the exploration of alternative reaction media such as ionic liquids and deep eutectic solvents presents exciting opportunities for advancing the green credentials of Sonogashira coupling. These novel solvents offer unique properties such as tunable polarity, high stability, and recyclability, making them attractive candidates for sustainable reaction environments. By harnessing the potential of green solvents, researchers endeavor to mitigate the environmental footprint associated with traditional solvent-based approaches while fostering the development of more eco-friendly synthetic methodologies in Sonogashira coupling and beyond. In addition to the use of green solvents, various non-conventional techniques such as microwave irradiation sonochemistry (Safaei-Ghomi & Akbarzadeh, 2015), and photochemistry have achieved remarkable success in recent years.

Conclusion

In this chapter, the role of solvents in the Sonogashira cross-coupling reaction has been thoroughly explored. The discussion encompassed the influence of solvent polarity and nucleophilicity on reaction rates and yields, as well as the impact of solvents on selectivity and regioselectivity. Mechanistic insights into solvent effects were also examined, including solvent coordination with palladium catalysts, solvent-mediated activation of reactants, and solvent-dependent ligand effects. Additionally, the importance of solvent screening approaches for optimizing Sonogashira coupling reactions was highlighted.

The findings reveal that solvent choice has a significant impact on the outcome of the Sonogashira cross-coupling reaction. Different solvents can modulate reaction rates, selectivity, and catalyst stability, ultimately affecting the efficiency and success of the reaction. Polar solvents tend to enhance reaction rates and yields by facilitating the solvation and stabilization of intermediates, while nonpolar solvents can improve selectivity by minimizing steric hindrance. Solvent effects on regioselectivity were also observed, with polar solvents favoring specific regioisomers.

The implications of solvent choice in the Sonogashira cross-coupling extend beyond reaction outcomes. Sustainable solvent choices, such as green solvents, renewable and bio-based solvents, and solventless or solvent-minimized approaches, can significantly contribute to greener and more environmentally friendly processes. By reducing the use of hazardous solvents, utilizing renewable resources, and minimizing waste generation, researchers can align Sonogashira coupling reactions with the principles of green chemistry.

Looking ahead, there are several exciting opportunities for further research in this field. Future studies can focus on developing more sustainable solvent choices and solvent screening strategies, considering not only reaction performance but also environmental impact. Additionally, exploring solvent effects on different classes of substrates and reactions can provide a broader understanding of the solvent-dependent behavior in Sonogashira cross-coupling. Furthermore, investigating solvent effects in combination with other catalytic systems for cascade transformations can open new avenues for complex molecule synthesis.

Acknowledgement

Biswajit Panda would like to express gratitude to City College, Kolkata, India, for their generous support in accomplishing this work. He extends heartfelt thanks to all the faculty members of the Department of Chemistry, City College, Kolkata, for their help and support. The author is also thankful to Dr. Bhaskar Paul, Dr. Moumita Ganguli, Kirtika Dutta, Suban Kundu, Barnali Roy, Dr. Sujay Nandi, Dr. Totan Mondal and Atanu Ghosh for their continuous assistance.

References

- Docherty, J. H., Lister, T. M., McArthur, G., Findlay, M. T., Domingo-Legarda, P., Kenyon, J., ... & Larrosa, I. (2023). Transition-metal-catalyzed C–H bond activation for the formation of C–C bonds in complex molecules. *Chemical Reviews*, 123(12), 7692-7760. <https://doi.org/10.1021/acs.chemrev.2c00888>
- Tabassum, S., Zahoor, A. F., Ahmad, S., Noreen, R., Khan, S. G., & Ahmad, H. (2022). Cross-coupling reactions towards the synthesis of natural products. *Molecular Diversity*, 26, 647-689. <https://doi.org/10.1007/s11030-021-10195-6>
- Cruz, A. C., Mateus, E. M., & Peterson, M. J. (2021). Process development of a Sonogashira cross-coupling reaction as the key step of tirasemtiv synthesis using design of experiments. *Organic Process Research & Development*, 25(3), 668-678. <https://doi.org/10.1021/acs.oprd.0c00524>
- Gao, Y., Feng, C., Seo, T., Kubota, K., & Ito, H. (2022). Efficient access to materials-oriented aromatic alkynes via the mechanochemical Sonogashira coupling of solid aryl halides with large polycyclic conjugated systems. *Chemical science*, 13(2), 430-438. <https://doi.org/10.1039/D1SC05257H>
- Chan, S. C., Yeung, C. F., Shek, H. L., Ng, S. W., Tse, S. Y., Tse, M. K., ... & Wong, C. Y. (2020). Iron (II)-induced cycloisomerization of alkynes via “non-vinylidene” pathways for iron (II)-indolizine and-indolizinone complexes. *Chemical Communications*, 56(83), 12644-12647. <https://doi.org/10.1039/D0CC05081D>
- Amin, P. M., Wang, W., Wang, C., Zhou, J., & Wang, Y. (2024). Gold-catalyzed benzannulations of 2-alkenylindoles with alkynes: a protecting-group-free regioselective

approach to carbazoles. *Chemical Communications*, 60(40), 5326-5329. <https://doi.org/10.1039/D4CC00176A>

Zhang, Z. X., Hu, T. Q., Ye, L. W., & Zhou, B. (2024). Organocatalytic Atroposelective Reactions of Alkynes. *Synthesis*, 56 (15), 2316-2328. <https://doi.org/10.1055/a-2241-3571>

Dieck, A. H., & Heck, F. R. (1975). Palladium catalyzed synthesis of aryl, heterocyclic and vinylic acetylene derivatives. *Journal of Organometallic Chemistry*, 93(2), 259-263. [https://doi.org/10.1016/S0022-328X\(00\)94049-X](https://doi.org/10.1016/S0022-328X(00)94049-X)

Cassar, L. (1975). Synthesis of aryl-and vinyl-substituted acetylene derivatives by the use of nickel and palladium complexes. *Journal of Organometallic Chemistry*, 93(2), 253-257. [https://doi.org/10.1016/S0022-328X\(00\)94048-8](https://doi.org/10.1016/S0022-328X(00)94048-8)

Sonogashira, K., Tohda, Y., & Hagihara, N. (1975). A convenient synthesis of acetylenes: catalytic substitutions of acetylenic hydrogen with bromoalkenes, iodoarenes and bromopyridines. *Tetrahedron letters*, 16(50), 4467-4470. [https://doi.org/10.1016/S0040-4039\(00\)91094-3](https://doi.org/10.1016/S0040-4039(00)91094-3)

Choy, P. Y., Gan, K. B., & Kwong, F. Y. (2023). Recent Expedition in Pd-Catalyzed Sonogashira Coupling and Related Processes. *Chinese Journal of Chemistry*, 41(9), 1099-1118. <https://doi.org/10.1002/cjoc.202200703>

Ljungdahl, T., Pettersson, K., Albinsson, B., & Mårtensson, J. (2006). Solvent and base dependence of copper-free palladium-catalyzed cross-couplings between terminal alkynes and aryl iodides: development of efficient conditions for the construction of gold (III)/free-base porphyrin dimers. *The Journal of Organic Chemistry*, 71(4), 1677-1687. <https://doi.org/10.1021/jo052423v>

Sherwood, J., Clark, J. H., Fairlamb, I. J., & Slattery, J. M. (2019). Solvent effects in palladium catalysed cross-coupling reactions. *Green Chemistry*, 21(9), 2164-2213. <https://doi.org/10.1039/C9GC00617F>

Gao, F., Bai, R., Ferlin, F., Vaccaro, L., Li, M., & Gu, Y. (2020). Replacement strategies for non-green dipolar aprotic solvents. *Green Chemistry*, 22(19), 6240-6257. <https://doi.org/10.1039/D0GC02149K>

Zhou, F., Feng, Y., & Zhang, B. (2014). Effects of substituent and solvent on the Sonogashira coupling reaction of β -bromoporphyrin. *Research on Chemical Intermediates*, 40, 1517-1524. <https://doi.org/10.1007/s11164-013-1056-9>

Panda, B., & Sarkar, T. K. (2010a). On the catalytic duo PdCl₂ (PPh₃)₂/AuCl (PPh₃) that cannot effect a Sonogashira-type reaction: a correction. *Tetrahedron Letters*, 51(2), 301-305. <https://doi.org/10.1016/j.tetlet.2009.11.003>

Panda, B., & Sarkar, T. K. (2013). Gold and palladium combined for the Sonogashira coupling of aryl and heteroaryl halides. *Synthesis*, 45(06), 817-829. <https://doi.org/10.1055/s-0032-1318119>

- Panda, B., & Sarkar, T. K. (2010b). Gold and palladium combined for the Sonogashira-type cross-coupling of arenediazonium salts. *Chemical communications*, 46(18), 3131-3133. <https://doi.org/10.1039/C001277G>
- Panda, B. (2021). Sonogashira coupling of arenediazonium salts: discovery and developments. *Arkivoc*, 2021, 177-199. <https://doi.org/10.24820/ark.5550190.p011.559>
- Liu, J., Peng, X., Sun, W., Zhao, Y., & Xia, C. (2008). Magnetically separable Pd catalyst for carbonylative Sonogashira coupling reactions for the synthesis of α , β -alkynyl ketones. *Organic Letters*, 10(18), 3933-3936. <https://doi.org/10.1021/ol801478y>
- Fairlamb, I. J., O'Brien, C. T., Lin, Z., & Lam, K. C. (2006). Regioselectivity in the Sonogashira coupling of 4, 6-dichloro-2-pyrone. *Organic & biomolecular chemistry*, 4(7), 1213-1216. <https://doi:10.1039/b518232h>
- Li, Y., Zhang, J., Wang, W., Miao, Q., She, X., & Pan, X. (2005). Efficient synthesis of tribenzohexadehydro [12] annulene and its derivatives in the ionic liquid. *The Journal of Organic Chemistry*, 70(8), 3285-3287. <https://doi.org/10.1021/jo047836v>
- Al-Zoubi, R. M., Al-Omari, M. K., Al-Jammal, W. K., & Ferguson, M. J. (2020). Palladium-catalyzed highly regioselective mono and double Sonogashira cross-coupling reactions of 5-substituted-1, 2, 3-triiodobenzene under ambient conditions. *RSC advances*, 10(28), 16366-16376. <https://doi.org/10.1039/D0RA01569E>
- Mansour, W., Suleiman, R., Fettouhi, M., & El Ali, B. (2020). Soft heteroleptic N-Heterocyclic carbene palladium (II) species for efficient catalytic routes to alkynones via carbonylative Sonogashira coupling. *ACS Omega*, 5(37), 23687-23702. <https://doi.org/10.1021/acsomega.0c02413>
- Safaei-Ghomi, J., & Akbarzadeh, Z. (2015). Sonochemically synthesis of arylolefinyl linked triaryl amines catalyzed by CuI nanoparticles: A rapid and green procedure for Sonogashira coupling. *Ultrasonics Sonochemistry*, 22, 365-370. <https://doi.org/10.1016/j.ultsonch.2014.05.016>