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Metal-Free Cross-Coupling Reactions: Green Pathways for C–C Bond Formation

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Abstract: The growing concerns of rapid population expansion, depletion of fossil fuels, climate change, and escalating environmental degradation pose significant challenges to the sustainable development of modern society. In response, the scientific community has increasingly focused on the development of green and sustainable chemical methodologies. Within this context, metal-free synthetic strategies have gained prominence due to their ability to eliminate the dependence on toxic, heavy, and non-renewable transition metals. These methodologies offer a cleaner alternative for the chemo-selective transformation of inexpensive starting materials into high-value products. Recent advances have led to the development of metal-free oxidation, reduction, hydrogenation, and condensation reactions that align with the principles of green chemistry. However, the replacement of transition-metal-catalyzed carbon–carbon (C–C) bond-forming reactions remains a critical challenge. Innovative approaches involving the nucleophilic addition of organometallic species to carbonyl or imine compounds, as well as radical-mediated C–C couplings in the presence of aryl halides, are paving the way for sustainable alternatives. This abstract highlight the recent progress and ongoing efforts toward achieving environmentally benign synthetic methodologies, emphasizing the pivotal role of metal-free reactions in shaping a greener chemical future.

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1. Introduction to Cross-Coupling Reactions

The growing demand for sustainable synthetic routes has inspired the development of metal-free reactions. It is noteworthy that the field of metal catalysis has emerged not only as a powerful tool for the efficient construction of organic compounds, but also as a green way for their synthesis. Base metal catalysis is considered a key strategy inspiring more sustainable reactions. During the past decades, multiple sustainable efficiency strategies have been used in organic synthesis, such as C-H functionalization, cross-dehydrogenation, as well as cross-coupling reactions with more abundant earth-abundant transition-metals. The most seminal procedure for the construction of a C(sp2)–C bond resulted from the reaction between an aryl iodide and an arylboronic acid mediated by copper salts. Palladium-catalyzed cross-couplings, on the other hand, have been known since 1973, and have completely revolutionized pharmaceutical and agrochemical industries, as well as the field of materials science. As a result, copper and palladium salts have been traditionally used in organometallic cross-couplings, fundamentally in C–C bond formations. A more recent advancement in this field has been the development of metal-free cross-coupling reactions for the construction of C–C bonds, inspired from their metal-catalyzed counterparts. It is noteworthy that all these reactions took place with vinyl- and amino-diones, suggesting that the presence of sulfur in the substrate could lead to unwanted side-reactions. Nevertheless, there are currently few reports in this area, with the most analogous cross-couplings being based on nucleophiles and aryl halides, or via photoredox-catalyzed processes. In this context, pyridines are subunits with extensive occurrence in pharmaceutical agents and agrochemicals. A common chemical manipulation in a bioactive compound is the construction of a biphenyl system. Since the C–C bond forming step between molecules A and B is a metal-free process, a new pathway for cross-couplings can be anticipated. THEME 2: SCOPE OF METAL-FREE CROSS-COUPLING REACTIONS

2. Background and Motivation

In modern drug-discovery industries, the growth of a substantial quantity of synthetically produced organic wastes has intensified concerns about environmental issues. Recently, the use of environmentally benign conditions and cost-effective processes has received increased attention due to regulations set by governing agencies and the pharmaceutical industry. The production of an excess of chemical waste can notably increase the cost of removal and disposal (T. Findlay et al., 2023). A significant portion of pharmaceutical compounds are synthesized using the cross-coupling of C-based building blocks. Generally, pharmaceutical industries were conducted with Pd, Ru, and Rh-based catalysts. Although these metals provide high activity toward desired products, their toxicity and susceptibility to coordination saturation led them to undesired impurities.

The world's rapidly growing pharmaceutical industry produces synthetic organic waste at an alarming rate, which is known to be harmful to human health and the environment. As a result, the pharmaceutical industry is constantly compelled to minimize waste production, which is in harmony with the Green Chemistry concept (Lee, 2017). The pharmaceutical and biotech industries are major contributors to synthetic waste generation. In order to comply with strict regulatory requirements, industries are constantly striving to reduce and minimize waste production through the development of environmentally aware processes. Such constraints have inspired research into the development of green protocols which require atom-economy, minimize the number of steps involved, use non-toxic and less hazardous solvents, and maximize the use of catalysis. Fundamentally, C-C connectivity is important to life. It is found at the heart of frameworks that stabilize the cycle to make biologically active molecules, and is fundamental to the function of all molecules. However, with the advent of modern synthetic strategies, which set single bonds with exquisite stereocontrol, this task has for the most part been overlooked in favor of more complex undertakings. If we wish to maintain the pace of discovery and avail ourselves of the wealth of C-C bond formation that surrounds many C-H bonds, other inventive methods for bond construction must be sought.

2.1. Limitations of Metal-Based Cross-Coupling: Toxicity, Purification Difficulties, Environmental Burden

The design of efficient catalytic C–C bond-forming methodologies without the use of transition-metal catalysts is an ongoing challenge and of paramount importance for Green Chemistry and for the broadest acceptance of chemical processes by society . By employing ball-milled mixtures of dehydroalanine (Dha) salts, the Suzuki-Miyaura coupling partners aryl halides and boronic acids are hit. By running the reactions in water an additional sustainable aspect is added, and the products can be conveniently separated by simple filtration.

Cross-coupling reactions represent one of the most important methods for the construction of carbon-carbon bonds in organic chemistry but most of them involve the use of transition metals. Transition-metals are expensive, can be toxic to man and to the environment, are limited in worldwide reserves, and has major drawbacks in terms of purifications of the products, waste generation and environmental burden. Several protocols have been developed attempting to circumvent these problems. Some of them involve the design of new ligands based in abundant elements or the use of aluminosilicates or zeolites. Another elegant approach uses ball-milling and is shown that ball-milling without any metal present is a valid strategy to accomplish the cross-coupling unhappy thing without metals leading to valuable biaryls or dienes.

2.2. Green Chemistry Principles Emphasize Atom Economy, Minimal Waste, and Reduced Use of Hazardous Substances

The development of greener industrial transformations is becoming increasingly important for both economic and environmental reasons. One approach to this problem involves the use of transition metal catalysis to create efficient, selective, and atom-economical synthetic methodologies. In particular, metal-catalyzed C–C bond forming cross-coupling reactions have revolutionized the field. When considering efficiency, step-economical transformations are highly desired that can construct intricate chemical architectures from simple starting materials in one-pot procedures. The same holds true for fully convergent reactions, where all components are present at the beginning and join to form the final product in one event.

Solutions to this fundamental challenge have been sought over the last decade in the form of a number of metal-free cross-coupling strategies. Direct nucleophilic substitutions at sp2 or sp sites have been developed, as well as ligand-accelerated coupling of aryl Grignard reagents and aryl carbamates has also been accomplished. Recently, the coupling of aryl boronic acids with aroyl hydrazides has been reported. Here, an unconventional C–C bond formation strategy is applied in which a vinylogous carbamate anion attacks an aryl halide electrophile. Importantly, these reactions proceed at room temperature, use only catalytic amounts of Cu2O, are confirmed to be zero-valent metal-free and stoichiometry-matched, and do not require harsh workup conditions (T. Findlay et al., 2023).

Before there were complex molecules, one imagines simple carbon skeletons. Then primitive ones, such as ethylene. In the presence of another primitive subclass, perhaps with the aid of a catalyst as equally primitive, would arise a cheap route to the first complex molecule. Likely too simple to work, this demands a fortuitously facile sequence of catalyzed reactions, a richness of especially reagent requiring attention and skill to combine (Lee, 2017).

2.3. Metal-Free Protocols Align Well with These Goals and Show Promise in Academic and Industrial Applications

Over the last decades transition metal catalyzed cross-coupling reactions have proven to be highly effective methods for C–C bond formation. Nowadays, a broad variety of different methods are available. However, all these reactions have in common that at least one of the building blocks has to be activated with a functional group. In this context, C–H activation forges C(sp^2)–C(sp^2) or C(sp)–C(sp^2) bonds directly by using one C–H bond as the coupling partner, thereby providing new green processes. The essence of C–H activation is the ability of a metal to remove a hydrogen atom from an organic substrate and form a metal aryl bond in a single catalytic cycle. A general scheme for a C–H activation cycle is shown. A metal complex forms a relatively stable 5-membered metallacycle intermediate after oxidative addition of a C–H bond, resulting in C–M and H-X. After a sequence of migratory insertion and reductive elimination, the desired C–C bond formation and the metal species are regenerated.

Despite the advances in many areas, cross-coupling of unreactive C–H bonds still represents a formidable challenge. Specifically, cross-coupling of two different unreactive C(sp^2)–H bonds remains in its infancy. Recently, a breakthrough study was made, disclosing an operationally simple methodology capable of C(sp^2)–C(sp^2) bond formation from C–H bonds of arenes and activated methylene compounds. Metal-free protocols for C–C bond formation have been reported using hypervalent iodine reagents, photoinduced transformations, chiral cyclopropanes, ionic liquids or solid state grinding. It has the attraction of improved atom efficiency: no metal byproducts are introduced into the reaction mixture and the catalyst can also be present on one substrate such as a halide ion.

3. Categories of Metal-Free C–C Coupling Reactions

The remarkable feat of combining readily available starting materials to produce structurally complex and diverse compounds is a cornerstone to the field of organic chemistry. Of particular interest, the assembly of sp2-sp2 or sp2-sp compounds, respectively, which involve the coupling of two carbon partners mediated by a transition metal catalyst, have emerged as the most practical and kinetically selective methods for forging carbon-carbon linkages. However, many of the most popular examples in this area rely on the use of toxic heavy metals such as Pd, Cu and Ni, which give rise to significant environmental and economic concerns. Tremendous recent research efforts have focused on the design of new and highly appealing metal-free alternatives to these classical transition-metal based reactions, aiming at rendering carbon-carbon (C–C) bond formation generally wider in scope,

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more cost-efficient and synthetically accessible. Broadly, recent breakthroughs in the field of metal-free C–C coupling processes have been categorized into four emerging concepts, as follows.

The inherent dominance of fluorine, relative to other halogens, in organic synthesis derives from its small atom size, high electronegativity, and consequent strong and selective electron-withdrawing properties. Accordingly, the notion of a 'fluorine echo effect,' by which a C–CF2R unit can drive the regioselective functionalization of sp3-C–H bonds, has been conceptualized. By the exploitation of this powerful chemical principle, a photocatalytic and oxidant-free method for gem-difluoroethylation of unactivated alkyl derivatives has been devised. Moreover, alcohols have been successfully engaged as sustainable surrogates of halides in a transition metal-catalyzed trifluoromethylation process. Both transformations are believed to proceed via a redox-neutral atom-transfer strategy, and underscore the potential of halogen-exchange mechanisms to define a new paradigm in the field of fac–metal-free approaches to C–C bond formation (Lee, 2017).

3.1. Base-Mediated Cross-Coupling

Carbon-carbon bond forming reactions form the backbone of organic synthesis efforts. In traditional cross-coupling reactions, one of the two cross-coupling partners, the electrophile, is usually an sp^2 hybridised aromatic system. More activation is, however, needed in order for a traditional cross-coupling to work with unactivated aliphatic substrates. Easy-to-handle alkyl halides are finally activated for cross-coupling with simple C–C, C–N or C–S nucleophiles by converting them first to the more reactive phosphonium salts. The nature of the metal used in the Ullman-type reaction was not crucial as long as Cu was used, this populating nearly any place in the periodic table. The X ligands are exchanged for most metals in a less controlled fashion. Palladium nanoparticles on activated carbon are employed as recyclable catalysts for the arylation of imidazole with aryl halides in combination with conventional coupling reactions using both C-Cl and C-Br. Palladium nanoparticles derived from Na_2 PdCl_4 give lower activity, but give consistent metal surface composition all along the cycle.

Also discussed is the rational design and synthesis of bis- and phosphosphine ligands for the C-Br coupling of imidazole with aryl halides results in complete catalysts with both the metal arrays and allowing several recycles without loss of activity. This uncommonly large ligand numbers meet the requirements necessary to couple imidazole with two electrophilic partners in the same reaction, aryl halides bearing additionally different reactive substituents. High atom economy processes deploying dicouplings C-C or C-N bonds are also described. Itemising and detailing problems that arose during catalyst development can facilitate the work of practitioners new in this field.

Many different cross-coupling reactions have been developed over the last two decades, to create a more selective and convenient way for C(sp^2)–C(sp^3) bond formation. Each cross-coupling reaction is usually effective for preparing a limited class of bond types represented by the pairing configuration of nucleophiles and electrophiles. Among these new green pathways for C–C bond formation, base-mediated cross-coupling is a powerful tool to prepare similarly structured unsymmetrical 1,2-diols in a single step reaction that can be used to easily link connect different systems.

3.1.1. Use of Strong Organic or Inorganic Bases (e.g., KOtBu, DBU)

In the metal-catalyzed C–C bond-forming reactions for aryl-aryl coupling, arylboronic esters generally react more slowly than aryl silanes, which restricts the broader use and versatility of such couplings. While many mechanistic studies have focused on the corresponding Pd-catalysed reaction, no rationalisation is currently available for the polymerisation side reaction observed in the corresponding Ni-catalysed reaction. Theoretical studies on several possible mechanisms for the Ni/PEPPSI-Catalysed reaction are presented, which provide strong support for a new two-step Ni(0)/Ni(II)/Ni(0) mechanism and establish the crucial roles of TCEP and DMF in the reaction. Finally, the analysis of polar substituent effects that establish samples of synergistic rate ratios for all

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transferrable group/10 (Pd, Ni) combinations confirms a change in mechanism between the two catalysts (Dahadha, 2012).

Coworkers report that NiCl2(PPh3)2, P(tBu)2cinnamyl (PCy2Ph), 1,3-bis(cinnamyl)tetramethyl disiloxane (BTMSDSO) catalyses the aryl–aryl coupling of both aryl silanes and aryl acids by nickel at 60 or 100 ˚C in NMP solvent containing KOH. Several 13C-labelled studies provide experimental support for the copper catalysis in this SCF system. On December 6th, 1997 in Jap. Pat. Appl. 9-330682 teaching of an SET based TTF ring and ether synthesis; according to Jap. Pat. Appl. 9-330682, Nobuhiro Kurihara; et al. claimed an NMP solvent and 5% to 25% commercial coupling solvent for the case of Form. 1. Claim 35 was filed for Sweden, but for types other than B1AE and glassy ACs (Wang, 2017).

However, as one prominent group in the field points out, the analogous reaction of boronates under identical superheating conditions has yet to be reported for any copper catalyst. Despite the deactivation by Pd0, several strong bases such as NaOtBu in polar aprotic solvent can restore activity. Also interestingly, a simple inorganic strong base, KOtBu, in MeCN promotes again the anticipated homocoupling under nitrogen protection, while adduct formation was observed if exposed to air. The use of a strong organic or inorganic base such as KOtBu, DBU, DBN, or NaN(TMS)2 is required in most base-promoted or catalysed decarboxylative cross-coupling reactions. In general, DCC of potassium carboxylates is simply initiated by copper catalyst activation under an oxygen atmosphere. Bulky, non-nucleophilic strong bases, such as N-heterocyclic carbenes (NHCs), are generally thought to act as organic base alternatives for the cross-coupling of aryl electrophiles in base-sensitive processes to avoid reaction failure or by-product formation with strongly basic nucleophiles. For decarboxylative series, common reactants are copper(II) salts, organic iodides, and aliphatic as well as aromatic carboxylic acids terminally substituted with electron-donating or electron-withdrawing groups. To carry out the desired C-C bond formation, the increased radical anion must either recombine, as above, or undergo an alternative, concerted reaction with another molecule of the carboxylate, for example, β-K elimination to release a carboxylic acid, or engage the electrophile in the desired homocoupling reaction. In (4+n)/2Case examples, with n being the only integer for a series of case examples. For these cases, the first one n = 4, followed by n = 6, then n = 8, and so on. Relevant activities occurring solely on a specific date are excluded, e.g. additional publications, oral disclosures, and scientific presentations.

3.1.2. Activation of Aryl Halides or Boronic Acids Without Transition Metals

For a long time, the development of a general procedure for the metal-free reactions of aryl halides or boronic acids would provide straightforward methodologies for the preparation of these inevitable intermediates with important applications in organic chemistry. Here, the development of heterogeneous boron loaded catalysts and/or inorganic catalysts that are capable of catalyzing the arylation of arenes or olefins without transition metals is discussed.

Metal residue arising from transition-metal-catalyzed cross-coupling reactions has generated interest in developing alternative metal-free reaction systems. Transition-metal-containing complexes have been decorated in various materials. When set in the presence of C–Cl compounds and light irradiation, these samples facilitate a visible-light metal-free C–C coupling. The same coupled materials were used to perform catalysis with ceramics, and good yields were obtained. Due to their narrow band gap and unique potentials in light harvesting and charge separation, several 2D ceramics have been developed and utilized comprehensively in the visible C–H or O–H coupling with good selectivities and yields. Doped atomic Fe was demonstrated to be a highly efficient electron-trapping center for enabling the activation of singlet oxygen with >95% selectivity to yield reactive oxygen species. An external photodevice, such as a UV lamp, green laser, red laser, or solar collector, is applied to enable ATRP under light irradiation. Here, 2D materials are prepared using a precursor which is a mixture of pure boron trichloride, melamine and 2-chloro-6-methylpyridine, and used to display a stable, anisotropic and scalable redox behavior for oxidative coupling of aryl-C-H and alkyl-C(sp3)-H bonds with comparable catalytic performance at gram scale.

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3.1.3. Example: Coupling of Aryl Halides with Enolates or Carbanions.

Oxidation of gramine containing aryl halide generated the reactive intermediate, which was followed by the coupling of the second aryl halide. Application of this approach to gramines containing dual aryl halides has enabled the synthesis of C2, C4, or C7 substituted 2(1H)quinazolinones in good to excellent yields. In addition, it has been demonstrated that the cross-coupling occurred at the less hindered aryl halide. It may be due to the higher acidity of protons at the neighboring position of the oxygen to the carbonyl group.

Metal-Free Cross-Coupling Reactions have emerged as efficient strategies for the green and sustainable synthesis of organic compounds. Generations of a variety of reactive intermediates from two different aryl halides, which can undergo subsequent biarylation to construct unsymmetrical biaryl compounds, have been developed. Those aryl halides, as a whole group of generic substrates, can take part in many other beautiful transition metal catalysis and organocatalysis. Corresponding biarylation of those aryl halides may shine new light to metal-free coupling chemistry.

3.2. Photoredox Catalysis

The development of metal-catalyzed cross-coupling significantly contributes to modern synthetic chemistry. The classical methods for C(sp2)/C(sp2) cross-coupling are based on the transition-metal catalysis with stoichiometric organometallic reagents. This method requires extreme reaction conditions, and many studies have also shown that the organometallic reagents are potential safety issues dealing with anaerobic toxic materials. Base-metal-catalyzed C–C bond formation avoiding the use of conventionally employed transition metals, such as Ni, Fe, and Cu, have been of great interest in the catalysis community. Additionally, most of the researches focus on the classical atom-economical and environmentally friendly green pathway. Metal-free reactions are still a welcoming candidate for their excellent functional group tolerance while excellent chemoselectivity can be achieved under sophisticated functionalized structure. Organic halide compounds are more easily gained than the corresponding organometallic reagents and other reductive precursors. In order to tolerate widespread functional groups, a milder condition is necessary for the cross-coupling reactions in chemoselective synthesis strategy. Photocatalytic reactions, using the natural sunlight or an inexpensive commercial UV lamp, have shown enormous potential in synthetic chemistry. Cross-coupling technologies employing photoredox catalysts to access novel reactivity have developed with increasing pace. The ability for transition metal catalysts to forge bonds between ligated fragments is a cornerstone of modern synthetic chemistry. Cross-coupling methodologies allow access to a variety of carbon–carbon and carbon–heteroatom coupled products. The vast majority of these methodologies rely on three two-electron elementary steps: oxidative addition, transmetalation, and reductive elimination. Many worthwhile challenges remain in this field.

3.2.1. Visible Light-Induced Electron Transfer Reactions Using Organic Dyes (e.g., Eosin Y, Rose Bengal)

Visible light-induced organic dye has the capacity to absorb weak wavelengths of visible light, in enhancement to operate as a less toxic photosensitive reagent than ordinary metal complexes or nanoparticle photocatalysts. Those virtues propose that organic dye could offer a practicable opportunity to introduce visible light photoinduced electron transfer reactions into the procurement of the field (Shirakawa et al., 2023). Visible light-induced electron transfer reactions with the help of organic dye photocatalysts have been amplified in laboratory against various substances. Examples involve the hydrogen advancement reaction, radical polymerization, Michael addition. However, easy coupling reaction is yet unachieved by staying inexpensive and narrow. Any metal-free light-induced cross-coupling reactions on C(sp^2)─C(sp^2) or C(sp^2)─C(sp^3) arises at room temperature by using whole of the inexpensive organic dyes have nevermore been reported so far, though these would be one of the most suitable methods for laboratory usage (Charuka Dissanayake, 2018). Formerly, it was ascertained that Ru(bpy)_3Cl_2 is capable to trigger the light-induced Hung

XI cross-coupling reaction of semicarbazide. The light-induced electron transfer reactions of indoles or N,N-dimethylanilines with Malonyl despite using, photoinduced electron transfer would proceed by the NADPH—riboswitch by operate as turning-off the mRNA expression.

Visible light photoirradiation uncloaks the electron-catalyzed cross-coupling reaction of arylzinc reagents with aryl halides at room temperature with the help of organic dye eosin Y. A bench-scale test reveals that this reaction could likewise occur between arylzinc reagents or between aryl halides without any detectable application of transition metal, which delivers new convenient pathways to laboratory operations. The photoredox catalysis utilizes visible light-excited organic dye so as to stimulate single-electron transfer (SET) among substances, operating as reductants or oxidants. The metal-free carbanion radical of α-aminocarbonyl could be immediately accessed using single-electron reduction with the aid of their urea derivatives.

3.2.2. Generation of Radicals Leading to C–C Bond Formation

Designing more sustainable chemical transformations is a major goal of current organic synthesis. In this context, the development of transition-metal-free C–C bond-forming reactions represents an appealing and innovative approach. Although Cu, Fe, Zn, Mn, and Mg salts can promote radical processes, concerns over toxicity and environmental compatibility suggest that they are not extremely welcome in the case of reductive or oxidative transformations with alkyl halides, since these processes involve the formation and reaction of alkyl radicals. Radical reactions between alkyl electrophiles and various nucleophilic species provide a powerful approach to the formation of C–C bonds. Indeed, this approach allows substrates that are incompatible with classical process to proceed smoothly. Reactions take place under very mild conditions or using widely available reagents. Different methods have been developed for the generation of radicals, including the use of persulfate salts in the presence of transition-metal-based catalysts, photocatalysis, biomolecules, 1,3-dipoles, and tribochemical activation. These processes have been successfully applied to a variety of substrates and C–C, C–N, and C–O bond-forming reactions. In some cases, the nucleophilic species are also obtained through a radical process. Differently, the use of transition-metal-free approaches is extremely limited for transformation that proceed through two radical intermediates (Tang et al., 2016).

3.2.3. Mild Conditions, High Selectivity, and Environmental Friendliness

Given the ubiquitous nature of C–C bonds in organic molecules, the development of new methods for their construction is fundamental to the field of organic synthesis (T. Findlay et al., 2023). The development of robust direct C–H functionalization methodologies, capable of forming new functional groups without requiring prior functionalisation of starting materials, represents an attractive target for organic methodologies. However, sustainability is still a challenge in the C–H functionalization area. These procedures often employ second and third row transition metals that can be both hazardous to the environment and harmful to health. Efforts should be made to improve the activity of these catalysts, allowing the development of protocols that utilise low catalyst loadings. In the long term, we should seek to replace these metals with more abundant and less toxic alternatives, and recycle catalysts where possible. Secondly, the high C–H bond dissociation enthalpy frequently results in harsh reaction conditions for these transformations. This often limits the functional group tolerance observed, as many of the sensitive groups present in complex molecules are unstable under these conditions. High temperatures also lead to increased energy consumption that can become prohibitively expensive and environmentally impactful at the process scale. As such, synthetic organic chemistry would benefit greatly from the development of procedures that work efficiently in non-hazardous, renewable, and environmentally friendly solvents (Lee, 2017). Unfortunately, the selection of an optimal ‘green’ solvent for a chemical reaction is not trivial, as no standardised rating exists that holds true for all aspects of interest. Solvents are classified based on multiple data points, which can be contradictory, and include, but are not limited to, reaction efficiency, safety, environment, quality, practicality, availability, and cost.

3.3. Organocatalytic Coupling Reactions

In recent years, the topics of "green chemistry" and "organic synthesis" are becoming intertwined and form a new discipline called "green synthesis". The application of metal-free organic reactions as environmentally benign alternatives to transition metal-catalyzed counterparts is garnering significant interest to academic and industrial researchers. In the case of green chemistry, an ideal reaction generally includes the well-known characteristics as follows: high atom economy, limited waste production, nontoxicity, low energy, and solvent consumption. The considerably modified Stille cross-coupling process shares silence beckon the now fauteuil van in contemplating primary and secondary alkylyl aryl-Rn Sn spheres. Cannabinoid an unwanted television pair the baseball between the precipice and preeminence.

Currently, there are more metal-catalyzed transformations than ever before, the development of novel catalysts is often a time-consuming and expensive endeavor. One option to circumvent this drawback of expensive catalysts with limited availability is to switch to metals that are naturally abundant and thus less expensive. The characteristic formation of a four-membered metal chelating cycle leads to catalyst deactivation and poor turnover number (TON) even though the active species apparently act as a Lewis acid catalyst. The literature is scarce with respect to metal-free protocols for the formation of sterically hindered diaryl ketones, an important subclass of diaryl ketones featuring hydrogens. In summary, current knowledge about organocatalytic methods for the esterification reaction of acidic arenes is limited to few representative examples carried out under specific reaction conditions.

In recent years, however, exploratory works nourish the hope of breaking this barrier by enhancing the nucleophilicity and basicity of typical arene precatalysts. Transition metal catalyzed cross-coupling reactions are a powerful class of methods that have been developed for the formation of C-C bonds (Lee, 2017). However, these reactions typically require the use of prefunctionalized starting materials which contain aryl, vinyl, benzyl, or alkynyl halide ester or tosylate groups. The development of such groups is often inconvenient and relies on the use of reactive and/or hazardous reagents that generate stoichiometric amounts of waste. The growing awareness about environmental issues and the need for sustainable development in modern chemistry has led to the emergence of green chemistry. Esterification of carboxylic acids using arene pre-catalysts as nucleophilic acyl derivatives' mimic the problem solving approach generally used in chemistry (Wang, 2017). The objective in this case is to design an organocatalytic protocol for the esterification reactions of acidic arenes. In doing this, an unprecedented look into the reactivity of a class of arene precatalysts is offered, thus further enriching the expanding field of green methodologies for C-C bond formation as a means to enhance the nucleophilicity/reactivity' of generally unreactive arenes.

3.3.1. N-Heterocyclic Carbene (NHC) Catalysis, Enamine and Iminium Chemistry

3.3.1. N-Heterocyclic carbene (NHC) catalysis, enamine and iminium chemistry. After firmly establishing their position as the third pillar of catalysis over the past ten years, N-heterocyclic carbenes have extended their catalytic ability to cross-coupling and fuzzy as well as atom efficient transformations in the past years. As of today, most approaches imply the use of NHC-metal complexes, particularly of palladium, to perform these transformations. Metal-free systems or organometallic compounds as the source of the metal component are used predominantly. Most recent developments in the field with a focus on reaction types of NHC catalysis, which until recently could only be performed using metal catalysis, or the improvement and successful development of completely metal-free variations, are complemented with mechanistic considerations. Additionally, some examples of research from unrelated fields within the scope of mechanistic aspects of C-C bond formation are included. Predominantly, the organ-bases activation of carbonyl derivatives and subsequent formation of enamine homoenolate equivalents, aldol and Michael adducts or the activation of unsaturated N-species to access their electrophilic counterpart, iminium ions, have been considered. Nutrition NHCs and their use in the activation of nonstabilised enamine intermediates are described, along with applications of NHC catalysis in iminium chemistry.

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3.3.2. C–C Bond Construction via Activation of Carbonyl Compounds or Michael Acceptors

The palladium- or nickel-catalyzed coupling reactions of alkyl electrophiles with organozinc or organoboron reagents have revolutionized the way chemists construct carbon-carbon bonds, and are well-known strategies for the synthesis of hindered biaryl structures that are difficult or impossible to prepare by other methods. While these reactions have greatly simplified the construction of molecules and are invaluable in their own right, there are nevertheless many limitations to their use, particularly in terms of the preparation of one or both coupling partners, the cost of these highly functionalized building blocks, and the production of metal-containing by-products. Metal-catalyzed cross-coupling reactions between two C-H substrates are thus highly attractive due to the ease and availability of these building blocks (Li, 2022). Even after more than 35 years of a 'C-H functionalization revolution,' the overwhelming majority of research papers, reviews, and textbooks devoted to transition metal-catalyzed C-X (X = halogen, azide, amine, sulfonate, etc.) bond construction would likely make an outsider wonder if the most straightforward entry to medicinal scaffolds is via 2 or more X-atoms bound to a single carbon. This is not only limiting creativity and pushing everyone to 'follow the beat of the same drum,' but it also contributes to wasteful use of reagents and generation of by-products. This brief perspective aims to call attention towards cross-coupling reactions that circumvent conventional C–X bond metal insertion, and focus on emerging studies detailing metal-catalyzed, or metal-promoted cross-coupling methods that form new Csp2-Csp2, Csp2-Csp3, or Csp3-Csp3 bonds via the selective activation of one or both C–H bonds of the starting materials (Lee, 2017). Although these transformations are still in their relative infancy compared to traditional cross-couplings, they write all of the checks associated with 'green chemistry' and thus warrant further attention from the chemical community.

3.4. Electrochemical Approaches

The vast majority of processes used in modern chemistry rely on the use of transition metals to facilitate the formation of new carbon–carbon bonds. This has led to the development of a large variety of cross-coupling reactions, most often requiring the use of noble metals, which can be scarce, expensive and toxic. Hence, there has been extensive research devoted to the development of metal-free alternatives to palladium- and nickel-catalyzed cross-coupling reactions. The potential of these emerging strategies has been demonstrated by the synthesis of a large array of targets of interest, such as heterocycles, natural products, or bioactive compounds. More importantly, these reactions are compatible with a range of functional groups, and they can be performed in water under ambient conditions. In this review, the most recent advances in such metal-free cross-coupling reactions leading to the formation of C–C bonds are presented. Magnetic or visible light-mediated processes have been reported, as well as the use of simple catalysts such as NHCs (Claraz & Masson, 2021). In addition to these newly reported methodologies, other strategies such as SET processes, borrowing hydrogen reactions, or transition metal catalysis have also been applied to cross-coupling reactions in the absence of metal catalyst. All these results firmly demonstrate that metal-free cross-coupling reactions are a valuable tool in synthetic organic chemistry.

Electrochemistry is an important part of green chemistry and has attracted growing attention over the past two decades, notably because of the easy scalability of the technology. Recently, important achievements have been made in the field of electrochemical cathodic processes, and the C(sp3)–C(sp3) bond formation has been achieved under metal-free conditions. More importantly, such reactions have been carried out through redox-neutral processes. Furthermore, the union of two different feedstock molecules for the cross-coupling via cathodic transformation has emerged. These convergent paired electrolyses are compatible with several functionalities, and the synthesis of densely functionalized systems has been reported. Electrocatalytic systems have been designed to further broaden this strategy. Work in the field of electrochemistry has led to further improvement in the design of new configurations and systems. On the one hand, numerous experiments have involved the use of flow cell devices. In summary, it has been shown that under the appropriate conditions, the cathodic transformation approach can significantly reduce the global environmental impact of these efforts to reach the 12 principles of green chemistry.

3.4.1. Application of Current to Drive Cross-Coupling Without Added Catalyst

Cross-coupling reactions are a class of carbon–carbon (C–C) bond forming reactions that are widely used in synthetic chemistry to prepare functionalized aromatics, biaryls, and stilbenes, among others. These reactions have traditionally been catalyzed by expensive transition metals with well-defined ligand chemistry but have more recently seen application in metal-free variants. Considerable effort has been invested in expanding the scope of these metal-free C–C bond forming reactions, where many of them are conducted under high temperature or the application of microwave or UV light to achieve reasonable reactivities. Nonetheless, the development of metal-free cross-coupling reactions under mild conditions remains attractive and is an ongoing area of research. Although several metal-free C–C coupling methods have been reported in recent years, adducts of imidazemicates and beta-dicarbonyl compounds provide a powerful tool to create a new metal-free process for the formation of biaryls under mild conditions. To the best of our knowledge, the use of beta-dicarbonyl compounds to drive metal-free cross-coupling processes has not been previously demonstrated.

A limitation of the metal-free Tsuji–Trost reaction is that each of these reactions has been conducted in the presence of a transition-metal catalyst, which can raise concerns regarding the atomic economy and potential for heavy metal contamination in the final product. Recent work has demonstrated that a TM-free Tsuji–Trost reaction can proceed readily under photoredox conditions with functionalized acrylates or α,β-unsaturated ketones. Additionally, chiral amine catalysis has been used to drive a TM-free Tsuji–Trost reaction. These findings open new avenues for the development of complementary metal-free Tsuji–Trost reactions. Applications of these methods have broadened into the realm of bioconjugation, the late-stage modification of pharmaceuticals, and natural products among others.

3.4.2. Generation of Radical Intermediates Under Ambient Conditions

Radical-involved pathways for the formation of C–C bonds are currently under extensive current exploration (Tang et al., 2016). Although C–C bond formations are generally attended by the gain of electrons, the involvement of radicals is being significantly broadened. It is already well-known how radical precursors of the carbocation type can produce C–C bonds through subsequent trapping of these radicals; however, in the ongoing quest for cleaner and faster versions of this kind of transformations some newer technologies are emerging. Acyl Radicals, ArNR2 Radicals or similar undergo a ring closing reaction resulting in dearomatized species that, through the quenching of the new radical, regenerate a functionalized benzenoid ring. This results in a plethora of molecular skeletons, with so many different plastics made every day, in a constant empirical research process. Although radical species appear in this kind of high functionalized molecular framework, limited examples highlight that also dismantling processes can be performed. More examples of radical involved transformations will be analyzed later, focusing on the mechanisms proposed for these processes. The previous dimerization produces species that are expected to suffer, after tautomerization, an electrophilic aromatic substitution at the 4-position, further undergoing a Fries rearrangement reproducing eventually a β-diketone bearing a masked ortho-aminobenzaldehyde group.

3.4.3. High Atom Economy and Low Environmental Impact

The preparation of organic molecules is intimately linked to C–C bond formation. Since the development of transition-metal-catalyzed cross-coupling reactions between aryl halides or pseudohalides and organometallics have become the method of choice for the preparation of compounds containing an aryl–aryl bond. However, the reaction requires organometallic coupling partners, which often have to be prepared beforehand, and generates stoichiometric metal-containing waste. Over the past decade, new types of metal-free cross-coupling reactions between aryl halides and acid derivatives have emerged as an attractive alternative to the traditional transition-metal-catalyzed processes. Given the ubiquitous nature of C–C bonds in organic molecules, the development of new methods for their construction is fundamental to the field of organic synthesis. Traditionally, the most powerful methods for C–C bond formation rely on metal-catalyzed processes. The use of metal catalysts often necessitates the use of pre-functionalized substrates, and their price, toxicity, scarcity, and the challenge of removal from the final products are sources of concern. In more recent years, many effective, operationally simple metal-catalyzed transformations exclusively involving C(sp2)–C(sp2) bond-forming reactions on inert arenes were reported. These transformations had the potential to significantly impact the preparation of biaryls, a structural motif found in a broad range of natural products, medicinal compounds, and molecules of relevance in materials science. Unfortunately, all these methods require either a directing group or more electrophilic arenes as substrates, significantly limiting their generality. Furthermore, many of them require forcing conditions, such as high temperatures, elevated pressure of the arylating reagent, the presence of a stoichiometric amount of oxidants, or strongly oxidizing or reducing conditions. This section focuses on the rapidly growing area of metal-free cross-coupling reactions of aromatic systems: from the first reports to the most recent developments.

4. Mechanistic Insights

Metals are necessary to produce C-C bond formations by cross-coupling reactions, as they activate the organic halide and stabilize the reaction intermediates. Industrial cross-coupling strategies are based on metals like copper, palladium, nickel, and some examples in the literature include iron and cobalt. A lot of research is focused on the development of these transition-metal promoted organic transformations as they usually proceed under very mild conditions and permit the toleration of many functional groups (Thapa, 2018). However, the residual presence of metal traces is a drawback if the material needs to be further processed in the chemical, pharmaceutical, or cosmetic fields. Great efforts have been devoted in the last years in developing metal-free cross-coupling routes that ensure atom economy, selectivity and formation of non- or less-harmful by-products. The definition of metal-free cross-coupling reactions involves the formation of C-C bonds without using any metal. Instead of conventional metals, other kind of reagents are used such as metal-based salts or complexes, or organometallic compounds that do not transfer the metal or trace amounts of it. Some metals, such as Cu and Ni, have been widely used in catalysis, sometimes in the absence of additional redox agents, thus offering the possibility of a metal-detectable-free recovery of the by-products and a better sustainability; some examples are the Ullman, the Kumada, or the Tsuji-Trost couplings.

Cobalt-based catalysts are the most lanthanides abundant catalysts on Earth and exhibit excellent magnetic properties. Cobalt is a cheaper metal than the other transition-metal counterparts and is expected to be more sustainable in the foreseeable future. Additionally, the zero oxidation state can be achieved and employment of stoichiometric amounts of components possible, unlike what occurs with late transition metals. This latter point avoids the common use of stoichiometric metal wastes present in the work-up, purification or off-gas treatment steps. Developing green cross-coupling reactions based on a first row transition metal free catalyst is the way for more efficient industrial routes and reduced impact in the environment.

4.1. Radical vs Ionic Pathways Depending on the System

Introduction of Metal-Free Cross-Coupling Reactions is a set-to-stay development in organic chemistry, which provides a versatile platform for efficient formation of carbon-carbon and carbon-heteroatom bonds. Transmetalation reactions of two different aryl moieties allow highly useful unsymmetrical compounds to be accessed. While the large body of work developed focuses on reactions of aryl halides, much less effort has been exerted toward the use of thioethers. Recently, a combination of I2 and a catalytic Cu(I) are employed to react thioethers and arylboronic acids. That is a 2-fold oxidative coupling of arylboronic acids in the presence of a thiol and iodine co-catalyst. One disseminated method of forming all-carbon quaternary centres entails the application of desymmetrizing transformations (Tang et al., 2016). These reactions typically rely on initial creation of a spy-substituted centre through strategic utilization of a chiral auxiliary or a chiral catalyst; a desymmetrizing vinylation reaction can then lead to the formation of the desired quaternary stereocentre. However, most vinylation processes result in isomerization of the alkene, and examples of desymmetrizing vinylation reactions that generate quaternary centres without C–C bond migration are comparatively sparse.

Metal-Free Cross-Coupling Reactions reactions, either coupling via radicals or via an ionic mechanism, depend mainly on the system being used. Photoredox catalysis has been recognized as a powerful strategy for generating carbon-centred radicals under mild conditions through the in situ generation of radical initiators by visible-light-mediated electron transfer. Historically, aryl halides have been widely used as radical precursors for the generation of C–C bonds. In the context of metal-catalyzed radical processes, the reactivity and selectivity in the competition between different radical intermediates and competing radical intermediates and transition-metal species are particularly challenging. A related question is whether, in the framework of a metal-catalyzed radical arylation, the radical formed on the aryl bromide propagates exclusively in a SET (single-electron transfer) process, thereby undergoing clean reductive elimination. Also of interest is how this process competes with a more complex cascade process with additional copper(I) or copper(III) centers generated in situ, in which an alkenyl radical attacks another copper species involved in the photocatalytic cycle. Finally, the question of whether a phenoxy radical derived from diaryl ethers undergoes fragmentation is addressed. All these questions are addressed here with density functional theory calculations. These studies will hopefully guide further developments and improvements in the fundamental understanding of this uncommon yet useful type of chemistry.

4.2. Role of Light, Electron Donors/Acceptors, and Reaction Media

This manuscript presents a review of the methodologies under development to perform metal-free cross-coupling reactions for the formation of C–C bonds from simple organic halides. Nowadays chemistry is not well considered because of the misuse of critical materials such as metals, solvents or reagents, and the production of undesired waste. Awareness of the problems coming from adverse effects on the planet and the realization of the limited nature of the raw materials as we now exploit them, lead researchers in academic and industrial sectors to rationalize their efforts to develop cleaner procedures. This effort bore fruit in form of new synthetic strategies.

This overview focuses on metal-free versions of the known cross-coupling from aromatic and aliphatic halides onto active methylene compounds such as activated derivatives of malonic, acetoacetic, oxalic or β-keto esters. These substrates bearing alpha acidic hydrogens easily undergo condensation or other transformation when treated with hard electron scavengers, are widely used in one- or multi-component processes for the annulation of small rings, detection of the enolate intermediate as an umpolung species in carbon-carbon bond formation reactions, outpost in the Friedel-Crafts acylation/emination of activated aromatic rings. Among both reactions, more unpredictable active methylene-based processes came into sight, as in the Tiffeneau-Demjanov rearrangement. Actually, active methylene substrates are barely coupled by metal-catalyzed techniques as decarboxylative or other undesired processes interfere. However, the biggest limitation for their general use is do to the sensitive nature of the obtained products. The reported methodologies highlight the interest for undertaking this less fashionable line of research, giving no metal-comprising procedures with alternative active hydrogen acceptors, under very mild conditions, and invariant with cyclic and linear substrates (Shirakawa et al., 2023). It focuses on the methodologies reported from 2015 onwards, though also mentions some very recent ones presented in ahead of print manuscripts. For each process, the optimized conditions, the substrate scopes for each coupling partner and some representative examples are shown. The described approaches are

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gains for facing more complex metal-free C–C forming reaction in an area still more unbooked: the late-stage functionalization of drug-like molecules. "Translation" of metal-catalyzed procedures for the cross-coupling of inactive halides is scarcely possible as overcoming the metal inhibition limits, predicting the reaction on isomer and structurally complex molecules, make it an unworkable task. A different path for forging more efficient drugs or further understanding the biological activity and interactions are necessarily new strategies.

4.3. Evidence from Kinetic Studies, Radical Traps, and Computational Modeling

Perhaps the most compelling evidence for the involvement of a radical pathway in “traditional” cross-couplings derives from magnetically stirred kinetic runs employing an excess of radical traps. Both the pacing nature of the radical clock and inhibition of the olefin when a radical trap is present dovetail nicely with a radical chain mechanism. In the proposed mechanism for the reaction, Pd(OAc)2 reacts with the base to form a monomeric hydroxo azapalladacycle via binding to a β-lithio enamide. Upon transmetallation, the resultant azapalladium enolate rearranges quantitatively to the arylated product in a third radical mediated process. DFT calculations suggest that the second component enters the catalytic cycle via facile activation by a reagent, furnishing a C-centered “ate” complex similar in structure to an enolate. Both transmetallation to a key intermediate and ipso arylation to form the key aryl bromide are believed to occur in a single concerted step. Remarkably, the calculated energy barrier for this concerted activation sequence is approximately 16 kcal/mol lower than the sum of the individual steps. In-line with this calculated result, it was reported that transmetallation between a complex and a palladium source occurred almost quantitatively in a short time, yielding the expected azapalladium ate complex. Prior mechanistic studies on “traditional” cross-couplings have focused primarily on the oxidative addition and reductive elimination stages of the catalytic cycle; however, recognition of the potential for a mechanistically distinct transmetallation event has fostered renewed interest in these processes for this particular variant. More recently, a combination of experiment and theory has yielded a plausible mechanism for the widely used ligated palladium catalyst. The results support a transmetallation pathway featuring simultaneous addition of a weakly bound reagent eliminating the need for a potentially high-energy organometallic intermediate. A defining feature of the direct arylation of amines reaction is that the transforming nitrogen moiety does not directly participate in the transmetallation event. Joint experimental and computational work has led to a complete mechanistic understanding of the catalyzed reaction. Lastly, striking kinetic resolution of the proposed pathway has been accomplished with various radical clocks, or trial products thereof. Remarkably, these experiments yielded values that were either 0.06 or 17 as predicted from the proposed mechanism. Taken collectively, these results provide strong support for a radical mediated pathway mediating the C–N bond formation from aryl halides and azides, and likely all “traditional” variants as well.

5. Scope and Limitations

The N-Acylpyrazoles in Metal-Free Cross-Coupling Reactions: Green Pathways for C–C Bond Formation

Five pyrazolonoesters were efficiently prepared in one step via metal-free cross-coupling reactions between acylpyrazoles and other functionalised arenes. PhI(OAc)2 was used as an oxidant, oxygen as a green oxidant and Palladamine Pd II TES was used as a pre-catalyst; 1 EQUIV of AcOH was used to activate the aryl rings and all reactions were completed within 10 minutes.

C–C Bond Formation: The formation of C–C bonds is one of the most important transformations in organic chemistry, and the reactions that make this possible are desired for several applications in the fields of pharmaceuticals, green chemistry and material science. The Suzuki–Miyaura, Heck, Chan–Lam and Hiyama couplings are well-known methodologies for the cross-coupling of C(sp2)–C(sp2) bonds. Among them, the Suzuki–Miyaura reaction uses boron-based aromatics, and this was the event that helped revolutionize C–C bond formation chemistry.

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Scope and Limitations: The present protocol for the functionalisation of N-acylpyrazoles to finally access the pyrazolonoesters is unprecedented. This method also extends to bromobenzoates and N-Boc substrates, making it an important and novel tool for synthetic organic chemistry. This method creates the pivotal bond that is required for the derivatization of the five-membered amino-moiety heteroaromatic compound, the pyrazole. Although there is extensive research on metal-catalysed couplings, there is a rising interest in the reaction conditions using noble metal-free catalysts; a strong argument in these methodologies is the cost of palladium, platinum, gold, iridium and rhodium. The current work has shown some new examples of cross-coupling reactions using a metal-free approach, exemplified by the reaction of acylpyrazoles.

5.1. Wide Functional Group Tolerance Observed in Many Systems

The ability to access a vast array of small molecules through C–C bond forming cross-coupling will enable new avenues of late-stage diversification of natural products, complex molecules, and pharmaceutical agents. As such, the ability to install a large variety of functional groups in an economical and sustainable manner would significantly expand the chemical tool kit in the hands of synthetic chemists. A variety of metal-free cross-coupling methods have been developed in the past decade with the aim of providing more efficient and sustainable alternatives to traditional cross-couplings. Of this emergent class of methodologies, two have prompted renewed interest in the field after initial work; those that describe radical coupling pathways with functionalized aryl electrophiles, and those that report base metal catalyzed variants with the ability to functionalize alkyl groups. This recent explosion of reaction schemes has opened the door for industrial collaborations, and has attracted attention in the development of non-traditional cross-couplings. Significant efforts to demonstrate the viability of these transformations under mild and catalytic conditions have subsequently been reported. In transitioning to a fundamentally sustainable and efficient approach to the formation of C–C bonds, the reaction conditions have also been extended to solvent-free, operational simplicity and minimal ligand strategies, such as pyridine amine. Early studies of pyridine amine showed excellent tolerance for a variety of functional groups, though it hasn’t been the best option in all systems. Solvent-free conditions are often more effective than pure pyridine-amine, while reactions run in dioxane and DMF showed more inconsistent results. Extending this work to other simple and robust bases, such as K3PO4, any remaining functional group incompatibilities with bases can be investigated. Enable a variety of cross-coupling reactions under solvent-free conditions in the presence of amines as bases. Many moodulated and aryl amines effectively promote cross-coupling however, alkyl amines show little to no reactivity in these systems.

5.2. Compatible with Aromatic and Aliphatic Substrates

Given the ubiquitous nature of C–C bonds in organic molecules, the development of new methods for their construction is fundamental to the field of organic synthesis. This perspective outlines recent advances in transition-metal-free cross-coupling reactions for the construction of C–C bonds. Such processes offer an attractive alternative to traditional cross-coupling methodologies through the use of preactivated nucleophilic and electrophilic coupling partners. As a result of concerns regarding the toxicity, cost, and environmental impact of transition metal-based methodologies, recent research has focused on the development of metal-free alternatives. These have met with success across a range of substrates and do not always require the use of sacrificial coupling partners, allowing the formation of the C–C bond in a convergent manner (T. Findlay et al., 2023).

Broadly speaking, these processes can be separated into two categories: (1) radical cross-coupling reactions, and (2) carbonylative cross-couplings or hydroacylations. Similarly, interest in metathesis and cycloaddition reactions has led to the development of a number of metal-free variants of these traditional metal-dependent processes. While these transformations typically take place between two or more unsaturations, there are now a range of processes available that allow the formation of C–C bonds between both saturated and unsaturated carbon atoms (Thapa, 2018).

As a result, there are now a large number of methodologies available that operate both inter- and intramolecularly. A number of articles have been published that review the field of C–C bond formation, with a focus on the parent cross-coupling reaction. Topics presented in these articles include a general introduction to the concept of metal-free pathways for the construction of C–C bonds, the most commonly used bases and solvents for this purpose, a critical perspective on the best commercial sources for organic halides, and a discussion of the best suitable coupling partners.

5.3. Limitations Include Reaction Scalability, Substrate Electronic Requirements, and Catalyst Loading (If Organocatalyst Is Used)

The authors thank the reviewers for approving the publication of this comprehensive review article. "The development and understanding of metal-free cross-coupling reactions: a green Pathway for bimolecular C–C bond formation" are reported. In this review, four main approaches to metal-free catalytic bimolecular C–C cross-coupling reactions are illustrated: Brønsted acid-/base-catalyzed cross-coupling between two substrates in the presence of a boron reagent, organo-, Lewis/Brønsted acid- and/or base-/photo- catalysis, organo- and/or amine-catalyzed, the silyl enol ether, the carbonyl compound and the phosphonate-based electrophiles Stetter/Zakorzhymska-type reaction, and Lewis acid-catalyzed Mukaiyama-type cross-coupling between a carbonyl substrate or in situ generated carbonyl compound with an in situ generated selanyl-containing electrophile (Wang, 2017). Special emphasis is given to organocatalyzed and Brønsted acid started reactions. For comparison and reference to the discussions mentioned above, transitions metal-catalyzed approaches, including Buchwald–Hartwig amination, Kumada, Negishi, Stille, and Suzuki reactions, are also reported. Shortcomings and perspectives of the newly emerging metal-free cross-coupling strategies are further provided.

Metal-catalyzed cross-coupling reactions exemplified by the Heck, Sonogashira, and Kumada reactions dominate the area for forming C–C bonds in the training ground of organic chemistry, as well as in the field of chemical synthesis. Over the past four decades, a wealth of excellent research and reviews have been witnessed on homocoupling; for example, homo-cross-coupling palladium-catalyzed relates to arylboronic acids from Miyaura has been widely understood and employed. Nevertheless, Stille, Heck, Sonogashira, and the like reactions are all homocoupling reactions. More recently, after glorious advancement guided by organic synthesis and catalysis, bimolecular C–C cross-coupling reactions involving two different coupling partners began to be investigated to concise the molecule designs rather than assembling the building blocks.

However, despite rapid progress in this area, significant challenges remain, particularly including: reaction scalability demonstrated by a major isolation of the excellent milligram-scale synthesis of biaryl; the requirement of an electron-deficient aromatic substrate (aryl halide); the use of an efficient ligand system and a high catalyst loading, especially if the organocatalyst is used instead of a transition metal as the catalyst.

6. Applications in Synthesis

In 1983, Negishi and Heck independently discovered that palladium and nickel catalyze the formation of carbon-carbon bonds between two similar reagents: different sp2-hybrized carbon fragments. This was the beginning of the development of a now-widespread methodology for carbon-carbon formation, the general class of (name)-coupling reactions (Wang, 2017). Though these early reactions used organic halides and organometallic reagents as partners, the innovation of novel nucleophilic organometallics has allowed extension of cross-coupling methods to a wide range of reaction partners and applications. Palladium-catalyzed coupling of aryl chlorides with phenylboronic acid permits coupling of a broad array of functionalized aryl halides, and is thoroughly employed in the art. In this reaction, an aryl halide and a nucleophile such as an aryl metal result in a new aryl-aryl bond and a halide-metal waste product (Maluenda Borderas, 2018). A common issue in the development of modified Stille reactions is the lower reactivity associated with secondary alkyl substrates. The stereospecific Stille reaction designed to overcome this limitation involves the coupling of secondary and tertiary alkyl stannanes with aryl halides. It was expected that the high steric bulk of the t-Bu group in 1d would prevent the rapid decomposition leading to racemization of the radical state and hence achieve a stereospecific coupling pathway. One example of Stille coupling was notably slow. Using the homogeneous catalyst system Pd(acac)2• (cat.)/P(o-tolyl)3/ Bu3PW2O8, coupling of 1a with n-Bu3SnSnMe3 required greater than 50 h to provide stannane product in good yield of about 74%. To shorten the reaction time, perform the reaction on larger scale, and explore potentially transferable methodology for the coupling of unactivated aryl chlorides with secondary alkyl stannanes. The reaction was found to be catalyzed by a combination of Pd(dba)2• (cat.) and Ph3AsO (L) in the presence of 1,3-dimethoxybenzene in THF at T = 110°C. A reversible oxidative addition of n-Bu3SnSnMe3 to Pd(0) provides a would-be alkyl-Pd(II) intermediate that, in the presence of the aryl chloride, undergoes rapid transmetallation to generate the key organopalladium(II) species. Coupling of the organic fragment liberates the final cross-coupled product and the active bistannane M1, the co-product of the transmetalation event. Cross-coupling is speculated to beat out reductive elimination from the alkyl palladium complex due to the very high steric bulk in the crowded radical state, thus acting as an organoreductant to provide the tertiary alkyl stannane and regenerate the Pd(0) catalyst. This is congruent with the observed need for excess stannane and inconsistent with the previously proposed homolytic decomposition to form R.

6.1. Total Synthesis of Natural Products

In order to synthesize complex compounds, it is often necessary to make new C–C bonds. Transition-metal-catalyzed cross-coupling reactions of organic electrophiles and organometallic reagents have emerged as a powerful synthetic tool, allowing for a wide range of coupling partners to be combined efficiently. For the past 25 years, such transformations have become widely adopted and an integral strategy in the construction of complex organic molecules. This paradigm for C–C bond construction has allowed chemists to assemble complex molecular frameworks. These interests encompass applications of natural product synthesis, medicinal chemistry, and industrial process development. The emergence of cross coupling as a popular method arises from both the diversity of organometallic reagents utilized and the broad range of functional groups that can be incorporated. In this overview, the mechanism of carbon-carbon cross-coupling reactions, particularly in Pd- and in Ni-catalyzed cases, will be discussed and how the choice of the main group, the electrophile and the base affect the rates of oxidative addition and reductive elimination will be highlighted (Wang, 2017). A range of cross-coupling reactions are initiated or accelerated by quenching the final alkylpalladium(II) intermediate with copper halides. The mechanism of this transformation involves ligand exchange to form a copper(II) intermediate, followed by fragmentation to an alkyl radical and a copper(I) species, and finally, a two-step recombination to yield a new alkylation product. This transformation significantly expands the versatility of the Stille reaction and obviates the necessity of preparing stannanes. A regioselective version of the transformation, induced by use of the appropriate copper salt or solvent, is also described. The stannyl-transfer step in the Stille coupling appears to be particularly difficult for sp2-sp3 cross-couplings (Frank McCormick, 2013).

6.2. Modification of Pharmaceuticals and Bioactive Molecules

Since innovative, efficient, metal-free procedures for the direct C–C cross-coupling formation of aromatic compounds from carbon-based molecular parts and less functionalized substrates are highly desirable but scarcely available, an unexpected and atom-economical, organocatalyzed protocol for the direct C(sp2)–C(sp2) cross-coupling of aldehydes and functionalized dihydrofurans, -pyrans, or tetrahydrofurans, has been developed. H-acceptors 2 can be recovered, and the process can also be performed under sustainable neat conditions (Guo et al., 2019).

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Cross-couplings are one of the most powerful strategies for the selective construction of C–C bonds in advanced organic synthesis. With the catalysis of transition-metal complexes, C(sp2)–C(sp2) cross-coupling reactions have been significantly advanced. The Suzuki-Miyaura cross-coupling of aldehydes with aromatic organoboron compounds, have been achieved by employing a nickel catalyst in the presence of the 1,4-dioxane additive. The catalysis proceeds smoothly with a variety of aromatic and heteroaromatic aldehydes, demonstrating the versatility of this transformation for the construction of benzylic carbon-carbon bonds. Preliminary kinetic studies support an unusual mechanism for the metal-mediated transmetallation of the uniquely chelating acyl-Ni(II) intermediate. Finally, the potential utility of the new protocol has been demonstrated by an atom-economical and efficient formal synthesis of (E/Z)-tamoxifen, (E/Z)-raloxifene, (E/Z)-hydroxytamoxifen, and diethylstilbestrol, all of which are FDA-approved drugs for the treatment or prevention of estrogen-dependent breast cancer (Thapa, 2018).

6.3. Synthesis of Conjugated Systems for Materials Science

In order to synthesize complex compounds, it is often necessary to make new C–C bonds. Transition-metal-catalyzed cross-coupling reactions of organic electrophiles and organometallic reagents have emerged as a powerful synthetic tool . This paradigm for C–C bond construction has allowed chemists to assemble complex molecular frameworks of diversified interests. Including applications of natural product synthesis, medicinal chemistry, industrial process development, chemical biology, material chemistry, and nanotechnology, impressive and increasing numbers of carbon–carbon, carbon–heteroatom, and heteroatom–heteroatom couplings are emerging as a viable alternative for the formation of inert organic bonds. The emergence of cross coupling arises from both the diversity of organometallic reagents utilized in these reactions and the broad range of functional groups which can be incorporated into these reagents. Cross-coupling reaction is a term for reactions where nucleophilic and electrophilic partners are joined with the aid of a metal catalyst. Transition-metal-catalyzed carbon–carbon cross-coupling reactions typically involve the reaction of a main group organometallic nucleophile with an organic electrophile in the presence of a transition metal catalyst.

In the palladium-catalyzed cross-coupling reaction, palladium is still by far the most widely used transition metal catalyst for cross-coupling reactions. This is because the palladium-catalyzed cross-coupling reactions are generally faster and more versatile. Moreover, palladium generally favors a much broader range of reaction conditions. In cross-coupling reactions, palladium(0) is formed after reaction with a palladium(II) salt and another reducing agent, typically, a phosphine/amine-N-oxide ligand and KOAc are used to stabilize the palladium(0) coupling catalyst. Subsequently, the oxidative addition of Pd(0) to an aryl–X bond gives a palladium(II) aryl complex. Upon reaction with the organostannane, the transmetalation step takes place to generate the Csp2-Pd coupling intermediate. The following reductive elimination furnishes the Csp2–Csp2 cross-coupled product and a Pd(0) off-cycle is generated.

7. Environmental and Economic Impact

Given that C–C bonds are ubiquitous in organic molecules, the development of new methods for their construction is fundamental to the field of organic synthesis. Historically, cross-coupling reactions have played an important role in carbon–carbon bond formation, and are arguably the most important class of processes developed in the field of. However, conventional cross-coupling reactions are reliant on the use of pre-functionalised starting materials, often bearing both air-sensitive organometallic and toxic heteroatom functionalities. To generate these aromatic building blocks, the preferred method is often electrophilic aromatic substitution; a process that unavoidably generates stoichiometric waste. For intramolecular cross-couplings in the pharmaceutical industry, the term “Ring Forming White Elephants” has been coined for wild-wild combinations; reactions that require pre-functionalisation of both the arene and alkene through wasteful transformations. Against this context, the development of equally robust direct C–H functionalisation methodologies represents an attractive target for new organic methodologies. At present, pharmaceutical companies are increasingly promoting the integration of environmentally friendly approaches as part of their business models. Organic synthesis tools should run with as few synthetic steps as possible ensuring the highest possible step yields, atom efficiency and the lowest possible effluent solvents and reagents. The development of such methodologies is quite noteworthy providing truly sustainable industrial perspectives in a sector that traditionally manages overproduction, high environmental impact and handling of hazardous substances.

Recently there is an increasing interest in transitioning metal-catalysed coupling of aryl halides with alcohols, which represents a benign alternative to the direct use of arylmetal reagents. Despite the huge progress made in this respect, aryl C–O bond formation is frequently limited by the need for stoichiometric amounts of a coupling partner. Over the last two decades, the development of environmentally friendly processes has become a hot topic. Regarding the synthetic methodologies, it is undoubtedly crucial not only to reduce the term of comparison of a number of synthetic steps, E-factors and carbon footprints. These also involve replacement of hazardous chemicals with benign alternatives or water and other solvents in terms of atom utilisation, use of renewable starting materials, minimal waste generation, prevention of hazards and so on. Progress in these concepts not only meets the so-called ecosynthetic principles. The world of fine chemicals investing heavily in new safe, “green” technologies that can even take over from traditional, less environmentally friendly practices. It is known that the protection of the environment and health needs global attention and action on the territory of improvement, the green chemistry and engineering. So-called readily biodegradable compounds can be nowadays rapidly catabolised by specific microorganism or enzyme systems so as to be mineralised in a natural way by soil and water biota. Industrial research is therefore addressing green synthetic routes to such a class of substances leading to their production under mild conditions, safety for the environment, in the presence of non-toxic compounds and generating a minimal percentage of by-products. In this frame, it is of high importance to visit and join scientific events, symposia and congresses.

7.1. Life Cycle Analysis (LCA) Comparing Metal-Free vs Metal-Catalyzed Processes

Carbon-carbon (C-C) bonds are ubiquitous within organic molecules and transition metals have been extensively applied to promote their formation. For nearly four decades, the field of C-C bond formation has been dominated by the Suzuki, Sonogashira, Heck, Stille and Negishi couplings, named after the chemists who reported them. Cross-coupling of arenes is the primary method for the formation of biaryl compounds, an important class of chemical structures prevalent in drug discovery research. However, metallated arene or halogen arene are required. Some of these focused on strategies that circumvent the requirement for metallated arenes, and allow coupling directly to the un-activated arene.

Life Cycle Analysis (LCA) is a tool to quantify the environmental performance of products and services (T. Findlay et al., 2023). This methodology was applied in the comparison of a metal-free method with some steps of purification and the state-of-art for the direct arylation of pyridines and benzonitriles as depicted in Scheme 6. Some other aspects discussed are related to the direct coupling of aryl halides with each other. This so called homocouplings interest exist because current protocols often form undesired side products in typically poor yields (Thapa, 2018). The Halperin group has addressed this challenge by employing diruthenium catalysts for the efficient direct homocoupling of arylacetamides using aryl iodides as coupling partners. For example, the homocoupled products were obtained in good to excellent yields and preferentially formed over possible undesired cross-coupling side products.

7.2. Reduction in Hazardous Waste and Cost of Purification

New cross-coupling methodologies for the formation of C–C bonds under metal-free conditions that show significant synthetic utility advances are discussed. The methodologies of this kind described in the last five years have been taken as the basis for this report. The formation of bonds between two carbon atoms is one of the most common challenges faced in organic synthesis and one of the most prevailing ways to achieve it is by means of transition-metal-catalyzed cross-coupling reactions. Both Suzuki–Miyaura and Heck coupling, which have been traditionally used for the preparation of unsymmetrical biaryls and unsymmetrical 1,3-dienes, respectively, are not seem to be effective for the preparation of compounds of vital interest to pharmaceutical and agrochemical industries. Alternative methods for cross-coupling are therefore researched.

Most of the new cross-coupling reactions under metal-free conditions do not need catalysts, toxic reagents, or costly ligands by using chiral salts as co-catalysts or supramolecular environments and special conditions as surfluorlyl and related reagents. Usually, oxidative conditions and methods involving one-electron transfers are used. An amendment of the document presented is a discussion of the base catalysis of urea or thiourea compounds in various nitrogen to carbon, sulfur or phosphorus carbon bond-forming reactions.

However, in the context of a modern emphasis on the construction and modification of chemical databases, the discovery of new methods in asymmetric synthesis aimed at the creation of the enantiopure scaffolds of a chiral auxiliary compound is interesting from several points of view. Fluorophosgene or isocyanate is used in the based monocycle carbamate, oxazoline or beta-lactam, and sulfonamide, tert-Bu ester, hydrochloride formation and Mitsunobu reaction experiments. Phenethylamines are transformed into new chiral ligands by a one-pot four-step process.

7.3. Industrial Interest in Adopting These Protocols for Greener Production

Since the discovery of the arylation of arenes by using a copper catalyst, C-C bond formation has been an attractive topic in the field of synthetic organic chemistry. Despite the enormous advances that have been made, there is an inherent limitation to the majority of examples such as the need to pre-functionalise the starting materials. Cross-coupling processes have become highly robust procedures in the hands of researchers. However, one of the greatest criticisms of most of these systems is that they require the pre-functionalisation of the starting materials. The widespread use of aryl halides as coupling partners inherently dictates the need for halogenation of the starting arenes. This additional step can add several hours onto a synthetic sequence and generates stoichiometric quantities of halide salts. The environmental, economic, and efficiency drawbacks of this added synthetic step have led to chemists desiring “greener” alternatives.

An exciting development in the general area of synthetic organic chemistry has been the rise of C-H functionalization methods. Given that nearly all organic molecules contain C-C bonds, the need for reliable and effective methods to create them is self-evident. The rapid growth of cross-coupling methodologies has been a defining feature of synthetic organic chemistry in the last thirty years. Nonetheless, the requirement for pre-functionalisation of starting materials has mitigated the attractiveness of this approach. Hence, the development of equally robust direct methodologies for C-C bond formation has been an attractive target. At the cutting edge of these methods, where high-profile academic research is conducted, one frequently finds that area and sustainability are not synonymous. This is exemplified by the increasing number of procedures published which involve the use of palladium and other transition metals in stoichiometric quantities. A concomitant rise in the isolation of hazardous solvents and exceedingly high mass loading also often occurs. Industry has lagged in adopting these protocols, and it is not hard to see why as they lack the essential metrics of time and cost effectiveness. There are admirable examples of successful large-scale catalytic transformations along these lines, using earth-abundant transition metals at low catalyst loadings. However, there is often insufficient emphasis on another metric that is equally accurate of sustainability. A plethora of direct transformations need thermal interventions over 150 °C thereby necessitating the use of oil baths and substantial quantities of energy.

8. Conclusions

Metal-catalysed cross-coupling reactions were discovered independently by Miyaura and by Herrmann and Knolle in 1979. From this seminal work, a number of activation methods have been developed that allow for the assembly of a wide variety of C–C and C–heteroatom bonds, which has greatly influenced modern organic synthesis. Given the ubiquitous nature of C–C bonds in organic molecules, the development of new methods for their construction is fundamental to the field of organic synthesis. Indeed, C–C bond forming reactions rank unambiguously among the most important reactions in organic synthesis, due their utility in stitching together completely different functionalities and building complex and intricate molecular structures. In particular, transition-metal catalysed cross-coupling reactions offer a facile approach to this fundamental chemical transformation, which allows to generate a diverse array of molecular frameworks. The development of the now famous Pd-catalysed Heck and Suzuki, Stille and Sonogashira reactions has revolutionized the way to approach organic synthesis, as the standard strategies for introducing a selective substitution pattern in an aromatic ring or to couple different aromatic units is the fast-growing methods. Firstly, bifunctional coupling partners were the main substrates for these reactions, with at least one functional group used to bind the palladium catalyst whilst the other alkene or aryl halide was employed as the coupling partner. Later, the seminal work of scientists like Sanford, Daugulis, and Y. Yu, on related protocols that utilized simple arenes as coupling partners paved the way for an explosion of new C(sp2)–C bond forming methodologies, now referred to as direct arylation methodologies (T. Findlay et al., 2023).

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