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Editorial

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Cross-Coupling Reactions

In 1989, OMCOS V[1] took place in Florence and being a major conference featuring new discoveries achieved with organometallic reagents in organic synthesis, it left me with the impression that *all* important transformations could—now or in the future—be performed with the aid of adequately fine-tuned metal catalysts. Today, it is safe to say that those early findings were key discoveries for a conceptional revolution that occurred in organic chemistry in recent years. Metal catalysts can be found everywhere, and many synthetic advances are directly linked to scientific progress and developments in catalytic chemistry.

In those early days, the seminal work by Heck, Negishi, and Suzuki on palladium-catalyzed cross-coupling reactions that led to their Nobel Prize in Chemistry in 2010[2] had already been known. Evidently, it was important for the formation of new carbon−carbon bonds, and the prospective ability of introducing new functional groups—both carbon- and heteroatom-based ones—attracted the attention of a large number of colleagues in academia and industry. Subsequent improvements included, for example, the expansion of the substrate scope, a better functional group tolerance, a deeper mechanistic understanding, and the search for even more environmentally benign processes.

After decades of intensive research, it is true that major progress has been achieved in this scientifically challenging area, and one might wonder if more can be done. The clear answer is "yes", and this joint Virtual Issue in the *Journal of Organic Chemistry*/*Organic Letters* is intended to be part of the illustrated answer. The 22 articles presented here were selected from a large number of contributions related to cross-coupling reactions published in the period of 2010 to early 2012 in the *Journal of Organic Chemistry*, *Organic Letters*, and the *Journal of the American Chemical Society*. These provide evidence of the scope and potential of cross-coupling chemistry and illustrate advances and limitations of this synthetically most significant field.

Aminomethyl groups are important substituents in bioactive natural products and synthetic intermediates. Their introduction can be difficult, and often harsh reaction conditions are needed. **Molander** has found that potassium Boc-protected aminomethyltrifluoroborate can be used as a primary aminomethyl equivalent allowing efficient Suzuki−Miyaura cross-coupling reactions with a variety of aryl and hetaryl chlorides under palladium catalysis.[3] The yields are commonly high, and the functional group tolerance is impressive.

Potassium trifluoroborates have also been used in catalytic reactions by **Ge**, but in this case, the boron reagent carried the aryl group.[4] Under palladium catalysis, a decarboxylative cross-coupling with α-oxocarboxylic acids takes place providing the corresponding aryl ketones in high yields. Impressively, the reaction occurs at room temperature and simple potassium persulfate serves as a stoichiometric oxidant.

Among decarboxylative cross-coupling reactions those starting from aryl and hetaryl carboxylic acids are the most prominent ones. A detailed report on palladium-catalyzed couplings with aryl halides has been provided by **Bilodeau** and **Forgione**.[5] The substrate scope and the effects of various parameters such as solvent, base, and additives on the reaction efficiency have been studied and mechanistic considerations have revealed possible reaction pathways. The fact that this study was conducted at a pharmaceutical company shows the importance of such cross-coupling reactions in the synthesis of new drug candidates.

Many cross-coupling reactions lead to biaryl structures. However, the analogous approach can also be used for the synthesis of substituted olefins. Along those lines, **Barluenga** and **Valdés** described palladium-catalyzed cross-coupling reactions between tosyl hydrazones and aryl nonaflates.[6] The process provides access to di-, tri-, and tetrasubstituted alkenes. The exclusive *E*-stereochemistry in the formation of trisubstituted olefins is remarkable, and the potential of this new catalysis has been demonstrated by the synthesis of sertraline, an important antidepressant.

Recently, very much work has been dedicated to transition-metal-catalyzed functionalizations of (hetero)arenes starting with C−H bond cleavages. They often involve a concerted metalation-deprotonation (CMD) pathway, which needs to be understood to allow the predictions of substrate reactivities and regioselectivities. **Gorelsky** and **Lapointe** performed detailed mechanistic work and analyzed the principles that dictate the activation parameters of the C−H bond cleavage in direct arylations following the CMD mechanism.[7] Palladium-catalyzed cross-couplings with aryl bromides served as experimental tools and the resulting data were compared to those obtained by theoretical means, such as DFT calculations.

Cross-couplings involving two C−H bonds are most challenging, and the development of efficient catalytic protocols is desirable for the preparation of various synthetic targets. **Yu** achieved a major breakthrough along those lines.[8] Using catalytic amounts of palladium acetate in combination with *N*-fluorobenzenesulfonimide (NFSI) as oxidant, a highly *para*-selective direct C−H arylation of monosubstituted arenes affording functionalized biaryls in good yields was developed. With the *ortho*-directing power of the arylamido group, excellent regioselectivities were observed with respect to both coupling partners.

Although the nickel catalysis of various aryl−aryl and aryl−heteroaryl cross-couplings is long established, the high efficiency of palladium catalysts has overshadowed the versatility of nickel catalysts in the preparation of structurally diverse, highly functionalized biaryls. In particular, for transformations of less reactive C−O derived electrophiles, nickel complexes are the catalysts of choice. In that context, **Percec** demonstrated that a Ni(COD)/PCy_3 combination effectively catalyzes cross-couplings of aryl and hetaryl neopentylglycolboronates with aryl and hetaryl mesylates and sulfamates.[9] The reactions proceed at room temperature with a wide range of

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substrates bearing both electron-withdrawing and -donating groups in all possible positions.

For several reactions, it has recently been shown that expensive and potentially toxic palladium catalysts can be substituted by simple copper species. This also holds true for decarboxylative cross-couplings. Along those lines, **Liang**, **Yao**, and **Li** reported copper-catalyzed three-component reactions between carbonyl compounds, amino acids, and alkynes, which can be described as tandem decarboxylation−Csp^3−Csp couplings.[10] In this manner, propargylic amine derivatives are obtained with H_2O and CO_2 being the only byproducts.

Because of the significant effects induced by fluoro-containing substituents, the introduction of such moieties on aryl and hetaryl core structures is of major interest and importance for synthetic organic chemistry. Three contributions related to copper catalysis shall be highlighted here. An oxidative trifluoromethylation of aryl and hetaryl boronic acids and trifluoromethyltrimethylsilane ($TMSCF_3$) as CF_3^- source has been reported by **Buchwald.**[11] Several features of this cross-coupling are noteworthy. For example, under benchtop conditions, dioxygen is the stoichiometric reoxidant. Furthermore, the substrate scope is wide, and various functional groups are tolerated. Finally, the reactions proceed at ambient temperature in a few hours. Shortly before, **Qing** had described essentially the same transformation although under slightly different reaction conditions.[12] Also here, the coupling between boronic acids and $TMSCF_3$ required an equivalent of a copper complex, and in this case the stoichiometric oxidant was silver carbonate and the coupling proceeded at slightly elevated temperatures. Using a cross-coupling/decarboxylation sequence **Amii** prepared difluoromethyl-substituted arenes using copper catalysis.[13] In this case, aryl iodides and α-trialkylsilyl difluoroacetates served as starting materials. As intermediates, 2-arylated difluoroacetates were obtained, which upon base-mediated hydrolysis underwent decarboxylation to provide the desired products in good yields. In light of the relevance of fluoro-substituted compounds as bioactives, it can be foreseen that more catalytic transformations of this type with higher catalyst efficiency will be developed in the near future.

The functionalization of aromatic cores by cross-dehydrogenative coupling (CDC) has recently attracted much attention. Metal catalysts and well-selected oxidants are key for the success in such processes. **Zhang** found that copper catalysis can be used for the selective sp^2 C−H/sp^3 C−H coupling of *N*,*N*-dimethylanilines with heteroarenes.[14] A number of nitrogen-containing heterocycles can also be applied, and although the structures of anilinic partners still appear restricted, the transformation demonstrates new perspectives in oxidative C−H/C−H couplings initiated by simple metal catalysts.

A different strategy was pursued by **Daugulis**,[15] who cross-coupled two (het)arenes using copper catalysis in the presence of iodine. Various substrate combinations were studied and the electronic effects induced by substituents on both coupling partners were elucidated. The reactions are proposed to begin with an iodination of one of the arenes, which provides the coupling partner for a subsequent arylation involving the most acidic C−H group of the second (het)arene.

Gold has emerged as an interesting metal for catalysis some time, but recently, several highly unusual transformations have been discovered. Many of those reactions are initiated by activation of an unsaturated moiety such as an alkynyl or alkenyl group. **Zhang** expanded this approach by developing gold-catalyzed carboaminations, carboalkoxylations, and carbolactonizations of terminal alkenes, which are followed by oxidative cross-couplings with aryl boronic acids.[16] Mechanistic studies suggest the involvement of an Au(I)/Au(III) catalytic cycle and the intermediacy of catalytically generated species with $C(sp^3)$−Au bonds, which are converted into $C(sp^3)$−$C(sp^2)$ bonds by cross-couplings.

The difficulties encountered when trying to identify catalytically active species in given reactions are highlighted in a contribution by **Espinet and Echavarren**, who challenged reports on gold-catalyzed (palladium-free) Sonogashira cross-coupling reactions.[17] After preparative studies with isolated gold complexes and based on mechanistic considerations, the authors conclude that the reported Au-catalyzed Sonogashira reactions "might well proceed thanks to Pd contamination of any of the compounds involved in the reaction ...". Although the last word in this context might not yet be said, it is clearly a stimulating article, which deserves to be highlighted in this joint Virtual Issue.

Rhodium might not be the first metal to be considered when thinking about cross-coupling reactions. However, recent developments and most scientifically stimulating reports should be taken into account; the work by **Chatani** truly belongs to this category.[18] It was demonstrated that, under rhodium catalysis, aryl nitriles could be converted into *trans*-triethylsilyl-substituted styrenes. Thus, conceptionally this transformation is a Mizoroki−Heck type cross-coupling initiated by a highly selective C−C bond cleavage reaction. Mechanistically, it is interesting because it appears to involve various silyl and arylrhodium intermediates.

Applying inexpensive nonprecious metals such as iron in cross-coupling reactions has been a long-standing goal. Recently, significant progress has been made and various iron salts have been identified that can be applied as catalysts for C−C bond formations, addition and substitution reactions, as well as C−H bond activations. A Perspective by **Nakamura** gives an excellent overview on recent findings, also highlighting the importance of in situ generated, low-valent iron species, which are considered to be the catalytically active intermediates in several reactions.[19] A particularly interesting case of iron catalysis was reported by **Nakamura**, who applied a well-defined iron dichloride bisphosphine complex for the stereospecific cross-coupling of alkenylboronates with alkyl halides to give substituted alkenes.[20] Mechanistic studies suggested the intermediacy of alkyl radicals. The observed retention of the olefin geometry was then assumed to be the result of a transmetalation (from boron to iron)/substitution sequence with both steps being stereospecific.

Many transition-metal-catalyzed cross-couplings involve electron-transfer processes, and **Kita** reported that those promoted by hypervalent iodine reagents can be utilized for specific C−H/C−H cross-couplings.[21] In these reactions, perfluorinated phenyliodine bis(trifluororacetate)s (PIFAs) proved particularly useful leading to alkoxylated biaryls with naphthyl/phenyl cores in high yields. In addition, **Zhang** and **Yu** focused on applications of iodine-based reagents in transition-metal-free cross-couplings,[22] but in their study diaryliodonium salts were applied. Various arenes including those containg nitrogen were arylated to provide the corresponding products in moderate to good yields. As intermediates, aryl radicals formed by single-electron-transfer processes (SETs) were assumed.

In the light of the recent advances brought into organic chemistry by organocatalysis, one might wonder about this approach for achieving catalytic cross-coupling reactions. Along those lines, new strategies have recently evolved. One of them has been introduced by **Glorius**, who demonstrated that N-heterocyclic carbenes (NHCs) are capable of catalyzing ketone formations starting from benzaldehydes and activated alkyl halides.[23] Although mechanistic details remain to be elucidated, the authors suggest stepwise or concerted alkylations of the Breslow intermediates obtained by addition of the catalytic nucleophilic carbene onto the aromatic aldehydes. The substrate range is still limited, but conceptionally, this approach represents an interesting synthetic alternative expanding NHC applications in organocatalysis.

That organocatalysis can also lead to biaryls has been demonstrated by **Kwong** and **Lei**, who reported direct C−H arylations of benzene with DMEDA as catalyst.[24] Evidence was provided that these cross-couplings starting from aryl iodides and benzene in the presence of potassium *tert*-butoxide proceeded via aryl radical anions. It remains to be seen if organocatalytic cross-coupling processes of such type really find their way to the synthesis of complex molecules. Stimulating discoveries are they for sure.

The selection of articles included in this joint Virtual Issue in the *Journal of Organic Chemistry*/*Organic Letters* is guided by the wish to illustrate what can be done in cross-coupling chemistry, where the limits are and where future studies are heading. Obviously, very much has already been achieved in this field, which is sometimes described as "mature", but for sure, more can be found, and I am convinced that we all are only at the beginning of a true success story.

Carsten Bolm, Associate Editor,
The Journal of Organic Chemistry

■ ADDITIONAL NOTE

The next joint virtual issue will be edited by *Organic Letters* and will appear late fall 2012.

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