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Initial Investigation of C–H Functionalization of Pentafluorobenzene with 2-Chloroquinoline Catalyzed by Palladium and Hemilabile Benzimidazolyl Phosphine Ligands

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Abstract **-** We report the first general examples of palladium-catalyzed C–H functionalization of pentafluorobenzene with 2-chloroquinoline, enabled by a family of hemilabile benzimidazolyl phosphine ligands bearing tunable P,O or P,N coordination motifs. These ligands, designed to exhibit both soft (phosphorus) and hard (oxygen or nitrogen) donor atoms, offer dynamic binding properties that enhance catalytic performance under reaction conditions. Among the ligand variants investigated, the one featuring a –P*t*-Bu_2 moiety and 5,6-dimethyl substitution on the benzimidazole ring demonstrated reasonable reactivity and efficiency with 1 mol% Pd catalyst loading. This study highlights the potential of modularly designed hemilabile ligands in facilitating challenging C–H functionalization reactions and provides a promising platform for further development of ligand-controlled catalytic systems.

Keywords**:** C–H Functionalization, Palladium-Catalyzed, Catalysis, Hemilabile

1. Introduction

Bi(hetero)aryl and heterocyclic derivatives are fundamental structural motifs that are prevalent in a wide array of natural products, biologically active compounds, and pharmaceutical agents. These motifs play essential roles in various therapeutic and functional applications, making them critical to the fields of materials science and pharmaceutical chemistry.[1] Notably, 2-substituted nitrogen-containing compounds hold significant relevance due to their diverse functionalities and applications. For instance, these derivatives are instrumental in the sensitization of titanium dioxide (TiO_2) nanoparticles and are incorporated into electrodes with perfluoroaryl motifs in organic semiconducting dyes for photochemical applications, such as Ph_5FQ-TiO_2.[2] Additionally, they are utilized in developing polymer and hybrid materials that act as electron acceptors, particularly those based on semiconducting perfluorophenylquinoline (P_5FQ).[3]

Given their crucial roles, the efficient synthesis of bi(hetero)aryl and heterocyclic derivatives remains a persistent challenge within the pharmaceutical industry. The demand for these compounds drives the need for innovative synthetic methodologies that are both mild and efficient. Researchers are increasingly focusing on developing straightforward synthetic routes that enable access to a diverse array of biaryl derivatives. Historically, transition metal-catalyzed cross-coupling reactions, such as Hiyama,[4] Kumada,[5] Negishi,[6] Stille,[7] and Suzuki–Miyaura couplings,[8] have been the standard approaches for constructing C–C bonds between (hetero)arenes. These methods typically require pre-functionalized substrates, which can limit the diversity of the starting materials and complicate the synthetic process.

However, in recent years, direct C–H functionalization strategies have emerged as powerful alternatives to traditional cross-coupling methods. These innovative techniques allow for the construction of bi(hetero)aryl structures without the necessity for pre-functionalization, thereby simplifying the overall synthetic workflow. Such methods not only enhance the efficiency of the synthesis but also broaden the scope of accessible compounds. [9]

In exploring these new avenues, various transition metal–ligand catalytic systems have been developed to facilitate C–H functionalization. Despite this progress, to the best of our knowledge, there have been no reported examples utilizing readily accessible P,O- and P,N-hemilabile benzimidazolyl phosphine ligands [10] in metal-catalyzed C–H functionalization systems. This class of ligands is particularly appealing due to its modular synthesis, which can be achieved through a one-pot assembly approach using three easily available starting materials: (1) benzimidazole scaffolds, (2) acid chlorides or sulfonyl chlorides, and (3) chlorophosphines (Fig. 1). This method allows for the generation of a diverse library of ligands, providing opportunities for fine-tuning their properties.[11]

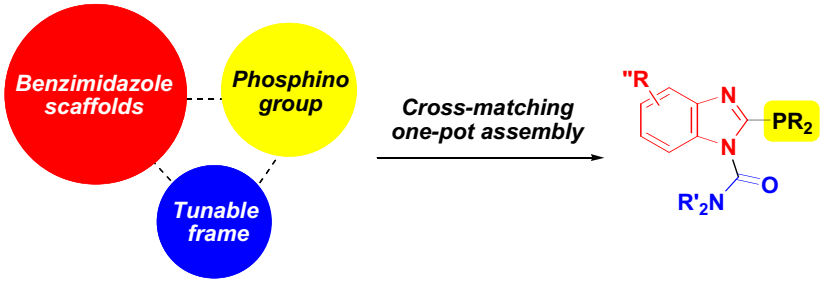


Fig. 1: A cross-matching one-pot assembly approach for achieving diversified benzimidazolyl phosphine ligand family.

What makes these ligands particularly noteworthy is their unique coordination characteristics, which include both soft (phosphorus) and hard (oxygen or nitrogen) donor atoms (Fig. 2). This duality in donor properties offers significant advantages during metal coordination. The hard donor atoms contribute weak, hemilabile binding, which stabilizes the metal center under harsh reaction conditions while also allowing for dissociation to create a vacant site for oxidative addition. This dynamic coordination behavior not only enhances the longevity of the catalyst but also improves its reactivity, making it more effective in various catalytic transformations.

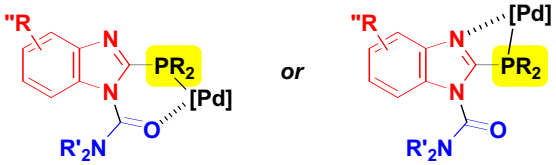


Fig. 2: Unique coordination modes of benzimidazolyl phosphine ligand.

Moreover, the tunability of this ligand family is a considerable advantage. The ability to modify phosphine groups and customize substituents on the benzimidazole scaffold allows researchers to tailor these ligands for specific catalytic applications. Previous investigations have demonstrated the high activity of these ligands in palladium-catalyzed reactions, including Suzuki–Miyaura coupling and Buchwald–Hartwig amination of aryl chlorides. Such versatility positions these ligands as valuable tools in synthetic chemistry.[11]

By leveraging this versatile ligand platform, researchers can explore a vast array of ligand structures optimized for specific C–H functionalization reactions. The insights gained from this research are anticipated to make significant contributions to the field of advanced C–H functionalization, potentially leading to new methodologies that can be applied in various areas of synthetic chemistry, thereby expanding the toolkit available for chemists and enhancing the development of novel therapeutic agents and materials.

2. Results and Discussion

In pursuit of advancing palladium-catalyzed cross-coupling reactions and the development of phosphine ligands,[11-17] we aimed to establish an efficient protocol for the coupling of electron-deficient polyfluoroarenes with heteroaryl chlorides. To assess the feasibility of palladium-catalyzed C–H functionalization, we initially selected various benzimidazolyl phosphine ligands (**L1-L4**) as potential candidates. For our studies, pentafluorobenzene and 2-chloroquinoline were utilized as benchmark substrates (**Fig. 3**). Notably, ligand **L4**, characterized by a bulky –P*t*-Bu$_2$ group and dimethyl substitutions at the 5,6-positions of the benzimidazole ring, exhibited superior performance, establishing itself as the optimal ligand for this reaction. These findings underscore the significance of both the steric bulk of the phosphino moiety and the electronic properties of the ligand scaffold in influencing the efficacy of C–H functionalization.

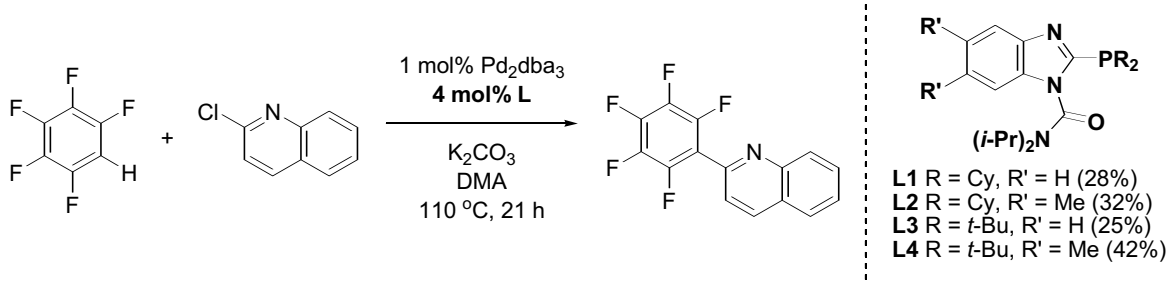
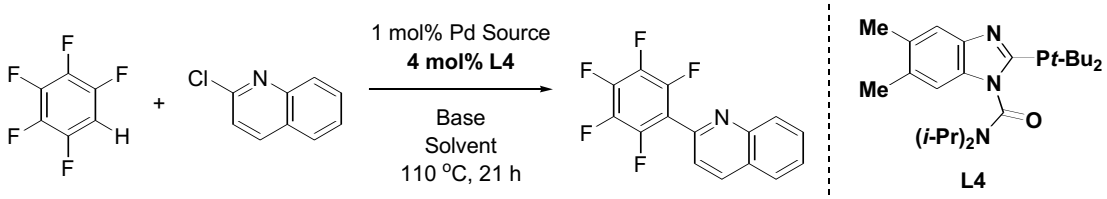


Fig. 3: Evaluation of benzimidazolyl phosphine ligands in Pd-catalyzed C–H functionalization of pentafluorobenzene and 2-chloroquinoline. Reaction conditions: 2-chloroquinoline (0.50 mmol), pentafluorobenzene (1.0 mmol), $Pd(OAc)_2$ (1 mol%), L (4 mol%), K_2CO_3 (0.75 mmol), and DMA (1.0 mL) were stirred at 110 °C for 21 h under argon. GC conversion yields are reported using dodecane as an internal standard.

Furthermore, we conducted a systematic ligand evaluation utilizing a catalyst loading of 1.0 mol% Pd to probe the effectiveness of the ligand **L4** (**Table 1**). Among the palladium sources evaluated, $Pd_2(dba)_3$ emerged as the most effective catalyst, outperforming alternatives such as $Pd(OAc)_2$ and $Pd(dba)_2$ (**Table 1**, entries 1 to 3). Additionally, the solvent dimethylacetamide (DMA) provided better results compared to other solvents, including tetrahydrofuran (THF), 1,4-dioxane, toluene, and triethylamine (TEA) (**Table 1**, entries 3 to 7). Among the bases tested for their ability to facilitate the reaction (**Table 1**, entries 7 to 10), potassium phosphate monohydrate ($K_3PO_4 \cdot H_2O$) was identified as the most effective option, further optimizing the coupling process.

Table 1: Initial screening of palladium-catalyzed C–H functionalization of pentafluorobenzene with 2-chloroquinoline.[a]



Entry	Metal	Base	Solvent	Conversion (%)[b]
1	$Pd(OAc)_2$	Na_2CO_3	THF	9
2	$Pd(dba)_2$	Na_2CO_3	THF	6
3	$Pd_2(dba)_3$	Na_2CO_3	THF	10
4	$Pd_2(dba)_3$	Na_2CO_3	1,4-Dioxane	14
5	$Pd_2(dba)_3$	Na_2CO_3	Toluene	9
6	$Pd_2(dba)_3$	Na_2CO_3	TEA	17
7	$Pd_2(dba)_3$	Na_2CO_3	DMA	20
9	$Pd_2(dba)_3$	$K_3PO_4 \cdot H_2O$	DMA	54
10	$Pd_2(dba)_3$	K_2CO_3	DMA	42

[a] Reaction conditions: 2-chloroquinoline (0.50 mmol), pentafluorobenzene (1.0 mmol), Pd source (1 mol%), **L2** (4 mol%), base (0.75 mmol), and solvent (1.0 mL) were stirred at 110 °C for 21 h under argon.
[b] GC conversion yields are reported using dodecane as an internal standard.

Following the initial screening of reaction conditions, our findings suggested that hemilabile benzimidazolyl phosphine ligands demonstrate significant potential in enhancing the efficiency of palladium-catalyzed C–H functionalization reactions. The positive outcomes observed with these ligands highlight their unique properties, which may facilitate the activation of substrates while simultaneously stabilizing the palladium catalyst.

To further refine and optimize these reactions, a systematic investigation into various parameters is necessary. This includes exploring different catalyst loadings and adjusting the stoichiometric ratios of the reactants to identify the most

favorable conditions for achieving high yields and selectivity. Such fine-tuning will not only improve reaction efficiency but also broaden the applicability of this methodology. Moreover, expanding the substrate scope of the C–H functionalization reaction by incorporating a diverse array of (hetero)aryl chlorides is essential. This expansion will enhance the versatility of the protocol, making it a valuable tool for chemists in the synthesis of complex molecules. By enabling the functionalization of a wider range of substrates, this approach could significantly contribute to the development of novel pharmaceutical agents and advanced materials, ultimately accelerating innovation in chemical research and industry.

3. Conclusions

Based on the findings, we conclude that the choice of ligand and catalyst significantly influences the efficiency of palladium-catalyzed C–H functionalization reactions involving electron-deficient polyfluoroarenes and heteroaryl chlorides. The best performance of ligand **L4** with –P*t*-Bu_2 moiety, characterized by its steric and electronic properties, highlights the importance of ligand design in optimizing reaction outcomes. Additionally, the selection of $Pd_2(dba)_3$ as the catalyst, along with DMA as the solvent and $K_3PO_4 \cdot H_2O$ as the base, further enhances the effectiveness of the coupling process. These insights contribute to the development of more efficient methodologies in cross-coupling chemistry, providing a valuable foundation for future research in this area.

4. Experimental Section

General Considerations: Unless otherwise noted, all reagents were purchased from commercial suppliers without purification. All catalytic reactions were performed in resealable screw-capped Schlenk tubes (approximately 20 mL volume) in the presence of a Tefloncoated magnetic stirrer bar (3 mm × 10 mm). Tetrahydrofuran (THF) was distilled from sodium and sodium benzophenone ketyl under argon.[18] Commercially 2-chloroquinoline and pentafluorobenzene were used as received. All bases were used without grinding. A new bottle of n-butyllithium was used (note: since the concentration of n-BuLi from an old bottle may vary, a titration is highly recommended prior to use). Thin-layer chromatography was performed on precoated silica gel 60 F254 plates. The GC yields described for the products were in accord with the authentic samples/dodecane calibration standard from the GC-FID system.

General procedure for initial condition screening of C–H functionalization of pentafluorobenzene with 2-chloroquinoline: Palladium source (Pd loading indicated in the entry table) and ligand (Pd:L1=1:4) were loaded into a Schlenk tube equipped with a Teflon-coated magnetic stir bar. The tube was evacuated and backfilled with argon (3 cycles). Precomplexation was applied by adding freshly distilled dichloromethane (1.0 mL). The palladium complex stock solution was stirred and warmed using a hair drier for 1 to 2 min until the solvent started boiling. The solvent was then evaporated under high vacuum. Base (0.75 mmol) and 2-chloroquinoline (0.50 mmol) were loaded into the tube, and the system was further evacuated and flushed with argon for three times. Pentafluorobenzene (1.0 mmol), and DMA (1.0 mL) were added into the tube via a syringe, and the mixtures were stirred at room temperature for 5 min. The tube was then placed into a preheated oil bath (110 °C) and stirred for 21 h. After the completion of the reaction, the reaction tube was allowed to reach room temperature. Ethyl acetate (~10 mL), dodecane (114 μL, internal standard), and water (~5 mL) were added. The organic layer was subjected to GC analysis. The GC yield was previously calibrated by an authentic substrate/dodecane calibration curve.

Acknowledgements

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References

[1] For selected reference, see: (a) I. J. S. Fairlamb, "Regioselective (site-selective) functionalisation of unsaturated halogenated nitrogen, oxygen and sulfur heterocycles by Pd-catalysed cross-couplings and direct arylation processes," *Chem. Soc. Rev.*, vol. 36, pp. 1036-1045, 2007. (b) C. Torborg and M. Beller, "Recent Applications of Palladium-Catalyzed Coupling Reactions in the Pharmaceutical, Agrochemical, and Fine Chemical Industries," *Adv. Synth. Catal.*, vol. 351, pp. 3027-3043, 2009.

[2] P. Giannopoulos, A. Nikolakopoulou, A. K. Andreopoulou, L. Sygellou, J. K. Kallitsis and P. Lianos, "An alternative methodology for anchoring organic sensitizers onto TiO_2 semiconductors for photoelectrochemical applications," *J. Mater. Chem. A*, vol. 2, pp. 20748-20759, 2014.
[3] A. A. Stefopoulos, S. N. Kourkouli, S. Economopoulos, F. Ravani, A. Andreopoulou, K. Papagelis, A. Siokou and J. K. Kallitsis, "Polymer and Hybrid Electron Accepting Materials Based on a Semiconducting Perfluorophenylquinoline," *Macromolecules*, vol. 43, pp. 4827-4828, 2010.
[4] T. Kyoko, M. Tatsuya, O. Yoshio, H. Tamejiro, "A new synthesis of HMG-CoA reductase inhibitor NK-104 through hydrosilylation-cross coupling reaction," *Tetrahedron Lett*., vol. 34, pp. 8263-8266, 1993.
[5] K. Tamao, K. Sumitani and M. Kumada "Selective carbon-carbon bond formation by cross-coupling of Grignard reagents with organic halides. Catalysis by nickel-phosphine complexes," *J. Am. Chem. Soc.*, vol. 94, pp. 4374-4376, 1972.
[6] S. Baba and E. Negishi, "A novel stereospecific alkenyl-alkenyl cross-coupling by a palladium- or nickel-catalyzed reaction of alkenylalanes with alkenyl halides," *J. Am. Chem. Soc.*, vol. 98, pp. 6729-6731, 1976.
[7] D. Milstein and J. K. Stille, "A general, selective, and facile method for ketone synthesis from acid chlorides and organotin compounds catalyzed by palladium," *J. Am. Chem. Soc.*, vol. 100, pp. 3636-3638, 1978.
[8] N. Miyaura and A. Suzuki, "Palladium-catalyzed cross-coupling reactions of organoboron compounds," *Chem. Rev.*, vol. 95, pp. 2457-2483. 1995.
[9] S.M. Wong and F. Y. Kwong, "Nondirected CH Bond Functionalizations of (Hetero) arenes," in *Strategies for Palladium-Catalyzed Non-Directed and Directed CH Bond Functionalization*, A. R. Kapdi and D. Maiti, Ed. Elsevier, 2017, pp. 49-466.
[10] F. Y. Kwong, S. M. Wong and C. C. Yeung, "Phosphines, synthesis thereof and their use in catalysis," U.S. Patent 10093692, October 9, 2018.
[11] S. M. Wong, P. Y. Choy, Q. Zhao, O. Y. Yuen, C. C. Yeung, C. M. So and F. Y. Kwong, "Design of Benzimidazolyl Phosphines Bearing Alterable P,O or P,N-Coordination: Synthesis, Characterization, and Insights into Their Reactivity," *Organometallics*, vol. 40, 2265-2271, 2021.
[12] W. C. Fu, Y. Wu, C. M. So, S. M. Wong, A. Lei and F. Y. Kwong, "Catalytic direct C2-alkenylation of oxazoles at parts per million levels of palladium/PhMezole-Phos complex," *Org. Lett.*, vol. 18, pp. 5300-5303, 2016.
[13] S. M. Wong, P. Y. Choy, O. Y. Yuen, C. M. So and F. Y. Kwong, "Palladium-catalyzed Buchwald-Hartwig amination and Suzuki-Miyaura cross-coupling reaction of aryl mesylates," *Org. syntheses*, vol. 92, pp. 195-212, 2015.
[14] O. Y. Yuen, S. M. Wong, K. F. Chan, C. M. So and F. Y. Kwong, "A General Suzuki–Miyaura Coupling of Aryl Chlorides with Potassium Aryltrifluoroborates in Water Catalyzed by an Efficient CPCy Phendole-phos–Palladium Complex," *Synthesis*, vol. 46, pp. 2826-2832, 2014.
[15] S. M. Wong, C. M. So, K. H. Chung, C. P. Lau and F. Y. Kwong, "An Efficient Class of P, N-Type "PhMezole-phos" Ligands: Applications in Palladium-Catalyzed Suzuki Coupling of Aryl Chlorides," *Eur. J. Org. Chem.*, vol. 2012, pp. 4172-4177, 2012.
[16] S. M. Wong, C. M. So, K. H. Chung, C. H. Luk, C. P. Lau and F. Y. Kwong, "P, N-Type benzimidazolyl phosphine ligands for the palladium-catalyzed Suzuki coupling of potassium aryltrifluoroborates and aryl chlorides," *Tetrahedron Lett.*, vol. 53, pp. 3754-3757, 2012.
[17] K. H. Chung, C. M. So, S. M. Wong, C. H. Luk, Z. Zhou, C. P. Lau and F. Y. Kwong, "Buchwald-Hartwig amination of aryl chlorides catalyzed by easily accessible benzimidazolyl phosphine-Pd complexes," *Synlett*, pp. 1181-1186, 2012.
[18] W.L.F. Armarego, *Purification of Laboratory Chemicals*. 8th ed., Butterworth-Heinemann: Oxford, U.K., 2017.