Researchers in This Field Still Have Many Challenges in Front of Them, but the Future is Indeed Very Bright

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The cross-coupling reaction is old enough that even I, no longer a young scientist, learned about it in college. Indeed, the problem of coupling sp^2-based carbon nucleophiles and electrophiles was recognized as being important but difficult as long ago as 1941 by Kharasch, who found that coupling reactions of Grignard reagents worked better when traces of transition metals were present in the system.[1]

As it often happens in science, the seeds for the discovery of this exciting modern synthetic tool lay dormant in the fertile soil of the scientific literature until the groups of Kochi,[2] Corriu,[3] and Kumada,[4] among others, realized in 1971–1972 that discrete transition metal catalysts (Ag, Fe, Ni) can be devised to carry out these reactions in good yield and with some generality. Palladium rose to center stage more slowly a few years later, through the work of Murahashi,[5] followed by many others.

But Grignard reagents were not the only organometallic species in the world, and indeed not the most synthetically useful. Negishi and co-workers must be credited with bringing more practical reagents into the menu of the synthetic organic chemist, i.e., Al, Zr and the now very popular Zn derivatives.[6] Indeed, among practitioners, cross-coupling reactions involving organozinc reagents are now referred to as “Negishi couplings”.

In 1968, even before the cross-coupling reaction made it to the forefront of organic synthesis, Richard Heck had brought to light the reaction that now bears his name. His first entry into the field was a stunning series of seven consecutive papers with his name as the only author.[7] The innumerable important observations contained in these early papers and those which soon followed transformed this unusual reaction into a general synthetic method. It has taken the synthetic community many years to realize the immense potential of the Heck reaction, and in the last 20 years countless refinements, extensions (e.g., enantioselective cyclizations), and applications have been reported.

In 1975, Sonogashira found that alkynes could be coupled directly with carbon electrophiles, without preparing first an organometallic reagent, if both a Pd and a Cu catalyst were used in tandem.[8] The Sonogashira coupling is now a very popular synthetic tool in academia as well as in industry.

In the late 1970s, tin derivatives were shown to also undergo Pd-catalyzed coupling with a broad range of electrophiles, mainly through the work of Kosugi and Migita[9] and Stille.[10] These couplings are now referred to as the “Stille reaction”, and constitute an extremely important tool in the discovery of pharmaceuticals, the total synthesis of complex natural products, the synthesis of materials and devices, etc.

It turned out to be more difficult to induce boron to undergo this reaction. I was a graduate student at the University of Alberta when I saw Akira Suzuki lecture for the first time. I was told by the organizers that Prof. Suzuki was going to disclose an important unpublished result. I listened carefully as he told us how he and Norio Miyaura had just found that organoboron compounds, easily available through a variety of synthetic means, can be made to cross-couple through the formation of “ate” complexes. The Suzuki reaction had been born.[11] For us in the pharmaceutical industry, this is now the most practical way to cross-couple aromatics and heteroaromatics, and we have become quite skilled

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at optimizing, developing, and scaling-up these particular cross-couplings.

From the latest arrivals among the organometallic species that have been shown to take part in the cross-coupling chemistry, I must single out silicon. Hiyama and co-workers showed us that, although silanes are quite stable and are not pushed very easily into a cross-coupling, introduction at Si of one or more electronegative substituents (like F) considerably enhances their reactivity, presumably by coordination expansion at Si.[12] The Hiyama reaction is also developing into a very important synthetic tool.

My own interest in this field matured in the early 1990s, from the viewpoint of a user of cross-coupling methodology. My modest contribution consisted in bringing to the tool box some new ligands that accelerated the Stille coupling substantially. After my lecture on this topic at the Gordon Conference on Organic Reactions and Processes in 1991, Paul Knochel came to talk to me and asked me if some of these ligands could be applied to the challenging problem of coupling sp^3-electrophiles using Pd catalysis. We exchanged ideas over a couple of beers. I was somewhat negative about the possibility of coupling primary or secondary halides with an organometallic compound using Pd or Ni. Paul is, however, an optimist. I realized that no argument was going to discourage him: he knew the obstacles, but was undaunted. Indeed, years later, he went on to disclose the first general coupling between organozinc compounds and akyl halides under Ni catalysis.[13] This first version of the coupling was later complemented by Fu's exciting results in the Pd area.[14] Fu introduced us to a new, important paradigm in organopalladium chemistry: the use of bulky phosphines of high donicity. Indeed, their use has allowed a variety of sp^3-sp^3 couplings to take place, and even the activation of aryl chlorides, an important class of electrophiles, is now possible.[15]

Glancing again at my review on the cross-coupling reaction, which was published in 1995,[16] I am struck by the complete absence of a type of reaction that has become another key staple in the toolbox of the synthetic chemist, i.e., the amination of aryl halides. Indeed, in 1983 again Kosugi and Migita had been able to couple stannylamines with unactivated aryl halides in low yields.[17] That was the only example of this reaction recorded in 1995! The huge significance of that short communication had not escaped my attention, but I thought that developing that simple transformation into a broad synthetic tool was going to require an immense amount of work. Indeed, a decade later, the groups of Buchwald and Hartwig had developed the C–N bond-forming reaction into a fantastically general tool, inventing a variety of new powerful ligands in the process.[18]

The same fate struck the arylation of non-stabilized enolates, a reaction that was difficult and capricious and mostly limited to tin enolates. Buchwald and Hartwig (and others), using the appropriate catalysts, have now turned this reaction into a superb synthetic tool.[19]

The brief story I sketched here can only capture what I consider the major highlights of the cross-coupling reaction, and I apologize to those chemists whose work I have not mentioned directly. Indeed, it is impossible to discuss and cite all the wonderful contributions to this exploding field in this brief introduction.

A recent informal survey I made by flipping through the pages of the major drug discovery journals, and classifying the synthetic methods employed, demonstrated without doubt that, of the synthetic methods developed in the last 30 years, cross-coupling reactions (C–C, C–N, C–O) and the Heck reaction are the ***only*** new methodologies that have made a major impact in drug discovery and are widely used.

As a process development chemist, I hardly encounter a process that does not contain a Pd-catalyzed step, or that cannot be simplified by introducing such a step. Indeed, it has been both challenging and fun to help scale these reactions in the pilot plant.

At the more fundamental research level, I have also had my share of fun: I remember fondly my search for new ligands, and the exciting collaborations with Greg Roth on the unraveling of the LiCl effect, and with Lanny Liebeskind, tackling the origin and scope of his now well-known "copper effect".

In spite of the many accomplishments, researchers in this field still have many challenges in front of them, e.g., the development of more robust, high TON catalysts, or the activation of C–H bonds for cross-coupling. As attested to by the quality and diversity of the papers contained in this issue, the future of the Pd-catalyzed coupling reaction is indeed very bright.

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