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Recent Advances in Palladium-Catalyzed Phosphonation of Aryl Halides, Sulfonates and Related Derivatives

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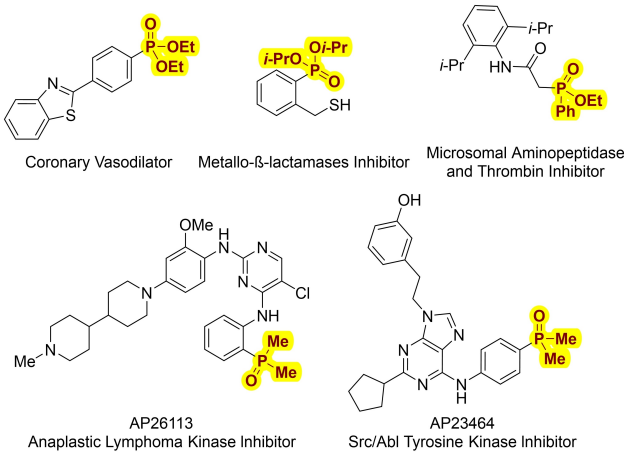
Palladium-catalyzed phosphonation has emerged as a significant development in the synthesis of organophosphorus acid compounds. This review covers the literature published from 1980 to 2024, systematically examining the current progress, challenges, and future directions in this rapidly evolving field. The review begins with an introduction to the significance of phosphorus chemistry in both academic research and industrial applications and then explores traditional methods for synthesizing phosphonation compounds, emphasizing the limitations of these methods and the need for innovative reaction conditions. The central focus is on recent advancements in palladium-catalyzed phosphonation, with detailed discussions of key milestones, reaction mechanisms, and the scope of substrate applicability. The review also analyzes the roles of different palladium sources, ligands, and reaction conditions, highlighting their effects on reaction efficiency and selectivity. Finally, the conclusion summarizes recent developments and proposes future research directions to address existing challenges and expand the scope of palladium-catalyzed phosphonation.

1. Introduction

Phosphorus compounds are ubiquitous in nature and play fundamental roles in biological systems, from DNA/RNA backbone structures to energy metabolisms (e.g., adenosine triphosphate, or ATP).[1] Beyond their natural occurrence, phosphorus-containing molecules have found widespread applications in medicinal chemistry, materials science, and catalysis.[2] The incorporation of phosphorus moieties into organic molecules often imparts unique properties that enhance their biological activities. For instance, AP26113 and AP23464 demonstrate potent inhibitory effects against anaplastic lymphoma kinase and Src/Abl tyrosine kinase, respectively,[3] highlighting the therapeutic potential of phosphorus compounds (Scheme 1). Oxidized phosphines, such as tertiary phosphine oxides (TPOs), are widely utilized as precursors for the reduction to phosphines, which serve as valuable ligands in catalytic reactions.



Scheme 1. Examples of Organophosphorus Compounds and Their Potential Applications.

The diverse applications of phosphorus compounds have driven continuous efforts to develop efficient synthetic methods for their preparation. Many natural products and drug molecules feature various functional groups such as halogen, hydroxyl, amino, and sulfonate moieties,[4] which provide opportunities for phosphonation reactions to create new phosphorus-containing compounds.

Traditional methods for the synthesis of phosphorus compounds, such as the Arbuzov–Michaelis reaction,[5] and nucleophilic substitution using organometallic reagents (e.g., Grignard or organolithium compounds), have been well established. However, these classical approaches often suffer from several limitations, including harsh reaction conditions, narrow substrate scopes, low functional group tolerance, and the generation of hazardous waste. Moreover, these methods typically lack control over stereoselectivity, making the synthesis of optically pure phosphorus compounds challenging.

Palladium-catalyzed phosphonation has emerged as a promising approach due to its high efficiency, mild reaction conditions, and broad functional group tolerance. Both aryl halides and aryl sulfonates serve as versatile electrophiles in organic chemistry, offering distinct advantages as reaction substrates in cross-coupling reactions.[6] Aryl halides, particularly bromides and iodides, are highly reactive in oxidative addition with transition metal catalysts, enabling efficient coupling reactions. At the same time, aryl sulfonates offer advantages such as easy accessibility from phenols, higher hydrolytic stability, and unique aromatic substitution patterns directed by the phenolic OH group, thus expanding the scope of organic synthesis. In addition to these electrophiles, carboxylic acid derivatives have recently gained attention as alternative substrates for palladium-catalyzed phosphonation. Their wide availability, structural diversity, and tunable reactivity make them valuable coupling partners in phosphonation reactions.

This review aims to provide a comprehensive overview of recent advancements in palladium-catalyzed phosphonation reactions, with emphasis on new catalyst systems, substrate scope, mechanistic understanding, and remaining challenges in this rapidly evolving field. The review focuses on literature published between 1980 and 2024, ensuring a thorough examination of both foundational studies and the latest developments.

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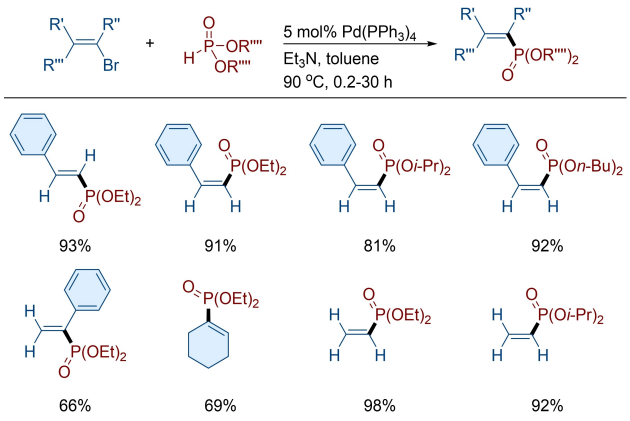
2. Palladium-Catalyzed Phosphonation of Aryl Halides

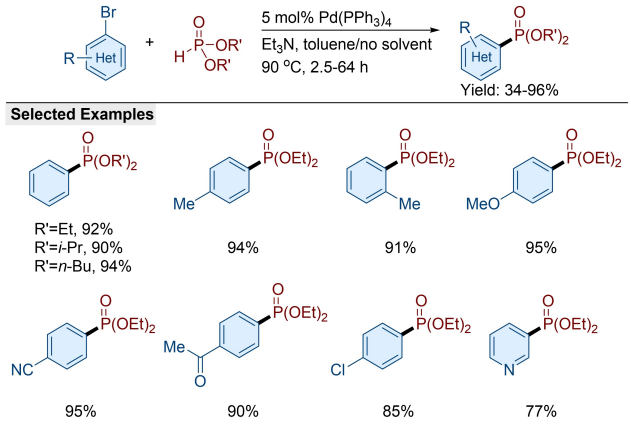
The Arbuzov and Michaelis–Becker reactions are well-established methodologies for the formation of carbon-phosphorus bonds. However, these protocols are inherently limited in their applicability to the synthesis of sp^2-hybridized carbon-phosphorus bonds. In 1980, Hirao et al.[7] reported a palladium-catalyzed phosphonation reaction that provided a novel approach for the synthesis of vinylphosphonates. By employing vinyl bromides and dialkyl phosphites as substrates, Hirao's team achieved the stereoselective synthesis of dialkyl vinylphosphonates in high yields. The reaction utilized tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$) as the catalyst and triethylamine as the base in toluene at 90 °C, representing a significant advancement in phosphonate chemistry (Scheme 2).

Building on this breakthrough, Hirao et al.[8] expanded the scope of the reaction in the following year by exploring aryl bromides as substrates. Using the same palladium catalyst, they successfully achieved the synthesis of dialkyl arylphosphonates (Scheme 3). Notably, bromobenzene and iodobenzene reacted smoothly with dialkyl phosphites, whereas chlorobenzene remained unreactive under the same conditions.

Compared to the research conducted in 1981, the study published in 1982 not only expanded the substrate scope but also placed greater emphasis on optimizing reaction conditions. Hirao et al. conducted a comprehensive screening of catalysts, bases, and substituent effects.[9] They explored the replacement of $Pd(PPh_3)_4$ with palladium acetate ($Pd(OAc)_2$), which led to a slight reduction in yield to 58%, while palladium chloride ($PdCl_2$) proved far less effective, providing a yield of only 7%. Among the bases tested, triethylamine was identified as the most effective, outperforming tri-*n*-butylamine and pyridine. Additionally, aryl bromides with a range of electron-withdrawing and electron-donating substituents were successfully con-



Scheme 2. Palladium-Catalyzed Synthesis of Vinylphosphonates via Hirao Reaction.



Scheme 3. A Novel Synthesis of Dialkyl Arylphosphonates.

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Chau Ming So is currently an Associate Professor in the Department of Applied Biology and Chemical Technology at The Hong Kong Polytechnic University. He received his B.Sc. (1st class honor) from PolyU in 2006. He pursued his postgraduate study at the same university and obtained his Ph.D. degree in 2010. In 2012–2013, he moved to Institute of Materials Research and Engineering (IMRE) as postdoctoral fellow in Prof. Tamio Hayashi's research group. So's research interests focus on the development of ligands and their application in transition metal-catalyzed chemo-/regio-/enantioselective reactions.

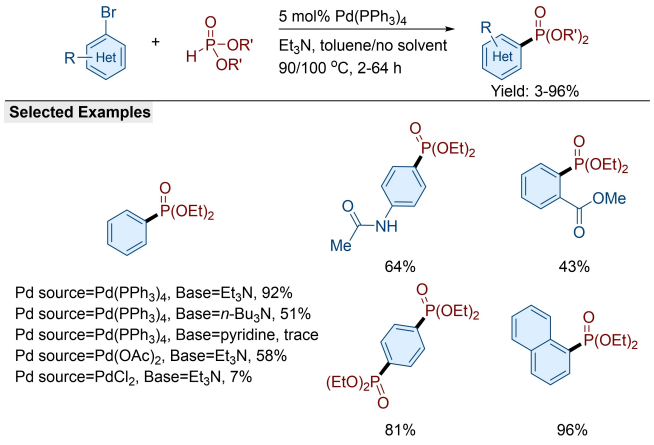
verted to dialkyl arylphosphonates in high yields (Scheme 4). However, chlorobenzene remained unreactive under these conditions.

The catalytic cycle of the Hirao reaction[10] is widely accepted as similar to the mechanism of well-known Pd-catalyzed C–C coupling reactions. It proceeds through three classical steps (Scheme 5). The first step is the oxidative addition of an aryl halide to the Pd^0L_n complex, forming the "Ar–$Pd^{II}L_n$–X" intermediate. In the second step, ligand exchange occurs, during which the deprotonated phosphonate reagent $R_1R_2P(O)H$ enters the catalytic cycle and replaces the X^- anion in the Pd(II) complex. Finally, reductive elimination from the resulting intermediate produces the desired coupled product, while regenerating the active Pd(0) catalyst to complete the cycle.

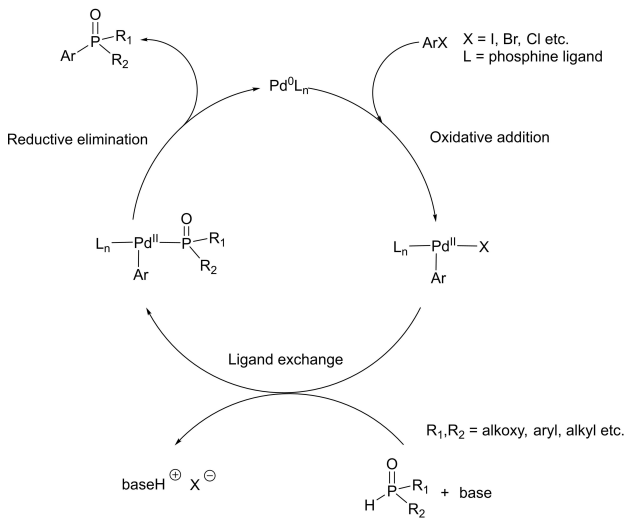
As research progressed, the substrate scope of the Pd-$(PPh_3)_4$-catalyzed Hirao reaction expanded significantly. Between 1983 to 1984, Xu et al.[11] applied Hirao's synthetic method to the reaction of aryl bromides with monoalkyl benzenephosphonites, monoalkyl alkanephosphonites and secondary phosphine oxides (SPOs) (Scheme 6), achieving the synthesis of various organophosphorus compounds with high yields. Additionally, they synthesized benzoxaphosphacycloalkane derivatives using palladium catalysis.[12]

While phosphonation reactions traditionally required non-aqueous media and elevated temperatures, a significant breakthrough was achieved in 1990 with the development of a water-soluble palladium catalyst, $Pd(PPh_2(m\text{-}C_6H_4SO_3M))_3$ (M = K^+, Na^+).[13] This catalyst enabled efficient phosphonation of dialkyl phosphite with aromatic iodide (Scheme 7) at room temperature in a water-acetonitrile mixture, achieving yields of up to 100% with only 10 mol% catalyst loading. The use of aqueous conditions not only simplified catalyst separation but also enhanced the environmental sustainability of the process.

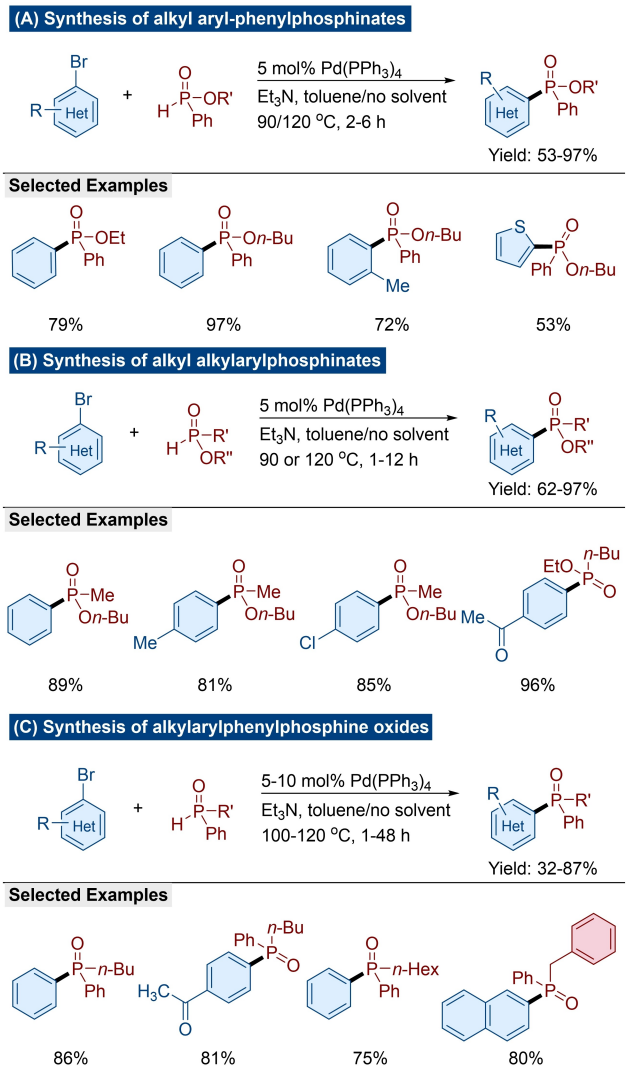
In 1997, building on earlier studies, Trost et al.[14] synthesized triarylphosphine oxides as part of their investigation into the role of a cation binding site in an asymmetric ligand for a palladium-catalyzed nucleophilic substitution reaction.



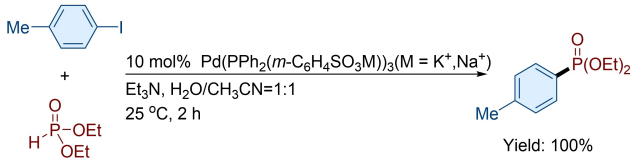
Scheme 4. Reaction Condition Screening for Palladium-Catalyzed Phosphonation and the Substrate Scope.



Scheme 5. Mechanism of Palladium-Catalyzed Cross-Coupling between Aryl Halides and H – Phosphonates.



Scheme 6. Extension of Hirao Reaction for Organophosphorus Compound Synthesis.



Scheme 7. Development of a Water-Soluble Palladium Catalyst for Room-Temperature Phosphonation.

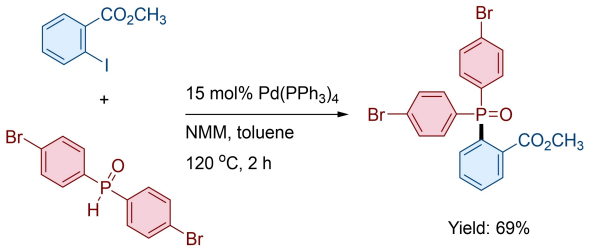
A key intermediate in the synthesis of these ligands was formed through a phosphonation reaction, yielding triarylphosphine oxides with three aryl groups. Notably, the reaction utilized *N*-methylmorpholine (NMM) as the base (Scheme 8) and employed aryl iodide and diarylphosphine oxide as reactants, achieving a yield of 69%.

In 1999, Marchand-Brynaert et al.[15] demonstrated that under Hirao reaction conditions (Scheme 9), *para*-substituted derivatives underwent efficient phosphonation, yielding the desired phosphonated products. In contrast, *ortho*-substituted derivatives could not be synthesized using this method. These findings highlight the critical role of substitution patterns in determining the efficiency of Pd-catalyzed phosphonation reactions.

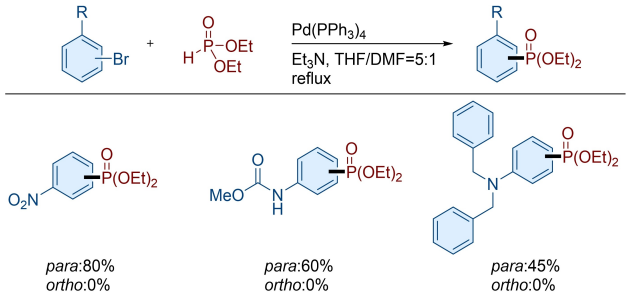
Despite the high efficacy of $Pd(PPh_3)_4$ in delivering excellent yields, its high cost limits its practicality for large-scale application. In 1999, while investigating the synergistic effects of hemilabile coordination and counterions in homogeneous catalytic hydrovinylation reactions, RajanBabu et al.[16] synthesized new tunable monophosphine ligands. During the synthesis of these ligands, they employed a more cost-effective catalyst system consisting of $Pd(OAc)_2$ (Scheme 10), the dppb phosphine ligand, and *N,N*-diisopropylethylamine (DIPEA) as the base in a key phosphonation step.

In 2001, Gouverneur et al.[17] reported the synthesis of a novel asymmetric diarylphosphinic acid, designed as a transition-state analogue for heterocyclic amide hydrolysis to facilitate the production of catalytic antibodies. They evaluated two phosphonation conditions (Scheme 11). Using $Pd(PPh_3)_4$ as a catalyst resulted in low yields due to steric hindrance and the formation of side products. By switching to a $Pd(OAc)_2$/dppf system, higher yields were achieved, showing its superior efficiency.

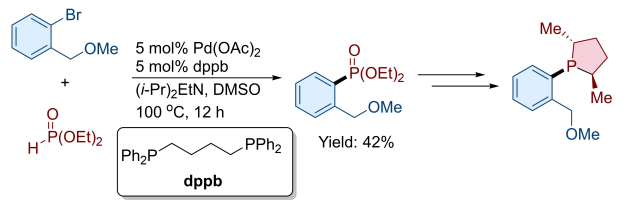
Monoarylphosphinic acids are essential precursors to pharmaceutical compounds and synthetic intermediates. However, hypophosphorus derivatives, with their two reactive P–H bonds, tend to form disubstituted or reduced products, making selective synthesis particularly challenging. In 2001, Dumond et al.[18] reported the palladium-catalyzed cross-coupling reactions of anilinium hypophosphite for the synthesis of monosubstituted phosphinic acids (Scheme 12).



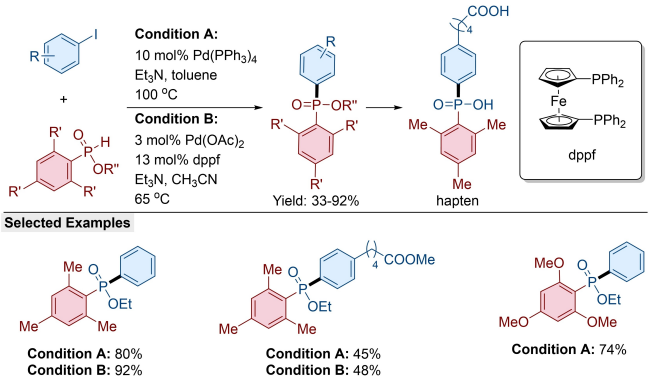
Scheme 8. Synthesis of Triarylphosphine Oxides Using Aryl Iodide.



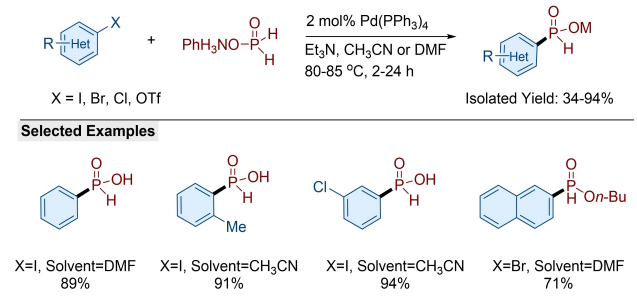
Scheme 9. Direct Phosphonylation of Bromonitrobenzene and *N*-Protected Bromoanilines.



Scheme 10. Synthesis of 1-Aryl-2,5-dialkylphospholanes.



Scheme 11. Synthesis of Asymmetric Diarylphosphinic Acid Derivatives.

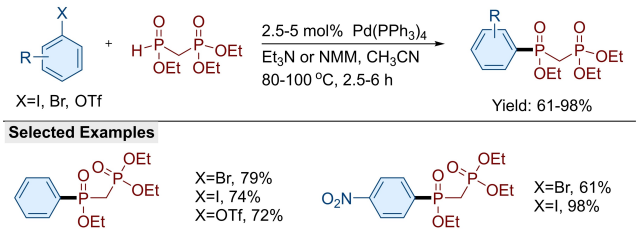


Scheme 12. Synthesis of Monosubstituted Phosphinic Acids: Palladium-Catalyzed Cross-Coupling Reactions of Anilinium Hypophosphite.

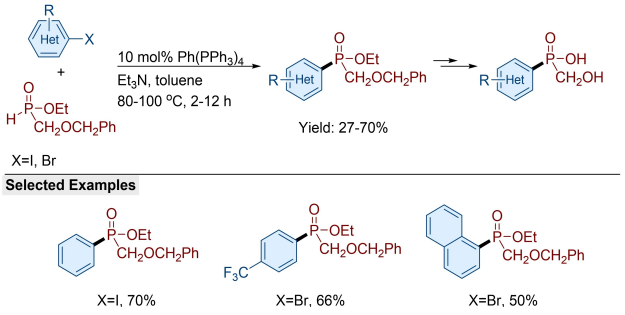
The phosphinylmethylphosphonate (PMP) group plays a crucial role in biologically active molecules, often serving as a stable pyrophosphate mimic. PMP-containing compounds have demonstrated various biological activities, including inhibition of Na^+-phosphate cotransport in renal brush border membranes. In 2002, Luke[19] developed a mild and efficient palladium-catalyzed method for synthesizing arylphosphinylmethylphosphonates (arylPMPs) through the phosphinylation of aryl halides and triflates with diethyl (ethoxyphosphinyl)methylphosphonate (Scheme 13).

Phosphonic acids are important intermediates in biomolecular chemistry but face bioavailability challenges due to their high ionic character. In 2003, Virieux et al.[20] developed a palladium-catalyzed method to synthesize hydroxymethyl-containing arylphosphinic acids (Scheme 14). Through the arylation of ethyl benzyloxymethylphosphinate with aromatic or heteroaromatic halides, ethyl arylbenzyloxymethylphosphinates were obtained. Selective or complete deprotection then yielded the target hydroxymethylphosphinic acids.

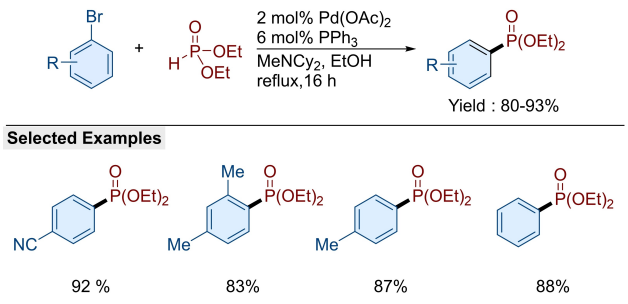
In 2005, Gooßen et al.[21] developed an improved protocol for the palladium-catalyzed synthesis of arylphosphonates



Scheme 13. Palladium-Catalyzed Synthesis of arylPMPs.



Scheme 14. Synthesis of Arylhydroxymethylphosphinic Acid and Derivatives.



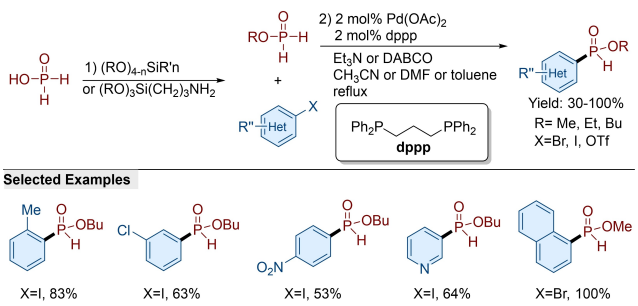
Scheme 15. Practical Protocol for the Palladium-Catalyzed Synthesis of Arylphosphonates from Bromoarenes and Diethyl Phosphite.

(Scheme 15). Gooßen's key innovation was the introduction of alcoholic solvents, particularly ethanol, which significantly enhanced reaction efficiency. They then examined several Pd sources(e.g., $PdCl_2$, $Pd(dba)_2$, $Pd(PPh_3)_4$, etc.), and found $Pd(OAc)_2$ to be the most effective precatalyst. The choice of phosphine ligand was also critical. Neither chelating nor electron-rich alkyl phosphines gave satisfactory results in this transformation, although these ligands had proven to be highly effective in other Pd-catalyzed couplings. Instead, the best results were obtained with simple triaryl phosphines such as P(*p*-MeO–Ph)$_3$ and P(*p*-Cl–Ph)$_3$. However, since the inexpensive triphenylphosphine was found to be almost as effective, it was considered the optimal choice. The method demonstrated a broad substrate scope, successfully coupling electron-rich and electron-poor aryl bromides, even those bearing sensitive functional groups.

Cross-coupling reactions involving compounds with two phosphorus-hydrogen bonds remained challenging due to the inherent risk of competitive transfer hydrogenation. In 2005, Montchamp et al.[22] developed a one-pot method for synthesizing H – phosphinates, utilizing the hydrolysis of preformed alkyl phosphinates into phosphonates in aqueous media. These phosphonates then coupled with electrophiles and underwent in situ esterification to form H-phosphinate products. This method demonstrated broad applicability to aromatic and heteroaromatic electrophiles, as well as benzyl and heterobenzyl chlorides (Scheme 16). While satisfactory results were obtained with PPh_3 as a ligand for aryl iodides, dppp proved to be the most versatile ligand.

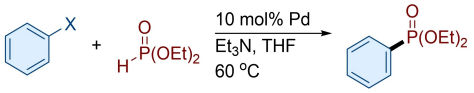
In 2007, Stawinski[10a,23] conducted a systematic investigation into the influence of various palladium sources on the cross-coupling reaction between aryl halides and diethyl phosphinate. Notably, $Pd(OAc)_2$ demonstrated superior performance with shorter reaction times, particularly when combined with anionic additives (Table 1). Furthermore, the effects of various anionic additives such as chloride, bromide, and acetate ions were investigated (Table 2). The addition of anionic additives further shortened the reaction times. Following this discovery, in 2009[24], it was revealed that acetate ions significantly enhance reaction efficiency by forming reactive κ^2-acetate palladium intermediates, facilitating both ligand substitution and reductive elimination steps.

The traditional Hirao reaction requires high palladium loadings ($\geq$3–5 mol%), which poses considerable economic and



Scheme 16. One-Pot Synthesis of H – Phosphinates.

Table 1. Comparison of Different Palladium Sources in a Cross-Coupling Reaction between $(EtO)_2P(O)H$ and Bromo- or Iodobenzene.



Entry	Palladium source (+ ligand)	Reaction time (h) Ph – Br	Ph – I
1	$Pd(PPh_3)_4$	18	8
2	$Pd(OAc)_2 + 3PPh_3$	16	7
3	$Pd(dba)_2 + 2PPh_3$	24	10
4	$PdCl_2 + 2PPh_3$	No reaction	No reaction

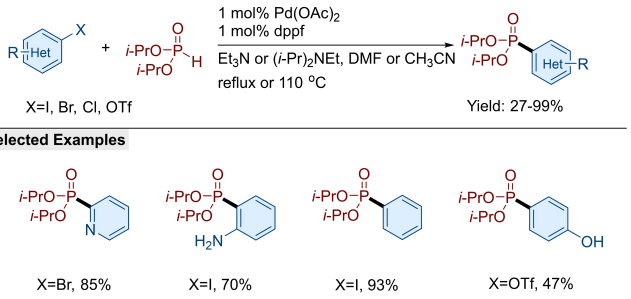
Table 2. Effect of Anionic Additives on the Reaction Times of $(EtO)_2P(O)H$ with Bromo-or Iodobenzene.

Entry	Palladium source (+ ligand)	Reaction time (h) Ph–Br	Ph–I
1	$Pd(PPh_3)_4$	18	8
2	$Pd(PPh_3)_4 + 10Cl^-$	11	2.5
3	$Pd(PPh_3)_4 + 10Br^-$	10	4
4	$Pd(OAc)_2 + 3PPh_3$	16	7
5	$Pd(OAc)_2 + 3PPh_3 + 10Cl^-$	11	2
6	$Pd(OAc)_2 + 3PPh_3 + 10Br^-$	11	4
7	$Pd(OAc)_2 + 3PPh_3 + 10OAc^-$	2.5	1

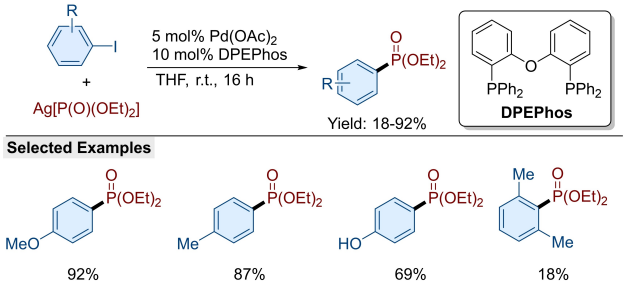
practical challenges, especially on large, multi-gram scales. Moreover, this classical protocol is generally restricted to reactive aryl bromides and iodides, rendering it ineffective for less reactive aryl chlorides. For instance, under standard Hirao conditions, no product formed even with 2-iodopyrazine. In 2008, Montchamp et al.[25] developed a more efficient catalytic system using $Pd(OAc)_2$ (1 mol%) and dppf as the ligand. This system significantly reduced catalyst loading and enabled the coupling of aryl chlorides with phosphonates (Scheme 17). The method showed a broad substrate scope, including challenging heterocycles, and was valuable for synthesizing heterocyclic phosphonic acids for metal-organic frameworks (MOFs).

In 2009, Stockland Jr et al.[26] developed a new method for the synthesis of arylphosphonates via a palladium-catalyzed reaction at room temperature (Scheme 18). This method utilized a large-bite-angle bisphosphine ligand, DPEPhos, and silver phosphonates as the core, enabling the production of aryl-phosphonates in moderate to excellent yields. Initial attempts with 4-iodoanisole and diethylphosphite resulted in only trace amounts of the desired product, even after extensive screening of catalysts, ligands, bases, and solvents. The breakthrough came with the use of silver phosphonates, achieving near-quantitative yields at 25 °C under optimized conditions. The sterically hindered DPEPhos ligand exhibited higher catalytic activity compared to less bulky ligands (dppe). This reaction system is suitable for a wide range of aryl iodides, including those with electron-donating and electron-withdrawing groups, as well as acid-sensitive functional groups. However, for aryl iodides with two *ortho* substituents, the reactivity decreases.

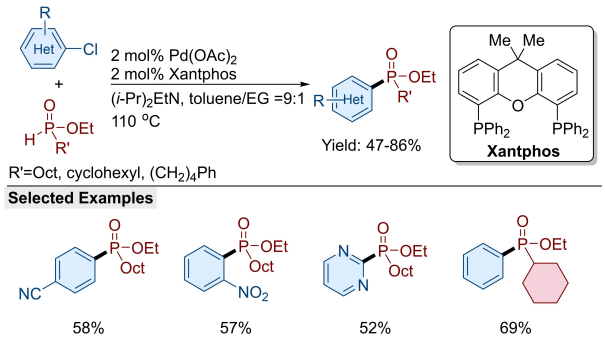
In 2011, Montchamp et al.[27] developed a palladium-catalyzed method for cross-coupling H – phosphinate esters with chloro(hetero)arenes (Scheme 19), addressing their lower reactivity compared to aryl bromides and iodides. Using 2 mol% $Pd(OAc)_2$ and ligands such as dppf, Xantphos, and polymer-supported nixantphos, efficient C–P bond formation was demonstrated. Notably, the addition of ethylene glycol (EG) was a key innovation, as it promoted the tautomerization of P(V) H-phosphinates into the reactive P(III) form, likely through intermolecular hydrogen bonding. EG also appeared to stabilize the palladium catalyst, reducing decomposition and enhancing reaction efficiency. Additionally, the experiment demonstrated that a range of chlorinated (hetero)arenes could be cross-coupled with various representative H – phosphonates.



Scheme 17. Optimized Catalyst/Ligand System for Reducing Palladium Catalyst Loading.



Scheme 18. Palladium-Catalyzed Reaction of Aryl Iodides with a Silver Phosphonate.



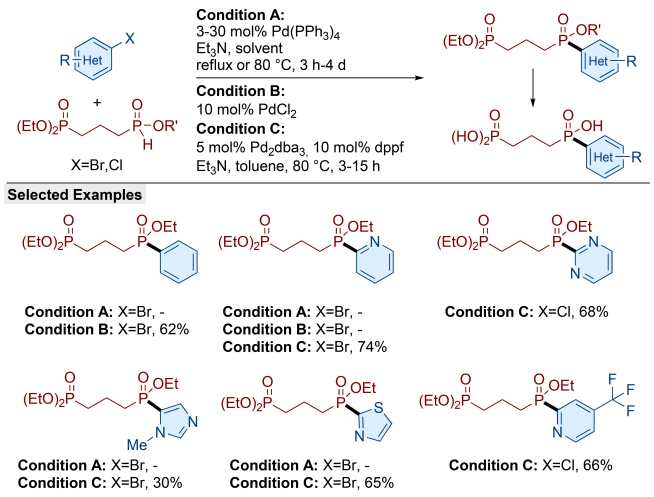
Scheme 19. Incorporating EG to Facilitate the Phosphonation Reaction of Aryl Chlorides.

In 2012, Virieux et al.[28] investigated various catalytic systems for synthesizing aryl and heteroaryl phosphonic acids through the coupling of H-phosphinates with aryl halides (Scheme 20). Using $Pd(PPh_3)_4$ as a catalyst, they achieved the coupling of O-benzyl-protected H-phosphinates with bromobenzene, but the reaction suffered from moderate yields, low selectivity, and side reactions such as debenzylation. $PdCl_2$, a more air-stable and easily handled catalyst, improved yields compared to $Pd(PPh_3)_4$; however, for some heteroaryl halides such as 2-bromopyridine, the target products were difficult to isolate. The best results were obtained using Pd_2dba_3 combined with the bidentate ligand dppf, which significantly enhanced efficiency and selectivity. This system successfully coupled H-phosphinates with a wide range of heteroaryl chlorides and bromides, outperforming $Pd(PPh_3)_4$ and $PdCl_2$ in both yield and selectivity, establishing a robust method for synthesizing functionalized phosphonic acids.

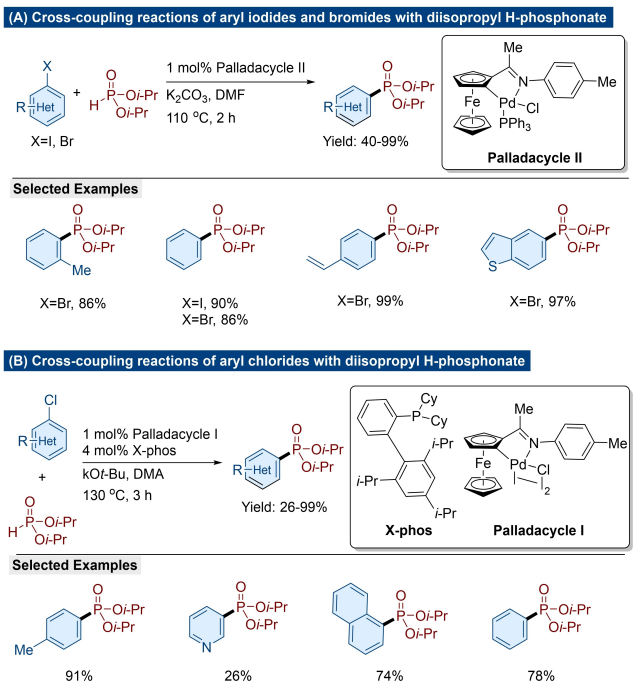
To further improve reaction yields, Wu et al.[29] developed an efficient catalytic system based on palladacycles (i.e., cyclopalladated ferrocenylimines), which catalyze the phosphonation of aryl iodides, bromides, and chlorides (Scheme 21). A key achievement of this system is its excellent performance in the phosphonation of aryl chlorides, which are typically less reactive. This work also extended to the phosphonation of arylmethyl bromides and chlorides, employing the more economical base K_2CO_3 as a promoter, further broadening the substrate scope and synthetic utility of this methodology.

The following year, Wu et al.[30] addressed the issue of the easy decomposition of dialkyl H-phosphonates in water by devising a general and highly efficient catalytic system for the palladium-catalyzed phosphonation of aryl halides in pure water (Scheme 22). This system employs cyclopalladated ferrocenylimines as the catalyst, with TBAB and isopropanol serving as additives. This innovative method successfully enabled the reaction between aryl halides and H – phosphonates in water, opening new avenues for the synthesis of phosphonylphosphonic acids.

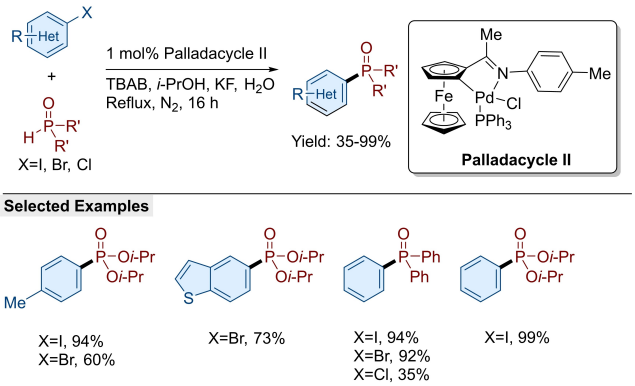
In the same year, Verboom et al.[31] reported a synthesis method involving the $Pd(dppf)Cl_2$-catalyzed cross-coupling reaction of chloropyrazines with phosphorus-containing nucleophiles, resulting in the formation of a series of 2,6-disubstituted phosphorylated pyrazine compounds (Scheme 23). $Pd(dppf)Cl_2$ was chosen as the catalyst after being identified as one of the



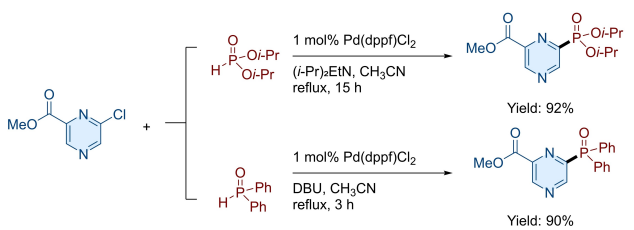
Scheme 20. Optimized Synthesis of Phosphanyl-Phosphonic Acids.



Scheme 21. Palladacycle-Based Catalytic System for High-Yield Phosphonation of Aryl Halides.



Scheme 22. Reaction of Aryl Halides with H – Phosphonates in Water Catalyzed by Palladacycles.



Scheme 23. Examples of Palladium-Catalyzed Cross-Coupling of Various Phosphorus Pronucleophiles with Chloropyrazines.

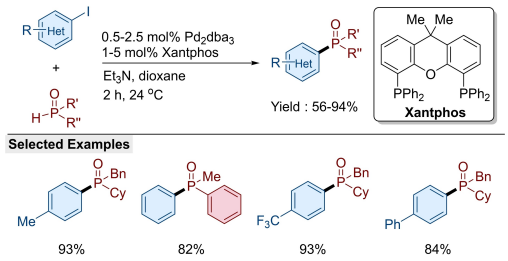
most effective second-generation catalysts for carbon–heteroatom couplings, particularly in cases where other palladium complexes with bidentate phosphine ligands were unsuccessful. Similarly, other palladium catalysts such as $Pd(OAc)_2$/Buchwald ligand, $Pd(PPh_3)_4$ or $Pd(dppe)_2$, showed no conversion under the tested conditions.These compounds were evaluated as potential extractants for trivalent cations, and their performance as lanthanide/actinide extractants was investigated.

Herzon et al.[32] also explored the coupling reaction of various aryl iodides with SPOs, catalyzed by Pd_2dba_3 and Xantphos, providing a new route for the synthesis of tertiary phosphines (Scheme 24). Using the coupling of dimethylphosphine oxide and iodobenzene as a model reaction for catalyst optimization, they systematically evaluated a panel of bidentate phosphine ligands ((*S*)-BINAP, (*R*)-(*S*)-Josiphos, dppf, and Xantphos) with Pd_2dba_3 as the catalyst precursor and triethylamine as the base. They discovered that reaction efficiency increased with increasing ligand bite angle, with Xantphos (bite angle = 108°) providing 97% yield of dimethylphenylphosphine oxide after just 1.5 h at 24 °C. The superior performance of larger bite angle ligands was attributed to their ability to displace dba from the palladium precursor and promote the oxidative addition of iodobenzene.

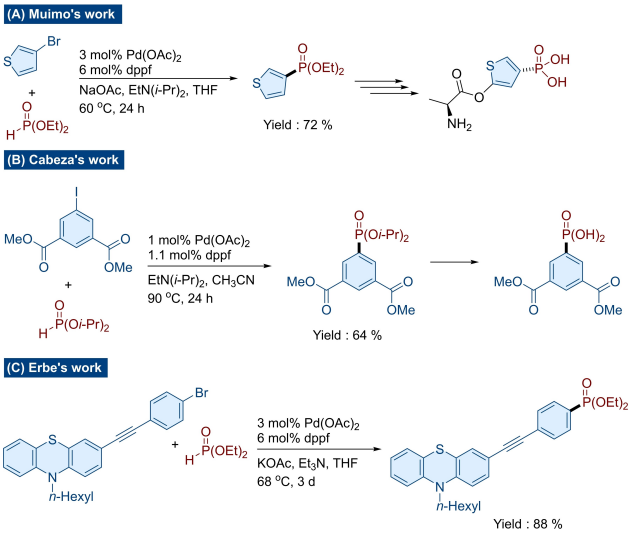
The $Pd(OAc)_2$/dppf catalytic system has extensive applications. Muimo et al.,[33] recognizing the importance of protein tyrosine phosphatases (PTPs) as potential therapeutic targets and the lack of specific inhibitors, focused on developing stable analogues of phosphotyrosine (pTyr). In 2014, 3-diethoxylphosphothiophene was successfully synthesized, enhancing the reaction yield to 72% by incorporating OAc ions and DIPEA as the base in THF (Scheme 25A). Cabeza et al.[34] also employed the $Pd(OAc)_2$/dppf system in the synthesis of open-framework hybrid materials, using acetonitrile as the solvent (Scheme 25B). Erbe et al.[35] utilized similar reaction conditions for the synthesis of compounds capable of forming organic layers through chemical adsorption on metal surfaces (Scheme 25C).

Research has shown that the Hirao coupling reaction can efficiently introduce phosphonyl groups at specific positions of imidazopyridine derivatives. In 2020, Virieux et al.[36] optimized the conditions for the Hirao coupling reaction, using 3-bromo-2-phenylimidazo[1,2-a]pyridine and diethyl phosphite as the starting materials. Initially, the reaction did not yield the expected phosphonate when using $Pd(OAc)_2$ and Xantphos as the catalyst and triethylamine as the base (Table 3). By altering the palladium source or ligand, they found that $Pd_2(dba)_3$ and Xantphos could produce the target phosphonate with a yield of 60%. Shortening the reaction time to 4 hours further increased the yield to 72%. This reaction was highly ligand dependent, as other bidentate ligands such as dppf, dppp, and SPhos only led to the formation of reduction products. Subsequently, Virieux et al. introduced phosphoryl functionalities at the 3, 5, and 6 positions of imidazo[1,2-a]pyridine derivatives, discussing the efficiency and selectivity of different positions.

In 2023, Chang et al.[37] reported a novel palladium complex (Scheme 26) as an efficient catalyst for the Hirao coupling reaction. Under ethanol reflux conditions at 90 °C, the reaction achieved a conversion rate of 99% within 10 minutes, demonstrating exceptionally high conversion and yield. This system offers significant advantages, including reduced reaction times, high yields, and compatibility with environmentally friendly solvents. It demonstrated a broad substrate scope, efficiently coupling aryl bromides with various functional groups, including challenging nucleophile-sensitive substrates when EG was used as an additive.

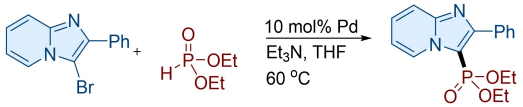


Scheme 24. Scope of the SPO and Aryl Iodide Components.

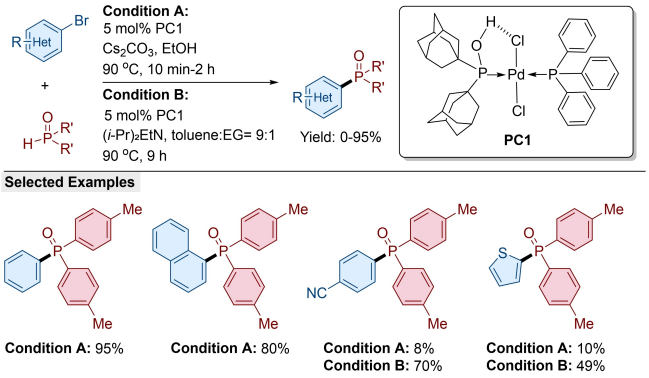


Scheme 25. Applications of the Hirao Reaction.

Table 3. Optimized Hirao Reaction of Imidazopyridine Derivatives.



Entry	Pd	Ligand	Condition	Yield (%)
1	$Pd(OAc)_2$	Xantphos	KOAc, THF, reflux, 36 h	0
2	$Pd(OAc)_2$	Xantphos	KOAc, THF, μW, 90 °C, 10 min	0
3	$PdCl_2(PPh_3)_2$	/	Toluene, 110 °C, 24 h	0
4	Pd_2dba_3	Xantphos	Toluene, 110 °C, 21 h	60
5	Pd_2dba_3	Xantphos	Toluene, 110 °C, 4 h	72
6	Pd_2dba_3	dppf	Toluene, 110 °C, 46 h	0
7	Pd_2dba_3	dppp	Toluene, 110 °C, 4 d	0
8	Pd_2dba_3	SPhos	Toluene, 110 °C, 4 d	0



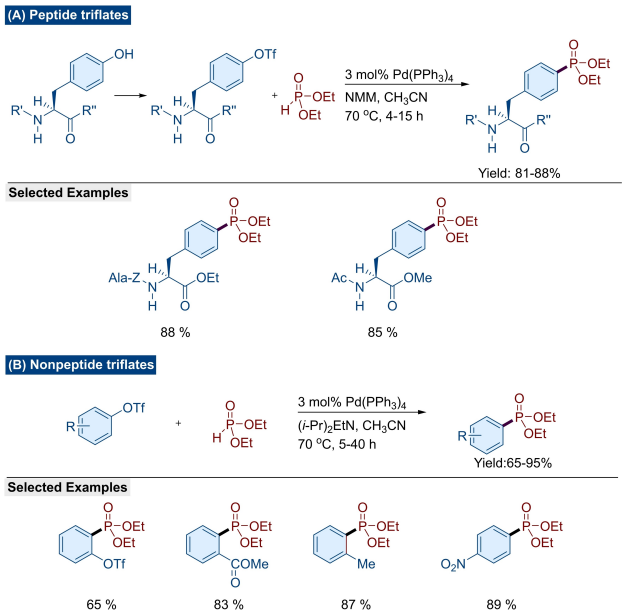
Scheme 26. High-Efficiency Hirao Coupling Catalyzed by a Novel Palladium Complex.

3. Palladium-Catalyzed Phosphonation of Aryl Sulfonates

Traditionally, the synthesis of aryl phosphonates has primarily been achieved through the Hirao reaction, which involves the palladium-catalyzed coupling of aryl halides with H—phosphonates. However, in recent years, aryl sulfonates (e.g., aryl tosylates, Ar—OTs; aryl triflates, Ar—OTf) have emerged as superior alternatives to aryl halides, offering numerous significant advantages.

Compared to aryl halides, aryl sulfonates offer distinct advantages as substrates in organic synthesis, making them particularly attractive for various transformations.[6] Aryl sulfonates are readily accessible from phenolic compounds and are relatively inexpensive, enhancing their appeal for synthetic applications. Additionally, the regioselective aromatic substitution patterns of aryl sulfonates often differ from those of aryl halides due to the directing effect of the phenolic OH group, enabling the synthesis of compounds with unique structural features. This is particularly valuable for biologically active molecules that exist exclusively in phenolic form and cannot be easily accessed via halogenation. Despite the inherent chemical inertness of aryl sulfonates, which can complicate oxidative addition in catalytic reactions, advancements in catalytic systems, including the development of optimized ligands and solvents, have enabled efficient C—P bond formation. Overall, aryl sulfonates are cost-effective, hydrolytically stable, and versatile substrates that provide unique opportunities for the synthesis of structurally complex and functionally diverse compounds.

Tyrosine kinase inhibitors are vital compounds in anticancer and antiviral therapies. Nagabhushan[38] developed an enzymatic inhibitor design strategy, which involves converting tyrosine-containing peptides into 4-phosphonophenylalanine derivatives, and discovered that the efficient synthesis of diethyl arylphosphonates can be achieved through the reaction of aryl triflates with diethyl phosphite in the presence of NMM or DIPEA and a $Pd(PPh_3)_4$ catalyst in acetonitrile (Scheme 27). Further investigation revealed that this method exhibits high versatility and efficiency for simple aryl triflates, although



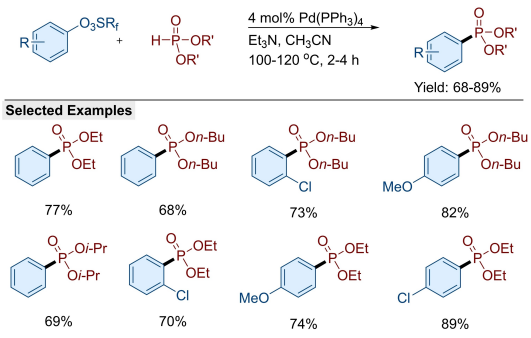
Scheme 27. Palladium-Catalyzed Substitution of Triflates to Form Phosphonates in Peptides and Hydroxyarenes.

hindered by steric effects, as evidenced by decreased reaction rates observed for *ortho*-substituted substrates.

Zhu et al.[39] investigated the use of aryl polyfluoroalkanesulfonates and O,O-dialkyl phosphonates as substrates in 1987 (Scheme 28), finding that the presence of electron-withdrawing or electron-donating groups on the benzene ring had little influence on the reaction, and that the substituents on the phosphorus atom also had negligible effects on reaction efficiency.

Axially chiral compounds, particularly 2-substituted-1,1′-binaphthyls, have demonstrated extensive utility in asymmetric induction reactions.[40] These compounds often serve as stoichiometric auxiliaries or as chiral ligands for transition metal catalysts in chemical reactions.[41] Studies have shown that binaphthyls can significantly enhance the chiral selectivity of products in asymmetric catalytic reactions.[42]

In 1990, Ward et al.[43] utilized a palladium-catalyzed phosphonation reaction to react (R)-(–)-1,1′-bi-2-naphthol tri-

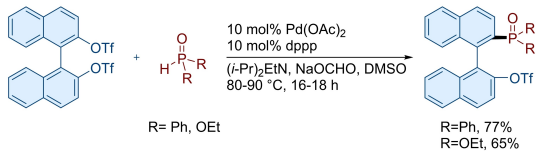


Scheme 28. Palladium-Catalyzed Reaction of Aryl Polyfluoroalkanesulfonates with Dialkyl Phosphonates.

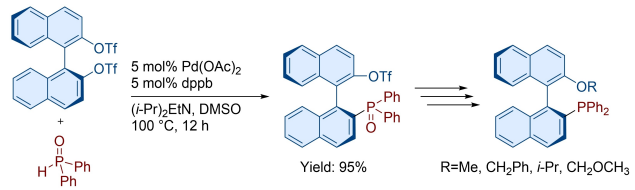
flate with the phosphorylating agents ($Ph_2P(O)H$ or $HPO(OEt)_2$). Initial attempts, employing previously reported conditions for Hirao reactions, yielded only a 32% product, with the main side reaction being triflate hydrolysis. Upon optimization of the reaction conditions using the $Pd(OAc)_2$/dppp catalytic system (Scheme 29), the yield increased to 65–77%, with complete retention of the substrate's chirality. No bis-phosphorylated side products were observed, demonstrating the excellent selectivity of the reaction.

In 1993, Hayashi et al.[44] conducted a systematic study on the synthesis of chiral monodentate phosphine ligands MOPs using the $Pd(OAc)_2$/dppb catalytic system and developed a series of MOP derivatives (Scheme 30).

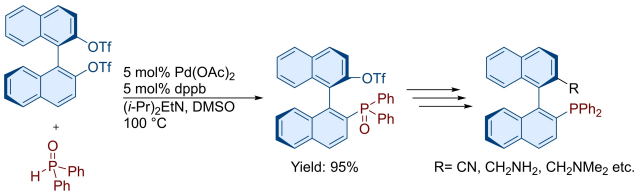
The following year,[45] Hayashi and colleagues further modified the MOP ligands by introducing several functional groups at the C2-position to enhance the utility of chiral binaphthyl monophosphines. These modified ligands exhibited varying catalytic activity and selectivity in asymmetric palladium-catalyzed hydrosilylation reactions of olefins (Scheme 31).



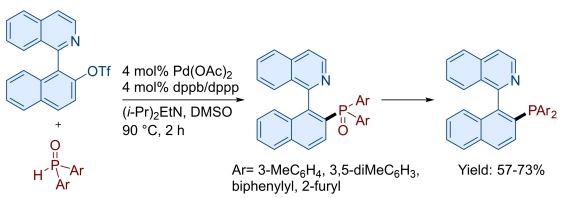
Scheme 29. Synthesis of BINAP Derivatives Using the $Pd(OAc)_2$/dppp Catalytic System.



Scheme 30. Synthesis of Optically Active 2-(Diarylphosphino)-1,1′-Binaphthyls, Efficient Chiral Monodentate Phosphine Ligands.



Scheme 31. Extended Synthesis of MOPs.



Scheme 32. Synthesis of 1′-(2-(diaryiphosphino)1-naphthyl)isoquinolines.

As early as 1993, Brown et al.[46] conducted research on the catalysis of phosphonation using the $Pd(OAc)_2$/dppp catalytic system to obtain N,P chelate catalysts. In 1997, Brown et al.[47] optimized the reaction condition and employed 1′-[1-(2-trifluoromethanesulfonylnaphthyl)]isoquinoline as the substrate for the phosphonation reactions (Scheme 32). To investigate the impact of varying the electronic properties of the ligand on the reactivity and enantioselectivity in asymmetric catalysis, they also synthesized a series of SPOs using distinct diarylphosphine oxides as the phosphorus source.

In 1998, Sansoni et al.[48] utilized this reaction template to connect a phosphino group and a phosphinyl group onto the 2,2′-carbon atoms of the binaphthalene backbone, resulting in the asymmetric binaphthalene-templated diphosphines, BINAPO. This ligand was subsequently applied in the palladium-catalyzed asymmetric hydrosilylation of styrene.

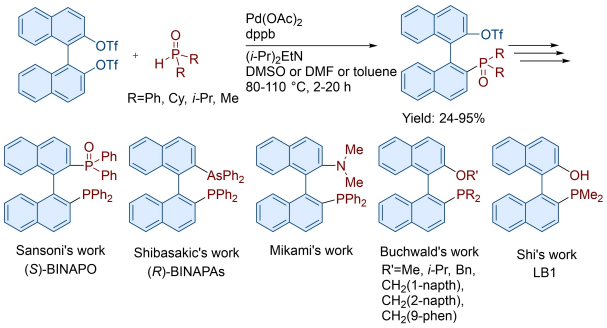
In the same year, Shibasaki et al.[49] successfully synthesized 2-diphenylarsino-2′-diphenylphosphino-1,1′-binaphthyl (BINAPs) and determined that it was a chiral ligand in asymmetric Heck reactions. Their findings revealed that BINAPAs exhibited greater effectiveness compared to BINAP that use aryl triflates.

In 1999, Mikami et al.[50] synthesized binaphthyl amino phosphine, featuring a rigid chiral binaphthyl scaffold and chelating groups containing P and N. In 2002, Buchwald et al.[51] reported a series of novel ligands derived from dialkylphosphino-binaphthyl that proved to be effective in Pd-catalyzed asymmetric arylation of ketone enolates with aryl bromides.

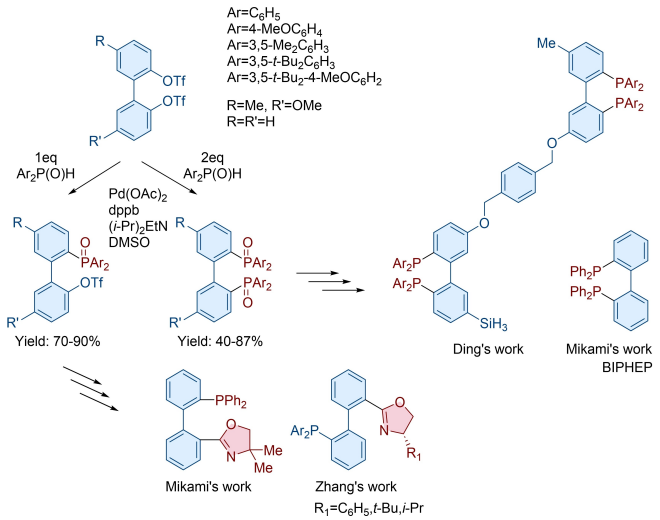
Building on these efforts, in 2005, Shi et al.[52] employed a similar strategy to synthesize a chiral phosphine Lewis base for the catalysis of asymmetric aza-Baylis–Hillman reactions (Scheme 33).

In 2001, Mikami et al.[53] described an efficient and general synthetic route for the preparation of a variety of substituted BIPHEP ligands from biphenol. Previous BINAP syntheses had employed $Pd(OAc)_2$ for the coupling of one equivalents of $Ph_2P(O)H$ with binaphthyl ditriflate, yielding only the binaphthyl monophosphine oxide. They discovered that, by contrast, treating biphenyl ditriflate with $Pd(OAc)_2$ and two equivalents of $Ph_2P(O)H$ that produced the diphosphine oxide derivative of BIPHEP (Scheme 34).

Building on this methodology, in 2006, Ding et al.[54] employed a similar approach to obtain bridged bis-BIPHEP-type ligands (Scheme 34) that, when assembled with Ru(II) metal



Scheme 33. Extended Synthesis of BINAP Derivatives.

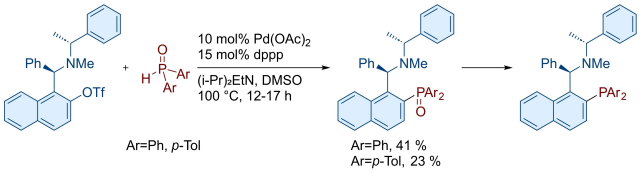


Scheme 34. Synthesis of BIPHEP Ligands Using the $Pd(OAc)_2$/dppb Catalytic System.

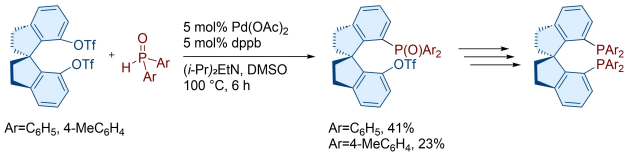
ions, resulted in self-supported catalysts exhibiting good activity and enantioselectivity for the hydrogenation of certain aromatic ketones. Furthermore, in 2009, Zhang et al.[55] developed a novel class of chiral phosphine-oxazoline ligands featuring an axially unfixed biphenyl backbone and bearing diverse substituents on both the oxazoline ring and the P-phenyl ring (Scheme 34).

In 2002, Ding et al.[56] reported the synthesis of novel chiral amino phosphine ligands for asymmetric catalysis (Scheme 35). The triflate derivative of amino naphthol was coupled with diphenylphosphine oxide or di(*p*-tolyl)phosphine oxide under $Pd(OAc)_2$/dppp catalysis, yielding intermediates that were subsequently reduced to produce the final ligands.

Constituting another important class of axially chiral ligands, spirodiphosphines had not been synthesized prior to this effort. Zhou et al.[57] previously designed chiral phosphoramidite ligands (SIPHOS) containing a 1,1′-spirobiindane scaffold and discovered their high efficiency in Rh-catalyzed asymmetric



Scheme 35. Synthesis of the Chiral Amino Phosphine (N,P) Ligands.



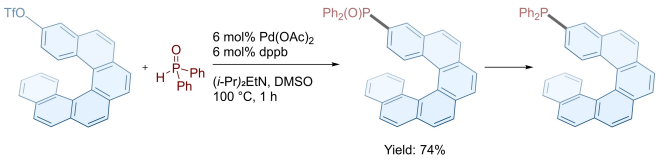
Scheme 36. Synthesis of SDP Ligands Using the $Pd(OAc)_2$/dppb Catalytic System.

hydrogenation of functionalized olefins. Subsequently, in 2003, Zhou et al.[58] further designed and synthesized spiro diphosphine (SDP) ligands featuring a novel 1,1′-spirobiindane chiral backbone that also exhibited high efficacy in the asymmetric hydrogenation of ketones (Scheme 36).

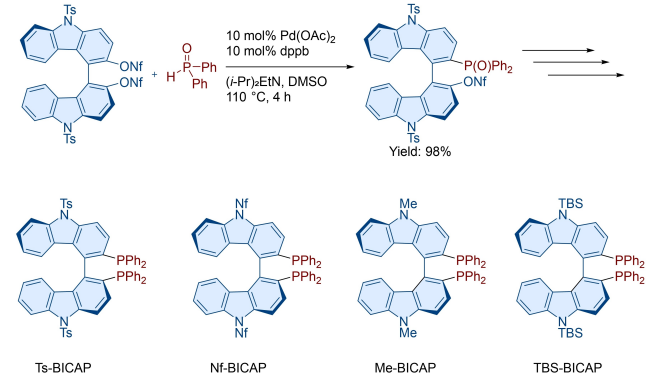
Carbohelicenes represent a stable class of nonplanar aromatic systems that are inherently chiral. Nevertheless, the variety of functional groups in the hexahelicene series is limited.[59] In 2003, Fiedler et al.[60] drew inspiration from Hayashi's work[44] in the binaphthyl series to successfully synthesize novel 3-hexahelicenyl diphenylphosphine ligands (Scheme 37).

Building on their previously developed BIFAP ligands, in 2004, Hiemstra et al.[61] reported the further development of a new family of C_2-symmetric bicarbazole-based diphosphine ligands, designated as BICAP (Scheme 38). The reaction was carried out using aryl nonaflates as substrates, specifically chosen for this purpose.

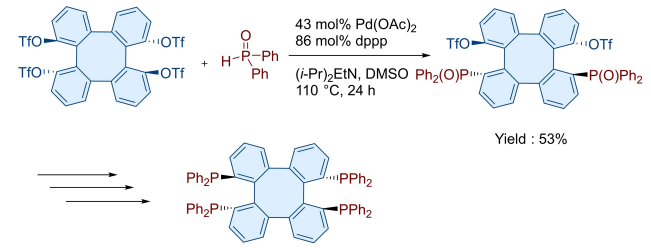
For the construction of chiral rodlike platinum complexes, in 2005, Wong et al.[62] revealed the synthesis of tetraphenylene-based phosphine ligands (Scheme 39) that served as potential asymmetric hydrogenation ligands for acetamidocinnamate derivatives.



Scheme 37. Synthesis of 3-Functionalized Hexahelicenes Using the $Pd(OAc)_2$/dppb Catalytic System.



Scheme 38. Synthesis of the BICAP Family.



Scheme 39. Synthesis of Tetraphenylene-Based Phosphine Ligands.

Aryl imidazolylsulfonates emerged as a novel class of electrophilic coupling substrates, exhibiting significantly enhanced reactivity in palladium-catalyzed coupling reactions, compared to aryl tosylates (mesylates), and superior stability, handling properties, and cost-effectiveness over aryl triflates.[63]

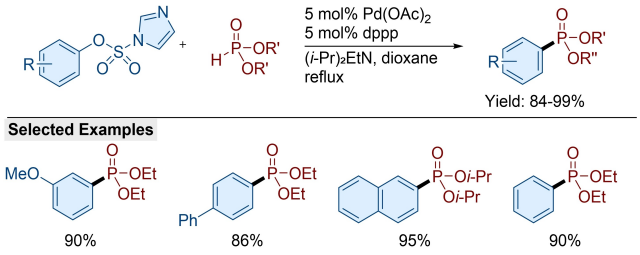
Consequently, in 2009, Wu et al.[64] selected aryl imidazolylsulfonates and H—phosphonate diesters as reactants to develop an efficient synthesis of arylphosphonates (Scheme 40). In their initial studies, no reaction occurred without the addition of a ligand. However, when $Pd(OAc)_2$ (5 mol%) and dppp (5 mol%) were used as the catalyst and ligand, a 19% yield of the desired phenylphosphonate was achieved. The use of alternative ligands, such as XPhos or dppf, resulted in only trace to 10% yields. After optimizing the reaction condition, this method demonstrated a broad substrate scope, tolerating both electron-rich and electron-poor aryl imidazolylsulfonates, including functional groups such as carbonyls, and providing excellent yields across a variety of substrates.

Aryl mesylates and tosylates are desirable substrates due to their cost-effectiveness, high stability, and environmental friendliness; however, their chemical inertness poses a challenge in catalytic reactions. In 2015, Kwong et al.[6b] reported the first general palladium catalyst system for the phosphonation of aryl mesylates and tosylates (Scheme 41). In their initial investigation, nonactivated 4-*tert*-butylphenyl tosylate and diisopropyl phosphite were selected as benchmarking substrates. A series of ancillary ligands were evaluated for their efficacy in this C—P bond coupling reaction. Among them, CM-Phos was found to be the most effective, delivering the highest yields. Mor-DalPhos and XPhos also showed moderate activity, albeit with lower efficiencies. Other ligands, including monodentate phosphines, bidentate phosphines, and an *N*-heterocyclic carbene, were tested but proved ineffective, likely due to the challenging oxidative addition of aryl tosylates, as evidenced by the unreacted starting materials.

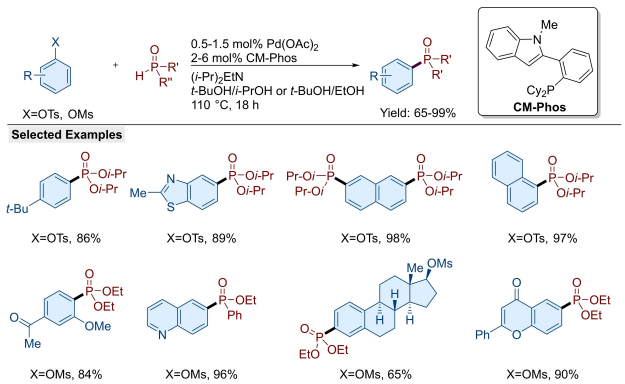
Notably, the catalyst not only efficiently catalyzed the phosphonation of a wide range of substituted aryl tosylates, encompassing electronically neutral, electron-rich and electron-deficient arenes, and heterocycles, but it also accommodated substrates bearing sensitive functionalities such as ketones and NH-amides, achieving even dual phosphonation. Furthermore, the system facilitated the phosphonation of aryl mesylates, including those with complex functionalities such as esters, enolizable ketones, free amines, and heterocycles. This innovation represents an efficient new approach for the synthesis of organophosphorus compounds.

In 2018, Qiu et al.[65] designed and synthesized a series of novel binaphthyl monophosphine ligands with a naphthofuran skeleton to enhance catalytic performance in palladium-catalyzed Suzuki-Miyaura coupling reactions (Scheme 42). The ligands were synthesized using a key phosphonation step to form a phosphine oxide intermediate, followed by reduction to yield the final ligands.

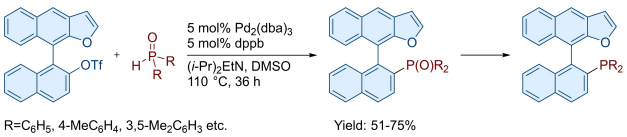
Subsequently, in 2021, Ding et al.[66] reported the successful phosphonation of aryl fluorosulfonates with phosphites, catalyzed by a combination of palladium and DPEPhos (Scheme 43). A comprehensive exploration of reaction conditions for the palladium-catalyzed process was conducted, evaluating various phosphine ligands. Initial attempts with $Pd(OAc)_2/PPh_3$ as the catalyst afforded the desired product in 20% yield. Further ligand screening revealed that BINAP improved the yield to 42%, while DPEPhos proved to be the most effective ligand, delivering the product in 89% yield. DPEPhos was identified as the optimal ligand. Additionally, the substrate scope was investigated, revealing that aryl fluorosulfonates with electron-



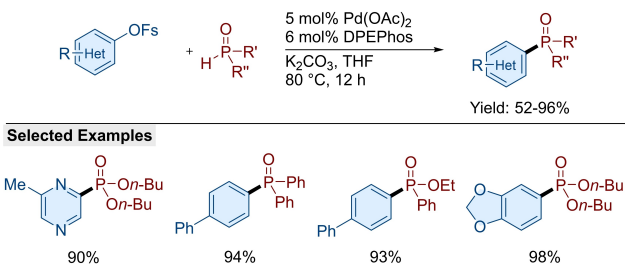
Scheme 40. Palladium-Catalyzed Reactions of Aryl Imidazolylsulfonate with H—Phosphonate Diester.



Scheme 41. Palladium-Catalyzed Phosphonation of Aryl Mesylates and Tosylates Utilizing CM-Phos.



Scheme 42. Synthesis of Binaphthyl Monophosphine Ligands.



Scheme 43. Palladium-Catalyzed Cross-Coupling of Aryl Fluorosulfonates with Phosphites.

withdrawing groups produced higher yields than those with electron-donating groups under the reaction conditions.

Due to the advantageous properties of aryl nonafluorobutanesulfonate (nonaflates), including their facile synthesis from phenols, as well as their cost-effectiveness, stability, and amenability to purification via column chromatography, Sutherland et al.[67] developed a novel palladium-catalyzed cross-coupling reaction with aryl nonaflates. The study demonstrated that the addition of iodide accelerates the reaction, significantly reducing reaction time, and that the method does not require additional ligands. Upon screening various additives (Table 4), they discovered that the addition of sodium iodide reduced the reaction time from 24 hours to 4 hours and increased the yield to 78%, while the addition of sodium chloride and sodium acetate showed no significant improvements. The optimized reaction conditions were applicable to a wide range of substrates.

4. Palladium-Catalyzed Phosphonation of Carboxylic Acid Derivatives

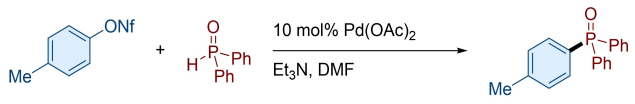
The palladium-catalyzed phosphonation reaction has long been a cornerstone for the synthesis of C–P bonds, traditionally relying on aryl halides or pseudohalides as electrophilic partners. However, recent advances have demonstrated the potential of carboxylic acid derivatives, including amides, as alternative electrophiles in phosphonation reactions. These approaches exploit the inherent stability and accessibility of carboxylic acid derivatives, offering streamlined and versatile methods for the synthesis of aryl phosphonates.

Amides are readily available, facile to prepare, and stable under a variety of conditions, rendering them ideal candidates for prefunctionalization of aromatic rings. This significantly broadens the scope of electrophilic reagents accessible for cross-coupling reactions. In 2017, Szostak et al.[68] reported an innovative method for the catalytic decarbonylative phosphonation of a wide range of amides using a palladium catalyst (Scheme 44).

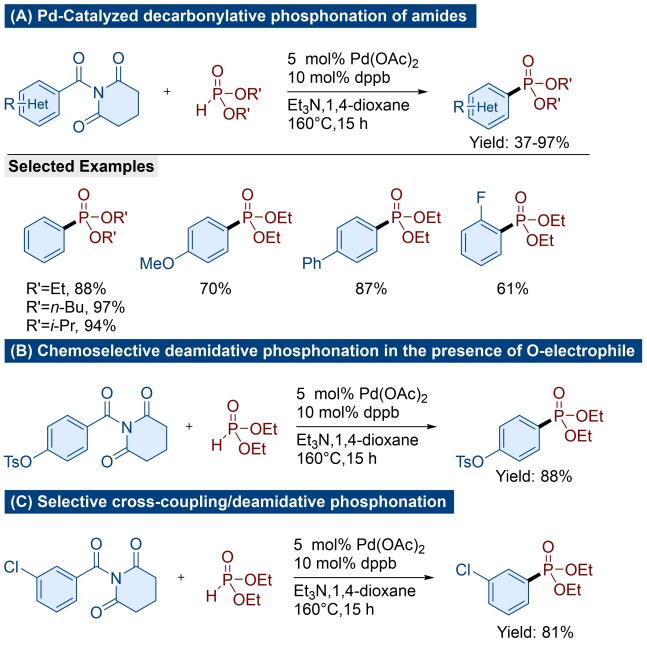
This novel approach exhibits a high tolerance towards a myriad of functional groups, encompassing aryl halides, ethers, nitriles, esters, ketones, naphthalenes, biaryls, dioxolanes, dioxanes, vinyl amides, and thiophenes, among others. This versatility further accentuates its potential application in the synthesis of complex molecules. Notably, the resonance destabilization effect from n_N to $\pi^*_{C=O}$ in amides facilitates the activation of the N–C bond, enabling region-selective reaction control. Even in the presence of aryl esters or aryl sulfonates, which are prone to metal-catalyzed C–O bond cleavage, the reaction selectively targets the N–C bond of amides while preserving the integrity of other functional groups, underscoring its unique advantages and high selectivity in synthetic chemistry.

Building on this breakthrough, Liu et al.[69] in 2023 expanded the scope of the Hirao cross-coupling by employing carboxylic-phosphoric anhydrides as direct electrophiles. This study introduced a novel strategy for the decarbonylative phosphonation of carboxylic acids, utilizing phosphites as dual activating and nucleophilic agents. They demonstrated that benzoic acids could be directly converted into aryl phosphonates via a dehydrogenative and decarbonylative pathway, with carboxylic-phosphoric anhydrides serving as key intermediates (Scheme 45). Detailed density functional theory (DFT) studies

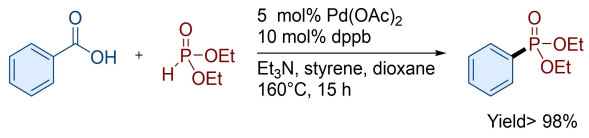
Table 4. Optimization for Palladium-Catalyzed Synthesis of (*p*-Tolyl)diphenylphosphine Oxide.



Entry	Additive (eq)	Time (h)	Temperature (°C)	Isolated yield (%)
1	/	24	90	41
2	/	24	110	58
3	/	24	120	79
4	NaOAc (1)	22	120	55
5	NaCl (1)	32	120	64
6	NaI (1)	4	120	78
7	NaI (0.1)	8	120	76



Scheme 44. Decarbonylative Phosphonation of Amides by Palladium Catalysis.



Scheme 45. Decarbonylative Hirao Cross-Coupling of Carboxylic Acid.

elucidated the reaction mechanism, particularly the selective activation of C–O and P–O bonds during oxidative addition and decarbonylation steps. This approach eliminates the need for pre-activation of carboxylic acids, significantly simplifying the synthesis of organophosphorus compounds and broadening the applicability of the Hirao reaction.

5. Palladium-Catalyzed Synthesis of Chiral Organophosphorus Compounds

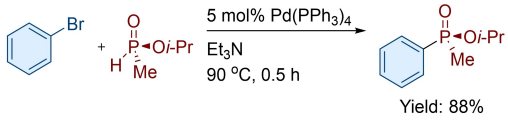
Chiral organophosphorus compounds are integral to asymmetric catalysis, pharmaceutical development, and functional materials, owing to their distinct stereochemical properties and outstanding coordination abilities.[70] The stereochemical configuration of these compounds critically determines their effectiveness in applications, underscoring the need for efficient synthetic methods that maintain chirality-a challenge of both scientific importance and practical relevance.

Traditionally, the synthesis of chiral organophosphorus compounds has predominantly relied on the Mislow-Evans method and its derivatives.[71] These strategies typically involve the synthesis of chiral phosphine oxides via the reaction of chiral thiols with phosphorus reagents such as phosphoryl chlorides, followed by reduction to obtain chiral phosphine ligands. However, these methods face notable limitations, including reliance on expensive or inaccessible chiral thiol esters for stereoselective substitution reactions, intricate multistep procedures with low overall yields, and stringent reaction conditions.

As a result, the development of efficient, cost-effective, and environmentally sustainable methods for synthesizing chiral phosphorylated compounds has become a central focus in this field of research.

Building upon the foundational work of Hirao, Xu and Zhang investigated the stereochemical aspects of palladium-catalyzed coupling reactions involving chiral phosphates in 1986.[72] They employed (R)-(+)-isopropyl methylphosphinate as the substrate, reacting it with bromobenzene in the presence of a palladium catalyst ($Pd(PPh_3)_4$) and triethylamine (Scheme 46) to determine whether the chiral configuration was retained during the reaction. By comparing the specific optical rotations of the starting material and the product, they demonstrated that the reaction exhibited high stereospecificity, with nearly complete retention of chirality in the product, albeit with minor occasional losses in optical purity.

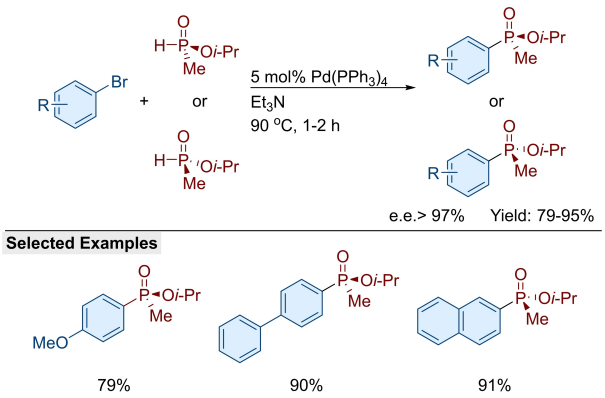
Motivated by these findings, Xu and Zhang expanded their research[73] to develop an efficient palladium-catalyzed method for synthesizing chiral isopropyl arylmethyl phosphates (Scheme 47). This new approach addressed the limitations of traditional methods, such as the extensive time required for the recrystallizations of menthyl alkylarylphosphinates, which often resulted in low yields and poor chiral control. The resulting products exhibited optical purities exceeding 97%. However, this method remained dependent on the availability of chiral substrates and did not provide a direct synthetic route to P-chiral compounds from achiral precursors.



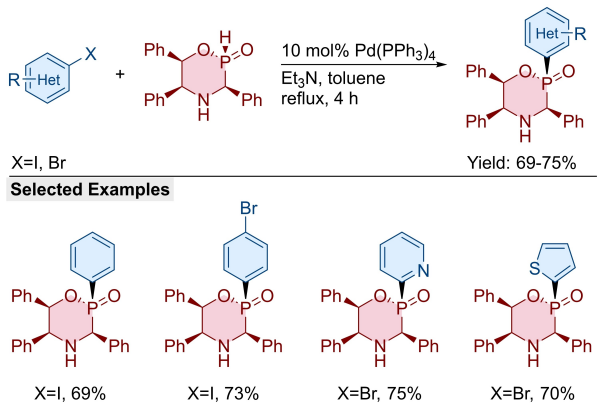
Scheme 46. Pd-Catalyzed Carbon-Phosphorus Bond Formation with Chiral Phosphorus Configuration Retention.

Morpholinol aryl derivatives have been extensively investigated due to their antidepressant activities. Cristau et al.[74] reported a palladium-catalyzed arylation of 2-hydrogeno-2-oxo-1,4,2-oxazaphosphinanes and sought to develop chiral phosphorus heterocycles using biological activities (Scheme 48). The reaction successfully synthesized a variety of aryl and vinyl oxazaphosphinanes in yields ranging from 69% to 75%. The stereochemical retention of the phosphorus atom during the reaction was confirmed.

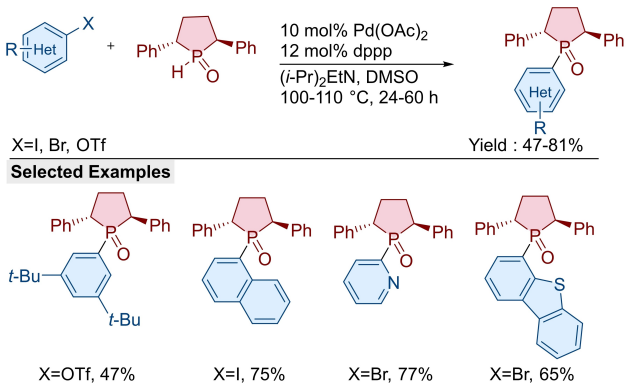
In 2006, Fiaud et al.[75] developed a novel approach for the preparation of chiral phosphorus heterocyclic oxides utilizing an enantiopure trans-2,5-diphenylphospholane framework as the scaffold (Scheme 49). This method demonstrated excellent reactivity towards aryl halides and triflates. Furthermore, the strategy allowed for the efficient synthesis of a wide range of P-aryl-2,5-diphenylphospholane oxides with high stereochemical



Scheme 47. Synthesis of Enantiomerically Pure Isopropyl Arylmethylphosphinates.



Scheme 48. Arylation of 2-hydrogeno-2-oxo-1,4,2-oxazaphosphinanes.



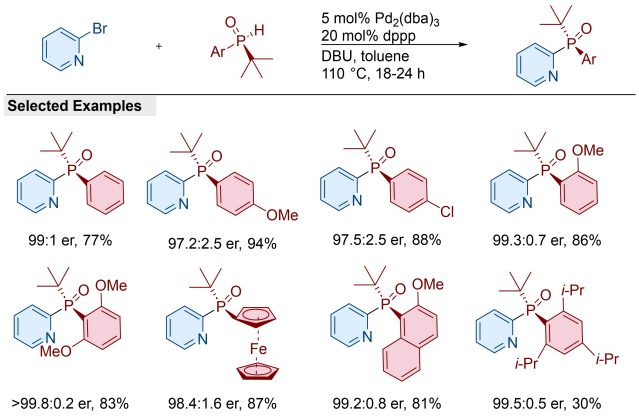
Scheme 49. Synthesis of (2*S*,5*S*)-1-aryl-1-oxo-2,5-diphenylphospholanes.

integrity, as no epimerization at the benzylic carbon atoms of the phospholane ring was observed.

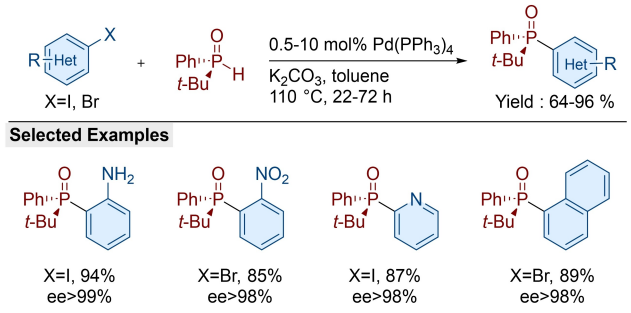
Chiral TPOs have garnered significant attention as valuable precursors to P-stereogenic compounds (P-SCPs). SPOs are promising precursors to TPOs due to their easily functionalizable P–H bonds and reduced steric hindrance, facilitating the introduction of bulky substituents. This provides an alternative route for synthesizing sterically encumbered TPOs. In 2017, Senanayake et al.[76] reported a transition metal-catalyzed coupling reaction between SPOs and aryl halides via P–C bond formation, conducted in toluene in the presence of 5 mol% $Pd_2(dba)_3$ and 20 mol% dppp (Scheme 50). Under similar reaction conditions, various pyridyl-containing P-chiral TPOs can be synthesized, achieving high yields and good enantiomeric purities even for sterically demanding products. Furthermore, the synthesis of P-chiral bisphosphine oxides is also feasible.

Similarly, for the obtention of P-chiral TPOs, in 2018, Drabowicz et al.[77] developed an efficient method for synthesizing a series of enantiomerically enriched aryl-*tert*-butylphenylphosphine oxides (Scheme 51). Under optimized reaction conditions, the method yielded highly functionalized P-chiral phosphine oxides with enantiomeric excesses exceeding 98%.

In 2019, Zhang et al.[78] reported a Pd/Xiao-Phos-catalyzed asymmetric P–C cross-coupling reaction of readily available SPOs with aryl bromides (Scheme 52). The introduction of substituents on the *ortho*-aryl ring of the Xiao-Phos ligand significantly enhanced the enantioselectivity of the reaction. After condition optimization, $Pd_2(dba)_3$ was chosen as the palladium source. Solvent screening revealed that toluene and trifluorotoluene were suitable for high enantioselectivity, while anisole exhibited higher reaction efficiency. Lowering the reaction temperature to 35 °C could further improve the enantioselectivity. The reaction demonstrates a broad substrate scope, with yields up to 96% and enantiomeric excesses (ee) as high as 97%. Additionally, the synthesis of DiPAMP ligands and their analogs was successfully accomplished.



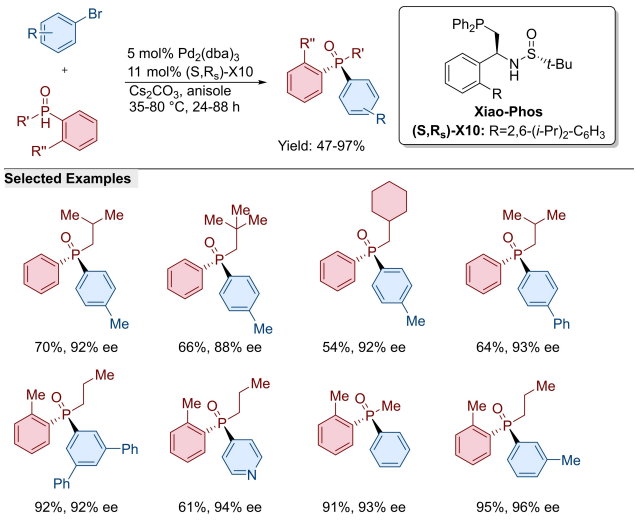
Scheme 50. Synthesis of Chiral TPOs via Pd-Catalyzed Coupling Reaction.



Scheme 51. Synthesis Approach for the Arylation of *tert*-Butylphenylphosphine.

6. Chemoselective Palladium-Catalyzed Phosphonation

Palladium-catalyzed cross-coupling reactions occupy a central role in organic synthesis. Among these, the advancement of chemoselective coupling reactions has paved efficient pathways for constructing complex molecules. The ability to achieve selective phosphonation on substrates containing multiple



Scheme 52. P-Chiral Phosphines Synthesis Using Pd/Xiao-Phos-Catalyzed Asymmetric P–C Coupling.

halogens or pseudohalogens is particularly significant for the synthesis of phosphorus-containing compounds.

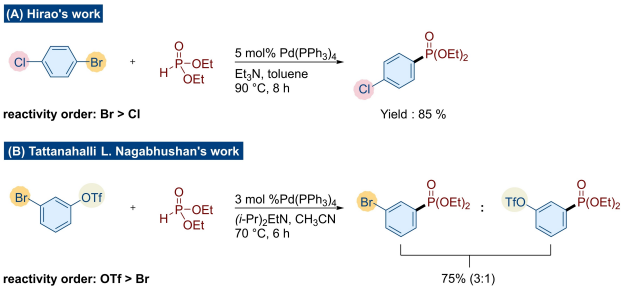
Conventional palladium-catalyzed phosphonation reactions generally adhere to a standard reactivity sequence (I > ONf > Br ≥ OTf > Cl > OTs > OMs) that forms the basis for achieving selectivity. However, this inherent reactivity hierarchy poses challenges when selective transformations are required at a specific site in substrates with multiple reactive groups.

In 1981, Hirao achieved phosphonation reactions by employing 1-bromo-4-chlorobenzene as a substrate (Scheme 53A), where the reaction selectively targeted the bromine site. Subsequently, in 1987, Nagabhushan reported the selective phosphonation of aryl triflates containing bromine, achieving a 3:1 selectivity in favor of the OTf group over Br (Scheme 53B).

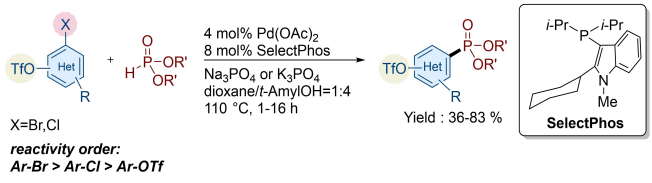
These findings underline the persistent difficulty to achieve chemoselectivity in phosphonation reactions, especially for substrates with multiple reactive sites, and emphasize the need for continued innovation in this field.

In 2024, So et al.[79] developed an efficient catalytic system for the chemoselective phosphonation of poly(pseudo)halides, enabling the synthesis of organophosphorus compounds with high selectivity and efficiency (Scheme 54). Using 3-chlorophenyl triflate and diisopropyl phosphate as model substrates, a series of ligands with varying steric and electronic properties were screened. SelectPhos with a -P(*i*-Pr)$_2$ group emerged as the optimal ligand, with the 2-cyclohexyl-indole moiety proving crucial for chemoselectivity. When this group was replaced with -PCy$_2$ or -P*t*-BuPh, the reaction still occurred selectively at the Ar–Cl bond but with reduced yields. Substitution of the 2-cyclohexyl group with tertiary alkyl groups further diminished both yield and selectivity. Other ligand types were also evaluated. Buchwald-type ligands such as XPhos, BrettPhos, and SPhos failed to promote phosphonation at the Ar–Cl bond. Beller's ligands showed poor chemoselectivity, while bidentate ligands directed reactivity toward the Ar-OTf bond instead. A ligand-free control experiment yielded only trace amounts of product, confirming the essential role of the ligand. Under optimized conditions, phosphonation selectively occurred at the Ar–Cl bond in chloroaryl triflates and the Ar–Br bond in bromoaryl triflates, with a reactivity order of Ar–Br > Ar–Cl > Ar–OTf.

The study also revealed that the C–H···Pd interaction between the methine hydrogen of the C$_2$-cyclohexyl group in the indolyl phosphine ligand and the palladium center played a pivotal role in achieving chloride-selective chemoselectivity.



Scheme 53. Examples of Chemoselective Phosphonation Trends.



Scheme 54. Palladium-Catalyzed Chemoselective Phosphonation of Poly(pseudo)halides.

7. Summary and Outlook

The development of palladium-catalyzed phosphonation reactions marks a significant breakthrough in organic synthesis, providing efficient and versatile methods for the preparation of organophosphorus compounds. These compounds are indispensable in fields such as medicinal chemistry, materials science, and catalysis, owing to their unique properties, including enhanced bioactivity, improved stability, and modified reactivity.

Traditional methods for synthesizing organophosphorus compounds often suffer from drawbacks such as poor atom economy and a limited substrate scope. By contrast, palladium-catalyzed phosphonation reactions offer distinct advantages, such as high yields, mild reaction conditions, and broad functional group tolerance. Over the years, significant progress has been achieved in optimizing these catalytic systems, including the integration of innovative techniques such as microwave irradiation and phase transfer catalysis, which enhance both reaction efficiency and environmental sustainability.

The choice of ligands in Pd-catalyzed Hirao cross-coupling reactions has proven critical for achieving achieving high efficiency, chemoselectivity, and substrate versatility. Phosphine ligands dominate in most reported protocols, with both monodentate (e.g., PPh$_3$) and bidentate ligands (e.g., dppf, dppp, dppb, Xantphos, BINAP) being widely employed. In addition to phosphine ligands, alternative ligand classes have been explored. N-based ligands, such as 1,10-phenanthroline dmphen,[80] dtbbpy,[80b] and 8-hydroxyquinoline,[81] have demonstrated utility in specific applications, particularly in microwave assisted, Ni-catalyzed or photoredox-catalyzed systems. Furthermore, recent developments have also focused on ligand-free systems to align with green chemistry principles. In such cases, the substrate itself or its tautomeric form (e.g., >P(O)H reagents) can serve as a ligand. For instance, Pd(OAc)$_2$-catalyzed ligand-free Hirao reactions under MW conditions, with excess > P(O)H reagent, have been shown to be highly effective.[82]

Significant advances have also been made using other transition metals, including Cu,[83] Ni,[84] Co[85] and Mn[86] complexes or their salts. Nickel catalysts have been successfully employed, especially when combined with bidentate phosphines (e.g., dppf, dppp) or N-based ligands, allowing the phosphonation of aryl halides, tosylates and mesylates under relatively mild condition.

Addressing the existing challenges of substrate reactivity and asymmetric induction could be potentially achieved by rational ligand design and optimization. For example, the development of more electron-rich or sterically well-defined ligands might enhance catalyst turnover and broaden substrate scope. Additionally, designing novel and more reactive phosphonating reagents could also help overcome current limitations. Alternative strategies, such as combining photoredox or electrochemical approaches with traditional catalytic methods, may offer new pathways to address these challenges.

In conclusion, palladium-catalyzed phosphonation has significantly advanced the field of organophosphorus chemistry, offering powerful tools for the synthesis of valuable compounds. While notable progress has been made, ample opportunities remain for further innovation. Continued research is expected to yield more efficient, versatile, and sustainable catalytic systems, paving the way for broader applications of organophosphorus compounds in diverse scientific disciplines.

Acknowledgements

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Conflict of Interests

The authors declare no conflict of interest.

Keywords: phosphonation · aryl halides · aryl sulfonates · phosphine ligands · palladium catalysis

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