

## GUEST EDITORIAL

### Cross Coupling

The substitution of an aryl, vinyl, or alkyl halide or pseudohalide by a nucleophile that takes place with catalysis by a transition-metal complex is generally referred to as a cross-coupling reaction if it follows the mechanistic course of oxidative addition, transmetalation, and reductive elimination.

While many types of cross-coupling reactions have been known for several decades, advances in recent years have greatly increased their scope and practicality. This progress has had a significant impact on academic research, and cross-coupling reactions are now widely employed in a variety of synthetic venues, from the total synthesis of natural products to the preparation of new materials to bioorganic chemistry. In addition, due to this progress, these reactions are increasingly being applied in industrial settings. This includes a high level of use not only in research but also in the preparation of large samples for clinical trials as well as for manufacturing. A number of industries have been impacted, including those that produce pharmaceuticals, agrochemicals, and polymers. This progress has been greatly facilitated by an increased understanding of the mechanism by which these and related reactions proceed. Furthermore, a tremendous upsurge in the development of new ligands has contributed substantially to the recent advances. Now, these and other transition metal-catalyzed processes are no longer considered out of the ordinary and, instead, have become part of the everyday repertoire of the synthetic chemist.

One common group of these processes utilizes carbon-based nucleophiles, such as aryl, vinyl, or alkyl derivatives of magnesium (Kumada–Corriu), boron (Suzuki–Miyaura), tin (Stille–Migita), zinc (Negishi), or silicon (Hiyama). In another very important cross-coupling process, a terminal alkyne serves as a pronucleophile in the presence (Sonogashira) or absence (Heck alkylation) of a copper cocatalyst. In both sets of cross couplings, the catalysts that are utilized most frequently are palladium-based. Only recently has the electrophilic component of these processes been extended to alkyl halides and pseudohalides. Thus, these substrates can now be coupled with aryl, vinyl, and alkynyl nucleophiles. Moreover, the past few years have seen the development of the coupling of a nucleophile and an electrophile where  $sp^3$ – $sp^3$  carbon–carbon bonds are being formed.

The definition of cross coupling has been broadened to include the combination of aryl and vinyl halides and pseudohalides with heteroatomic nucleophiles. Among the most venerable of all cross-coupling reactions are the Ullmann and Goldberg reactions, in which an amine, amide, or alcohol is coupled with an aryl halide, using a stoichiometric or catalytic quantity of a copper complex. In the past decade or so, a great deal of progress has been made in the area of palladium- and copper-catalyzed carbon–heteroatom bond formation. It is noteworthy that a good deal of progress has been made on the development of “green” cross-coupling reactions. This includes employing, in some instances, catalysts based on first-row transition metals, as well as using water or ionic liquids as the reaction medium.

This special issue has gathered contributions from many of the primary contributors to the development of new or improved cross-coupling methods. It is my hope that these Accounts will lead readers to embark on new research projects that further enhance the utility of such processes in organic chemistry.

**Stephen L. Buchwald**

*Massachusetts Institute of Technology*

*Guest Editor*

AR8001798