The Promise and Challenge of Iron-Catalyzed Cross Coupling


Abstract:

Transition metal catalysts, particularly those derived from the group VIII–X metals, display remarkable efficiency for the formation of carbon–carbon and carbon–heteroatom bonds through the reactions of suitable nucleophiles with organic electrophilic partners. Within this subset of the periodic table, palladium and nickel complexes offer the broadest utility, while additionally providing the deepest mechanistic insight into thus-termed “cross-coupling reactions”. The mammoth effort devoted to palladium and nickel catalysts over the past 30 years has somewhat obscured reports of alternative metal complexes in this arena. As cross-coupling reactions have evolved into a critical support for modern synthetic chemistry, the search for alternative catalysts has been taken up with renewed vigor. When the current generation of synthetic chemists reflects back to the origins of cross coupling for inspiration, the well-documented effect of iron salts on the reactivity of Grignard reagents with organic electrophiles surfaces as a fertile ground for alternative catalyst development. Iron possesses the practical benefits more befitting an alkali or alkaline earth metal, while displaying the unique reactivity of a d-block element. Therefore the search for broadly applicable iron catalysts for cross coupling is an increasingly important goal in modern synthetic organic chemistry.

This Account describes the evolution of iron-catalyzed cross coupling from its inception in the work of Kochi to the present. Specific emphasis is placed on reactivity and synthetic applications, with selected examples from acyl-, alkenyl-, aryl-, and alkyl halide/pseudohalide cross coupling included. The typical reaction partners are Grignard reagents, though organomanganese, -copper, and -zinc derivatives have also been used in certain cases. Such iron-catalyzed processes occur very rapidly even at low temperature and therefore are distinguished by broad functional group compatibility. Furthermore, recent advances in carbon–heteroatom bond formation and studies relevant to the general reactivity of in situ generated and structurally defined “low-valent” iron catalysts are presented. The preparative aspects of iron-catalyzed cross coupling are encouraging, but the inclination to classify these processes within the characteristic reaction manifold is premature, as mechanistic studies have evolved at a comparatively slow pace. A typical protocol for cross coupling employs an Fe(+2) or Fe(+3) precatalyst, which is reduced in situ by the organometallic nucleophile. The nature of the resulting active component(s) is still best described, more than 30 years later, in Kochi’s original terms as a “reduced form of soluble iron”. Despite huge gaps in our current knowledge, three distinct mechanisms have been formulated, largely based on empirical evidence: a “canonical” cross-coupling process, a manifold wherein alkylation of an organoiron intermediate replaces transmetalation as a key step, and finally a proposal reliant on the formation of nucleophilic ate complexes. Conjecture and speculation abound, but precisely what constitutes the catalytic cycle in iron-catalyzed cross coupling remains an extremely challenging unanswered question.
Copper-assisted Ullmann-type coupling reactions are valuable transformations for organic synthesis. Researchers have extensively applied these reactions in both academic and industrial settings. However, two important issues, the high reaction temperatures (normally above 150 °C) and the stoichiometric amounts of copper necessary, have greatly limited the reaction scope. To solve these problems, we and other groups have recently explored the use of special ligands to promote these coupling reactions. We first showed that the structure of α-amino acids can accelerate Cu-assisted Ullmann reactions, leading to the coupling reactions of aryl halides and α-amino acids at 80–90 °C. In response to these encouraging results, we also discovered that an l-proline ligand facilitated the following transformations: (1) coupling of aryl halides with primary amines, cyclic secondary amines, and N-containing heterocycles at 40–90 °C; (2) coupling of aryl halides with sulfinic acid salts at 80–95 °C; (3) azidation of aryl halides and vinyl halides with sodium azide at 40–95 °C; (4) coupling of aryl halides with activated methylene compounds at 25–50 °C. In addition, we found that N,N-dimethylglycine as a ligand facilitated Cu-catalyzed biaryl ether formation at 90 °C. Moreover, Sonogashira reactions worked in the absence of palladium and phosphine ligands, forming enamides from vinyl halides and amides at temperatures ranging from ambient temperature up to 80 °C. Furthermore, we discovered that an ortho-amide group can accelerate some Ullmann-type reactions. This functional group in combination with other ligand effects allowed for aryl amination or biaryl ether formation at ambient temperature. The coupling between aryl halides and activated methylene compounds even proceeded at −45 °C to enantioselectively form a quaternary carbon center. Taking advantage of these results, we developed several novel approaches for the synthesis of pharmaceutically important heterocycles: 1,2-disubstituted benzimidazoles, polysubstituted indoles, N-substituted 1,3-dihydrobenzimidazol-2-ones, and substituted 3-acyl oxindoles. Our results demonstrate that an l-proline or N,N-dimethylglycine ligand can facilitate most typical Ullmann-type reactions, with reactions occurring under relatively mild conditions and using only 2–20 mol % copper catalysts. These conveniently available and inexpensive catalytic systems not only accelerate the reactions but also tolerate many more functional groups. Thus, they should find considerable application in organic synthesis.

- A flavin-based [2]catenane
  Abstract:
We report the synthesis, solid-state and preliminary solution properties of a flavin-based [2]catenane.

- Cooperativity between – and H-bonding interactions–a supramolecular complex formed by C₆₀ and exTTF
  Abstract:

A highly stable supramolecular complex from C₆₀ and exTTF (K_s 10⁶ M⁻¹) has been achieved by means of – and H-bonding interactions; experimental evidence reveals the formation of a radical–ion pair (= 9.3 ps) upon photoexcitation.

- Synthesis of Amphidinolide E C10#C26 Fragment
  Abstract:

The key C10-C26 fragment in a total synthesis of (-)-amphidinolide E has been prepared from an oxolane-containing C10-C17 segment (9, derived from L-glutamic acid) via a Julia-Kocienski reaction with aldehyde 3, followed by a Sharpless AD to obtain the desired diol. The C22-C26 fragment was installed by means of an efficient Suzuki-Molander coupling, with an organotrifluoroborate reagent (4, arising from a cross-metathesis reaction between a vinylboronate and 2-methyl-1,4-pentadiene).

- [3]Rotaxane–Porphyrin Conjugate as a Novel Supramolecular Host for Fullerenes
Abstract:

A new supramolecular host with good affinity toward fullerenes has been developed. This host having a tweezer-like shape is built on a [3]rotaxane scaffold and contains two free-base porphyrin moieties as recognition units for fullerenes. The ability of this tweezer to bind fullerenes strongly depends on the solvent system used and the size of fullerene.

- A One-Pot Synthesis of Constitutionally Unsymmetrical Rotaxanes Using Sequential Cu¹-Catalyzed Azide-Alkyne Cycloadditions

Abstract:

A one-pot sequential Cu¹-catalyzed azide-alkyne cycloaddition (CuAAC) strategy is presented for the synthesis of constitutionally unsymmetrical cyclobis(paraquat-p-phenylene)-based rotaxanes in good yields from simple starting materials. The methodology consists of performing multiple CuAAC reactions to stopper a pseudorotaxane in a stepwise manner, the order of which is controlled through silyl-protection and Ag¹-catalyzed deprotection of a terminal alkyne. The methodology is highlighted by the synthesis of an amphiphilic branched [4]rotaxane. The methodology increases the ability to access ever more complicated mechanically interlocked compounds to serve in devices as sophisticated and functional molecular machinery.

- Symmetrically Tetrasubstituted [2.2]Paracyclophanes: Their Systematization and Regioselective Synthesis of Several Types of Bis-Bifunctional Derivatives by Double Electrophilic Substitution

Abstract:

The possible number of chiral and achiral tetrasubstituted [2.2]paracyclophanes possessing different types of symmetry (C₂, Cₛ, Cᵥ, C₂ᵥ, C₃ᵥ) is evaluated and a unified independent trivial naming descriptor system is introduced. The reactivity and regioselectivity of the electrophilic substitution of the chiral pseudo-meta- and achiral pseudo-para-disubstituted [2.2]paracyclophanes are investigated in an
approach suggested to be general for the synthesis of bis-bifunctional [2.2]paracyclopahanes. The mono- and diacylation of chiral pseudo-meta-dihydroxy[2.2]paracyclophane 14 with acetylchloride occur ortho-regioselectively to produce tri- 22, 23 and symmetrically 21 tetrasubstituted acyl derivatives. The same reaction with benzoylchloride is neither regio-, nor chemoselective, and gives rise to a mixture of ortho-/para-, mono-/diacylated compounds 27-31. The double acylation of pseudo-meta-dimethoxy[2.2]paracyclophane 18 is completely para-regioselective. Electrophilic substitution of pseudo-meta-bis(methoxycarbonyl)[2.2]paracyclophane 20 regioselectively generates the pseudo-gem-substitution pattern. Formylation of this substrate produces the monocarbonyl derivatives 35 only, whereas the Fe-catalyzed bromination may be directed towards mono- 36 or disubstitution 37 products chemoselectively by varying the reactions conditions. The diacylation and dibromination reactions of the respective achiral diphenol 12 and bis(methoxycarbonyl) 40 derivatives of the pseudo-para-structure retain regioselectivities which are characteristic for their pseudo-meta-regioisomers. Imino ligands 26, 25, and 39, which were obtained from monoacyl- 22 and diacyldihydroxy[2.2]paracyclophanes 21, 38, are tested as chiral ligands in stereoselective Et₂Zn addition to benzaldehyde producing 1-phenylpropanol with ee values up to 76 %.

- Synthesis, Chain Helicity, Assembling Structure, and Biological Compatibility of Poly(phenylacetylene)s Containing l-Alanine Moieties

**Abstract:**

A functional phenylacetylene monomer containing a naturally occurring building block of L-alanine, namely 4-ethynylbenzoyl-L-alanine methyl ester (PA-Ae), was synthesized. The monomer was polymerized by organorhodium catalysts, giving the corresponding “polyester” (PPA-Ae) with high molecular weights ($M_w$ up to $1.2 \times 10^4$) and stereoregularities (Z content up to 97%) in high yields (up to ~91%). The polyene backbone of PPA-Ae undergoes irreversible Z-to-E isomerization at ~180–250 °C. The ester groups in the pendants of the polymer are selectively deprotected by the base-catalyzed hydrolysis, producing a “polyacid” with “free” L-alanine pendants (PPA-A). While PA-Ae monomer is CD-inactive at wavelengths longer than 300 nm, both PPA-Ae and PPA-A polymers exhibit strong Cotton effects in the long wavelength region where their polyene backbones absorb, indicating that the chiral pendants have induced the polymer chain to take a helical conformation with an excess in one-handedness. Upon natural evaporation of its solutions, the amphiphilic chains of PPA-Ae self-associate in a cooperative fashion, furnishing a variety of organizational morphologies including twisting cables, spiral ribbons, spherical vesicles, and helical nanotubes. The polymers are biocompatible: the living cells are all survived after they have been subcultured in the presence of the polymers.
• Poly(tert-butyl methacrylate-b-styrene-b-4-vinylpyridine) Triblock Copolymers: Synthesis, Interactions, and Self-Assembly

Abstract:
Using atom transfer radical polymerization (ATRP), poly(tert-butyl methacrylate-b-styrene-b-4-vinylpyridine) or PtBMA-b-PS-b-P4VP linear triblock copolymers were synthesized. Different homopolymer and diblock copolymer macroinitiators were used for different block copolymerizations. For a selected triblock copolymer the self-assembly was studied with transmission electron microscopy (TEM), small-angle X-ray scattering (SAXS), and thermal analysis. Indications were found for a core–shell hexagonal ordering of coaxial cylinders with P4VP cylinders separated from the PtBMA matrix phase by a PS shell layer. To further support this, the interaction parameter between styrene and tBMA was investigated by a random copolymer blend miscibility study on blends of P(S-co-tBMA) random copolymers with PS and found to satisfy $0.08 < \chi_{S,tBMA} < 0.10$.

• Electrostatically Controlled Nanostructure of Cationic Porphyrin Diacid on Sulfate/Bisulfate Adlayer at Electrochemical Interface

Abstract:
Two different cationic tetraphenyl porphyrins, one with two carboxyphenyl groups in cis-position and the other in trans-position (cis- and trans-H$_4$DCPP$^{2+}$), have been examined to control the structure of their 2D supramolecular assemblies in 0.05 M H$_2$SO$_4$ at electrochemical interfaces. Electrochemical scanning tunneling microscopy (EC-STM) images revealed the formation of supramolecularly organized nanostructures of cis-H$_4$DCPP$^{2+}$ such as dimer, trimer, and tetramer on the ($\sqrt{3} \times \sqrt{7}$) sulfate/bisulfate adlayer, suggesting the importance of both electrostatic interaction between cationic porphyrin core and sulfate/bisulfate adlayer and the hydrogen bond formation between carboxyl groups of the nearest neighbor cationic porphyrins. Trans-H$_4$DCPP$^{2+}$ ions were also found to
be aligned in the V3 direction of the sulfate/bisulfate adlayer. The structure of these cationic porphyrin adlayers was found to depend upon the electrode potential; i.e., when the potential was changed in the negative direction, the \((V3 \times V7)\) sulfate/bisulfate adlayer disappeared, and no ordered arrays were formed. In contrast, when 0.1 M HClO₄ was used as an electrolyte solution, only a disordered array was observed. The results of the present study indicate that the \((V3 \times V7)\) sulfate/bisulfate adlayer formed on Au(111) in 0.05 M H₂SO₄ plays a significant role as a nanorail template in the control of electrostatically assembled dicarboxylic acid derivative. In addition, the high-resolution STM clearly distinguished between cis-H₄DCPP²⁺ ion and cis-H₂DCPP molecule. The cis-H₂DCPP molecules on Au(111) provided an adlayer structure and an electrochemical behavior which are different from those of cis-H₂DCPP²⁺ ions.

- **Diarylethynyl Amides That Recognize the Parallel Conformation of Genomic Promoter DNA G-Quadruplexes**
  
  **Abstract:**
  
  ![Diarylethynyl Amides](image)

  We report bis-phenylethynyl amide derivatives as a potent G-quadruplex binding small molecule scaffold. The amide derivatives were efficiently prepared in 3 steps by employing Sonogashira coupling, ester hydrolysis and a chemoselective amide coupling. Ligand-quadruplex recognition has been evaluated using a fluorescence resonance energy transfer (FRET) melting assay, surface plasmon resonance (SPR), circular dichroism (CD) and 1H nuclear magnetic resonance (NMR) spectroscopy. While most of the G-quadruplex ligands reported so far comprise a planar, aromatic core designed to stack on the terminal tetrads of a G-quadruplex, these compounds are neither polycyclic, nor macrocyclic and have free rotation around the triple bond enabling conformational flexibility. Such molecules show very good binding affinity, excellent quadruplex-duplex selectivity and also promising discrimination between intramolecular promoter quadruplexes. Our results indicate that the recognition of the c-kit2 quadruplex by these ligands is achieved through groove binding, which favors the formation of a parallel conformation.

- **Synthesis and Reaction of Fullerene C₇₀ Encapsulating Two Molecules of H₂**
  
  **Abstract:**
  
  ![Synthesis and Reaction](image)
New endohedral fullerene C70 encapsulating one and two H2 molecule(s) has been synthesized by organic reactions, the so-called “molecular surgery” method, and the first organic derivatization of H2@C70 and (H2)2@C70 has been conducted. Although the interaction between inner H2 and outer C70 is rather weak, (H2)2@C70 exhibits smaller equilibrium constants in the Diels–Alder reaction with 9,10-dimethylnanthracene than those of H2@C70.

- Highly Conducting Transmembrane Pores Formed by Aromatic Oligoamide Macrocycles
  Abstract:
  Oligoamide macrocycles 1d and 1e, which carry membrane-compatible side chains and contain a hydrophilic, noncollapsible cavity, were found to mediate high ion flux across a lipid bilayer, as demonstrated by results from 23Na NMR and planar bilayer conductance measurements. The measured transmembrane single channel currents are very high, rivaling those typically associated with pore-forming protein toxins. The obtained results have demonstrated the promise of developing large, highly conducting channels based on nanopores formed by oligoamide macrocycles.

- A Topography/Chemical Composition Gradient Polystyrene Surface: Toward the Investigation of the Relationship between Surface Wettability and Surface Structure and Chemical Composition
  Abstract:
  In this paper, we have prepared of a topography/chemical composition gradient polystyrene (PS) surface, i.e., an orthogonal gradient surface, to investigate the relationship between surface wettability and surface structure and chemical composition. The prepared surface shows a one-dimensional gradient in wettability in the x, y, and diagonal directions, including hydrophobic to hydrophilic, superhydrophobic to hydrophobic, superhydrophobic to superhydrophilic gradients, and so forth. These one-dimensional gradients have different gradient values, gradient range, and contact angle hysteresis, which lie on both the surface roughness and the surface compositions. From the trend of variation of contact angle hysteresis, it can be concluded that the transition from
the Cassie’s model to the Wenzel’s model occurs both by decreasing surface roughness and by increasing surface hydrophilic compositions. Moreover, the transition is more effective via changing surface chemical composition than changing surface roughness herein.

- Anchoring of a Nematic Liquid Crystal on a Wettability Gradient
  
  **Abstract:**

  We have studied the anchoring of the nematic liquid crystal 5CB (4’-n-pentyl-4-cyanobiphenyl) as a function of the surface wettability, thickness of the liquid crystal layer, and temperature by measuring the birefringence of a hybrid aligned nematic cell where the nematic material was confined between octadecyltrihexyoxysilane-treated glass surfaces, with one surface linearly varying in its hydrophobicity. A homeotropic-to-tilted anchoring transition was observed as a function of the lateral distance along the hydrophobicity gradient, typically in a region corresponding to a water contact angle of ~64°. The effect of the nematic layer thickness was measured simultaneously by preparing a wedge cell where the thickness varied along the direction perpendicular to the wettability. The detailed behavior of the onset of birefringence was found to be consistent with a dual-easy-axis model that predicts a discontinuous anchoring transition from homeotropic to planar. The anchoring was independent of temperature, except within 1 °C of the nematic-to-isotropic transition temperature ($T_{NI}$). As the temperature approached $T_{NI}$, the tendency for planar anchoring gradually increased relative to that for homeotropic anchoring.

- A Palladium-Catalyzed Approach to Polycyclic Sulfur Heterocycles
  
  **Abstract:**

  The synthesis of a variety of polycyclic thiophenes and benzothiophenes is accomplished via a palladium-catalyzed domino *ortho*-alkylation/direct arylation reaction. An examination of the intramolecular direct arylation of thiophenes suggests that an electrophilic metatation mechanism may be present. This method was further extended to include the synthesis of a (thieno)benzoxepine.

- Broader, Greener, and More Efficient: Recent Advances in Asymmetric Transfer Hydrogenation
  
  **Abstract:**
Asymmetric transfer hydrogenation has become a practically useful tool in reduction chemistry in the last decade or so. This was largely triggered by the seminal work of Noyori and co-workers in the mid-1990s and is driven by its complementing chemistry to hydrogenation employing H\textsubscript{2}. This Focus Review attempts to present a “holistic” overview on the advances in the area, focusing on the achievements recorded around the last three years. These include more-efficient and “greener” metal catalysts, catalysts that enable hydrogenation as well as transfer hydrogenation, biomimetic and organocatalysts, and their applications in the reduction of C\equiv O, C\equiv N, and C\equiv C bonds. Also highlighted are efforts in the development of environmentally benign and reusable catalytic systems.

- **Acid Catalysis in Basic Solution: A Supramolecular Host Promotes Orthoformate Hydrolysis**

  **Abstract:**

  Although many enzymes can promote chemical reactions by tuning substrate properties purely through the electrostatic environment of a docking cavity, this strategy has proven challenging to mimic in synthetic host-guest systems. Here, we report a highly charged, water-soluble, metal-ligand assembly with a hydrophobic interior cavity that thermodynamically stabilizes protonated substrates and consequently catalyzes the normally acidic hydrolysis of orthoformates in basic solution, with rate accelerations of up to 890-fold. The catalysis reaction obeys Michaelis-Menten kinetics and exhibits competitive inhibition, and the substrate scope displays size selectivity, consistent with the constrained binding environment of the molecular host.

- **The Azadirachtin Story**

  **Abstract:**

  Azadirachtin has been the subject of intensive research within the scientific community ever since its isolation from the neem tree in 1968. There are now over 1000 publications relating to this natural
product which cover all aspects of structural, biological and synthetic studies. Herein, we describe the worldwide synthesis efforts towards this fascinating molecule.

- Solid-Supported Synthesis and Biological Evaluation of the Lantibiotic Peptide Bis(desmethyl) Lacticin 3147 A2
  
  Abstract: 
  
  Lan-tastic! A lanthionine analogue of lacticin 3147 A2 (Lan-A2, 2) containing multiple thioether bridges (see picture) has been successfully synthesized by a combination of solid- and solution-phase peptide synthesis. Chemically synthesized Lan-A2 (2) exhibits synergistic biological activity similar to natural lacticin A2 (1) in the presence of natural lacticin A1 against Gram-positive bacteria.

- Multivalent, Saccharide-Functionalized Gold Nanoparticles as Fully Synthetic Analogs of Type A Neisseria meningitidis Antigens
  
  Abstract: 
  
  Antigen analogs of polyclonal antibodies specific for type A Neisseria meningitidis are prepared by covering gold clusters (2-5 nm in size) with a monolayer of saccharides that have the structure of the repeating unit of the capsular polysaccharide of this bacterium. These systems may find use as synthetic antigens for immunostimulation.

- Applications of Nanoparticles in Biology
  
  Abstract:
The wide variety of core materials available, coupled with tunable surface properties, make nanoparticles an excellent platform for a broad range of biological and biomedical applications. This Review provides an introduction to nanoparticle-biomolecular interactions as well as recent applications of nanoparticles in biological sensing, delivery, and imaging of live cells and tissues.