Science of Synthesis: Cross Coupling and Heck-Type Reactions 3, Metal-Catalyzed Heck-Type Reactions and C–C Cross-Coupling via C–H Activation; workbench edition, edited by Mats Larhed, Georg Thieme Verlag: Stuttgart, New York, **2013**, paperback/softback, 892 pp, €259.99, \$298.99, ISBN: 9783131728913

The affectionately prepared historical introduction by L. R. Odell and M. Larhed to Volume 3 of the magnificent *Science of Synthesis* three-volume set is recommended, if not compulsory, reading for the appreciation of the thoughtful organization of this almost 900 page volume. For history-interested chemists, the personal words of Heck in a *SYNLETT* dedicated issue are recommended.¹

'This chapter aims [...] to describe the depth and breadth [...] in making the Heck reaction of alkenes bearing electron-withdrawing groups a cornerstone of the art of C–C bond formation.' Thus begins the introduction of the chapter by C.-M. Andersson and M. Andersson which can rightly receive the added 'since the 1980s' because the cornerstone then to chemists, in teaching and in the lab, was the aldol reaction. This venerable reaction, and there is reason to give it the name *Mizoroki–Heck*, is immediately recognized today in a retrosynthetic sense in arylation of terminal alkenes bearing electron-withdrawing groups. As clearly evident in the selected tabular data sifted from the vast literature, aryl halides and pseudohalides, aroyl chlorides and, more recently, iodonium and diazonium salts serve as electrophiles in standard, oxidative, and industrially applicable Mizoroki–Heck reactions. As use advanced, so did the conditions and ligand/catalyst sources to provide the 'best practice' results so that a very broad scope applies, as defined already by Heck in the seminal paper and quoted by the authors: '... every functional group, except carbon–carbon double and triple bonds and α,β -unsaturated carbonyl compounds, are inert to these reagents' (Scheme 1).

The application of chemoselective Mizoroki–Heck reactions (I over Br) is illustrated in advantageous heterocycle and natural product construction and, vividly, in the kilogram syntheses of several pharmaceutical agents. The expectation of a mixture of E,Z-products in cases of α -substitution, the potential of double β -arylation, reactions linked to other modern methodologies and green, ionic liquid, and microwave aspects are topics, among others, which are addressed (Scheme 2).

The recent advent of flow technology is not denied by provision of an example that, more significantly, instructs regarding an observed leaching process which concurs with the mechanistic interpretation of the heterogeneous Mizoroki–Heck reaction. Very successful hetarylations are tabulated, including interesting multiple hetarylation

Scheme 1 Functional-group tolerance in the Mizoroki–Heck reaction; synthesis of an intermediate for glycocinnaspermicin D (all graphic materials are direct reproductions of the relevant *Science of Synthesis* volumes)

Scheme 2 Three-component coupling involving a benzyne, an aryl halide, and a Heck acceptor

reactions and their consequences. Diazonium salt reactions, discovered only five years after the decisive Heck and Mizoroki papers, are surprisingly widely explored and have advantages because of their aniline origin and their lesser expense in spite of their potential hazard even though fluoroborate salts are used. Minor sections on Mizoroki–Heck couplings of alkenes bearing sulfur and phosphorus groups are near the terminus of this chapter which is rich in well-chosen, not widely known examples. The benchmark reaction, arylation of styrenes, is given the concluding words in which mechanistic comment on rhodium-catalyzed versions of this process are worthy of attention. As opposed to a general observation in the three-volume work, many reactions are gram and not milligram scale, and other scale-up processes are available in cited reviews specific to industrial application.

In the introductory words to the (het)arylmatal and (het)arene reaction chapter, E. W. Werner and M. S. Sigman clearly provide the mechanistic difference between the Mizoroki–Heck [palladium(0)-initiated] and the oxidative Heck [transmetalation of an organometallic

reagent with a palladium(II) species] processes. The discussion concerning the still-contentious rationale for the reversal of migratory insertion to the internal α -carbon of alkenes bearing electron-donating groups is concisely presented for appreciation of the subsequent selected examples (Scheme 3).

Scheme 3 Selectivity of migratory insertion and β -hydride elimination in the Heck reaction

Speculation may abound as to why the synthetic community adopted the conditions for the oxidative Heck procedure only after two decades even though they were available in one of the first Heck publications. Valuable conditions which allow predictable, successful oxidative Heck reactions and the replacement of organostannanes with nontoxic arylsilanols, arylboronic acids and, more intriguingly, arylphosphonic acids are displayed and critically discussed. On the basis of the extensive survey of data, arylboronic acids surface as the reactants of choice. A brief section on the Fujiwara–Moritani coupling reaction (see also the chapter by E. Suna and K. Shubin described below), an oxidative Mizoroki–Heck with unfunctionalized arenes, invites more mechanistic and synthetic study in order to promote greater application. Among practical features in this enjoyably critical review, it is gratifying to note mildly critical statements about yields determined by GC and not by isolation, and unsupported mechanistic proposals.

Understanding mechanistic transition-metal-catalyzed chemistry most likely provided the rationale for testing decarbonylative and decarboxylative Mizoroki–Heck reactions. As reviewed by M. Zhang and W. Su, this area has expanded to include coupling with arenecarboxylates, arenecarboxylic anhydrides, aroylchlorides, and aroylsulfonyl chlorides (Scheme 4).

Scheme 4 Double desulfonylative Heck coupling

Searching for ‘best practice’ results, the reviewers concentrate on the type of catalyst (e.g., rhodium requires a

lower loading than palladium and is operationally simpler), the avoidance of stoichiometric release of salt waste (arenecarboxylic anhydrides), and a reminder that the released toxic and flammable carbon monoxide requires an incineration process. The decarboxylative version, mechanistically better understood, has arguably more franchise for utility in view of the availability of commercial catalogues of copious lists of benzoic acids. The obviously very desirable replacement of the required silver salt oxidant with benzoquinone and dioxygen has been achieved, thus giving this chemistry greater potential, although inconsistent yield profiles are apparent. The use of arenesulfonic acids at the early stages of investigation, may have an advantage because the extrusion of SO_2 occurs at lower temperatures than that of CO_2 . One 20 gram procedure is provided.

As noted by M. Weimar and M. J. Fuchter in the chapter on reactions of nonaromatic halides and sulfonates, the synthesis of 1,3-dienes by the Mizoroki–Heck tactic is at a disadvantageous position with the 2010 Nobelist cross-coupling procedures due to potential regio- and stereoisomer formation problems. (A review which compares these two and other methods of stereoselective 1,3-diene synthesis is encouraged by this reviewer.) A potpourri of results are tabulated, some furnishing high stereoselectivity (original Jeffery conditions), some requiring excessive silver salt, and others in the early stages of promising development (tetradentate phosphine ligands and enol nonafluorobutanesulfonates and alkenylboronate coupling partners). A catalytic Heck coupling of allyl alcohols with acrylates, cited as an alternative to the Tsuji–Trost reaction for the construction of 1,4-dienes, is similarly in need of augmentation.

J. Le Bras and J. Muzart observe, in their coverage of alkenes with allylic substitution and homologues, that the French chemist M. Julia also reported, in 1973, palladium-catalyzed coupling reactions of aryl, benzyl, and styryl halides with alkenes. The chemist reader will immediately note that the quest for selectivity in the coupling of allylic alcohols with RX partners has yet to be achieved in a fully satisfactory manner, as evidenced in the tabular results for reactions with aryl halides and aryl triflates. On the other hand, the coupling of homoallylic alcohols with aryl bromides results in products in which the double bond of the initial product has walked to give the thermodynamically more stable carbonyl terminus (Scheme 5).

Scheme 5 Homoallylic alcohol Heck coupling; the double-bond walk to carbonyl products

The as yet mechanistically uncertain and meagerly investigated coupling of homoallylic alcohols with arylboronic acids provides a synthetically interesting route to 2-aryl tetrahydrofurans. Alternative methods may be suggested to the couplings of allylic esters and carbonates with aryl halides or arylboronic acids in view of the superstoichiometric requirement of silver salts. Dehydrogenative Heck reactions of these derivatives are also as yet unsatisfactory for synthetic practice in view of the requirement of excess of arene partners and formation of mixtures of isomeric products. Reactions of allylic amines and amides appear as yet also inefficient or insufficiently studied for synthetic applications. Tertiary homoallylic and secondary allylic acetates undergo fragmentation of the oxygen-bearing C-substituent to afford allylarene products, reasonably efficient processes which may profit from further study. The invitation (p 198) to compare the former reaction with that described in section 3.1.1.2.1.1.2 presents a somewhat daunting undertaking.

Mizoroki–Heck reactions of electron-rich alkenes (e.g., vinyl ethers), advanced by studies [Hallberg, Cabri, Larhed (Volume 3 Editor)] of choice of coupling partner, ligand, solvent, and additive, now provide α -selective arylations which in turn furnish synthetically useful routes to methyl aryl ketones, hence representing the Friedel–Crafts equivalent acylation processes. As reviewed by S. Liu and J. Xiao, a considerable amount of work has been carried out in ionic liquids demonstrating reactions of high α -selectivity and rate acceleration, sensitive pharmaceutical agents have been modified by vinyl alkyl ether coupling in late stages of the synthesis where Friedel–Crafts protocols would not be tolerated, pyridyl ketones have been prepared which cannot be accessed by Friedel–Crafts chemistry, and efficient reactions have been carried out in water and ethylene glycol, among other interesting illustrated aspects in this chapter. Although with somewhat decreased rates compared to vinyl ethers, enamides undergo α -arylation in a fairly broadly explored reaction to give products that are conventionally available only by several steps (Scheme 6).

Scheme 6 Heck vinylation of enamides

β -Selective arylations to give aryl acetaldehyde precursors are available but appear to be less developed and used. The above highlights of this chapter are intended to point to areas of synthetic value for the non-expert; such a terminal commentary would have been welcome from the expert authors.

Oxidative Heck reactions with arylboronic acids and aryl halides with electron-rich alkenes constitute a short chapter by J. Lindh and M. Larhed, topics to which the Larhed laboratories have contributed considerably. A mechanistic preamble, substantiated in part by ESI–MS and MS–MS studies, shows rationalization of product regioselectivity in oxidative Heck and Mizoroki–Heck reactions by ligand control. Of significant convenience and value would have been a single-table comparison of the synthetic utility based on yields for the same product (e.g., 1,4-diacetylbenzene) for ArBr + vinyl ether (p 220, 91% yield, ionic liquid), ArBr + enamide (p 245, 85% yield of enamide product), ArB(OH)₂ + enamide (p 272, 96% yield, microwave), and ArB(OH)₂ + vinyl ether (p 275, 38% yield, base-free, microwave). In these particular cases, undoubtedly, cost and availability of starting vinyl ethers and enamides would also be a significant factor. Some repetitive information in the S. Liu and J. Xiao and J. Lindh and M. Larhed chapters is noted but is inconsequential [Scheme 41 (pp 255 and 256), and Schemes 14, 15 (pp 277 and 278)]. An initial test of flow conditions for the oxidative Heck reaction is available (Scheme 7).

Scheme 7 Continuous-flow Heck reaction

The equally short chapter on reactions with non-aromatic alkenyl halides and alkenyl sulfonates by P. Nilsson instructs us that these reactions are less widely known presumably because of greater sensitivity to stereochemical control, propensity to homocoupling and reduction, and, perhaps, simply insufficient use of the products. Additional facts to note are competition from standard cross-coupling reactions, for example Suzuki–Miyaura, and complementarity with Wittig protocols. The simple substrates tested to date do not suggest new advantageous synthetic utility, except perhaps the direct coupling–protection route to α,β -unsaturated acetals.

Cyclic alkene Heck coupling leading to an aryl- or alkyl-substituted product is presented by V. Coeffard and P. J. Guiry. From the 40 page coverage, it is clear that the development of efficient processes to avoid the inherently present problems of regio- and stereoisomeric mixtures and to achieve highly enantioselective reactions, especially by new ligand design, is at the forefront and early stages of activity in this area. Features emerging upon survey of this chapter include the fine-tuning of conditions and ligands that are necessary to obtain better than good selectivity in the isomer ratios of products, the utility of reactions of dihydrofurans where complete double-bond migration around the ring or its suppression may be

achieved, and the extension of such chemistry to other five- and six-membered-ring heterocycles (Scheme 8).

Scheme 8 Asymmetric intermolecular Heck reaction

To introduce the subject of asymmetric intermolecular Mizoroki–Heck reactions, a concise treatment of the neutral and cationic mechanistic paths is given which allows rationalization of the expected enantio-induction before proceeding into practical topics, including superiority of P,N-chiral ligands, the influential significance of axial chirality in certain ligand design, the favorable effects of microwave irradiation, and the predominance of studies on enol ether containing cyclic alkenes, for example dihydrofurans. A welcome concluding paragraph reinforces the second sentence above in the commentary to this chapter.

A. Trejos and L. R. Odell address chelation-control reactions by metal coordination, a historically prevailing guiding concept in organic chemistry, as applied to the Mizoroki–Heck reaction of alkenes. Noted is the application of chelation assistance in directed *ortho* metalation (DoM) processes which has noteworthy impact in academic and industrial organic synthesis via linking DoM to Suzuki–Miyaura and related cross-coupling reactions.² Parenthetically, the potential of a DoM–Mizoroki–Heck link has not been widely evaluated. As demonstrated by the data in several tables, a particular strong influence of chelation control is evident in achievement of highly β -selective product formation of electron-rich alkenes bearing two-carbon amine tethers with aryl halides, triflates, and boronic acids. The concept may be transmitted with excellent success to asymmetric β -arylation and -vinylation to afford systems exhibiting quaternary carbons (Scheme 9).

Scheme 9 Amine chelation-controlled enantioselective Heck coupling

As evidenced by substantial data, impressive results are also observed in the β -selective arylation and vinylation of 2-pyridyl vinyl silanes, the pyridyl group acting to direct the catalyst, to enhance reactivity, and, after reaction, to provide ease of purification by acid–base extraction. Unexplored, or at least unmentioned, is the fluoride-mediated reaction of the products to form unsaturated silynols or their derivatives. Asymmetric arylation under chiral sulfoxide control appears to be a promising but not yet adequately investigated reaction. Allylic alcohols also serve, not unexpectedly, as chelation directors for aryl and vinyl halide or triflate couplings to afford γ -substituted products with modest to excellent selectivity. Although apparently in early stages of study is the arylation of allyl acetates, where products clearly indicate, by the *meta* and *ortho/para* selectivity depending on the presence of electron-withdrawing or -donating groups respectively, that the reaction proceeds by an S_NAr and not C–H activation mechanism.

In the not-undaunting task of summarizing the vast literature, K. Georghegan and P. Evans take on the intramolecular Mizoroki–Heck reaction for the formation of carbocycles by an initial mechanistic analysis which guides the prediction and appreciation of the well-chosen examples subsequently provided. Following the Baldwin rules classification, the examples provide a smorgasbord of studies which invite a brief taste or a massive feast for learning, application, and conceptual extension. Furthermore, Georghegan and Evans make the effort to analyze the results, answering questions which are in the minds of the readers: Why was it successful? Why is it retrosynthetically valuable or unusual? What is mechanistically as expected or which alternative process has not been considered? The following cases, providing a glimpse of the rich results contained within this chapter, are fully understandable in the language of organic chemists – structural. Case 1: A cyclopentadiene, derived by acid-mediated hydrolysis from a Fischer carbene intermediate, leads to a bicyclic ketone by a 5-*exo*-trig intramolecular reaction which is 'a useful starting point for investigation of new intramolecular Mizoroki–Heck reactions'. What does this tell the alert chemist? That basic groups are tolerated, of course but that he/she really should look up the origin of the starting cyclopentadiene. Case 2: An inseparable mixture of isomeric tricycles, resulting from an intramolecular reaction of a seemingly easy to prepare aryl triflate teaches that reversible hydridopalladation proceeds via a rotationally free π -complex and the mixture problem can be solved by 'screening a range of bases and additives, especially silver salts'. Case 3: An intramolecular allylic alcohol–aryl bromide coupling proceeds unexceptionally via a 6-*exo*-trig cyclization mode; change the location and identity (to aryl triflate) in a somewhat different starting material and modify the recipe (to avoid decomposition) and the result is a mixture of 6-*exo* and 7-*endo* products. Case 4: An undoubtedly satisfying case for the chemists involved is the 240 gram reaction to give a tricyclic indole derivative (Scheme 10).

quaternary carbon centers. G. Broggini, E. Borsini, and U. Piarulli take up the task of reviewing this area with dedication by first defining the mechanistic features required for the occurrence of such reactions and advising general aspects of precatalyst, ligand, base, additive, and solvent needed in recipe consideration. Initial division into tertiary and quaternary stereocenters is followed by useful subdivisions according to acyclic/cyclic alkenes, nature of the 'leaving group' of aryl or vinyl reagents, and control of stereogenicity by prochiral and chiral ligand or by substrate-contained chirality. In the 60-page exposition, turning pages (*comme dans les temps anciens* in the library) reveals examples of isolated, fused, bridged, and spiroannulated rings of various sizes in simple and highly complex frameworks from which the following are randomly chosen together with hopefully useful commentary. Although the Baldwin rules terminology is not widely used in this chapter, 6-*exo* cyclizations are common behavior but 6-*endo*- and 5-*endo* modes are also not to be denied. The fairly widely appreciated fact that Heck reactions are industrially popular is noted and experimentally provided by one 18 kilogram run (nicotine receptor probe). Growing up with morphine and lysergic acid skeleta, among others, taught in natural product courses easily leads to retrosynthetic recognition of key tertiary centers to be constructed by intramolecular Heck reactions, and, as is evident, they now have been demonstrated several times. Similarly, consecutive Heck reactions for steroids, Heck followed by nucleophilic traps, and enantioselective *cis*-hydronaphthalene synthesis setting the stage for the key construct for vernolepin are exemplified cases of tertiary center formation processes. Oxindoles stand out as the most successful substrates for the installation of C-3 quaternary stereocenters in both acyclic and cyclic alkene series. Among the cases illustrated are: a proof-of-principle chirality transfer in an axially chiral arylacrylamide, a stunning double asymmetric Heck for the synthesis of the alkaloid quadrigemine C, and consecutive (or, if you prefer, domino³) Heck steps in the equally impressive construction of a halenaquinone natural product. What have we learned from this carefully constructed review? Many complex natural products, in particular indole alkaloids, have fallen to the intramolecular Heck reaction, functional group tolerance is close to spectacular, and ligand/leaving group choices are crucial in determining the outcome with respect to ring size, isomer distribution, enantioselectivity, and yield. Perhaps redundant to state is that imagination is the limiting factor in developing new Heck construction modes (Schemes 14 and 15).

With the welcome statement '... a systematic guide to the experimental procedures for C–H arylation, as presented here, is warranted,' we enter the chapter on C–C cross-coupling via C–H activation by A. Kantak and B. DeBoef and non-Heck territory although, as delineated, initial mechanistic speculation in this area involved, not surprisingly, Heck-type intermediates. While the mechanistic picture appears still to be uncertain (especially in copper-

Scheme 14 Intramolecular Heck reaction en route to ecteinascidin

Scheme 15 Double asymmetric Heck reaction

Scheme 16 Intermolecular *meta* arylation using diaryliodonium salts

catalyzed *meta* and *para* arylations, Scheme 16), the encompassing term Heck-type metalation is used.

With seminal leadership by S. Murai and his students, in particular N. Chatani and F. Kakiuchi, as well as D. Sames, the concept of heteroatom-containing directing groups (DGs) of aromatics for *ortho* C–H activation events has opened a new arena for synthetic chemists. In this review of intermolecular coupling via C(sp²)–H activation, selected examples of *ortho* arylation of DG = ketone, benzylic amine, imine, oxime, phenolic OH (reversibly incorporated into phosphite ligand), carboxylic acid, and 2-pyridyl (arguably the favorite) systems under palladium, ruthenium, iron- and rhodium-catalyzed conditions with or without additional oxidants are depicted, although, in view of the different DGs, comparison among them for potential use in synthesis is not easy to establish at this time with the possible exception of imine and ketone DGs. As may be expected from their position as

prevalent heterocycles in biologically active molecules, indoles have received the most thorough study under palladium-, rhodium- and copper-catalytic conditions and, although successful, high temperatures (exceptions are aryboronic acids and arylsilanes), superstoichiometric silver salts, and waste (iodonium salts) require amelioration. The retraction of some of the published results in the indole C–H activation–arylation area appears not to have been addressed. Among the conventional π -excessive systems, indolizine, pyrrole, furan, benzofuran, thiophene, benzothiophene, and pyrazoles are exemplified; among the π -deficient, pyridine and their *N*-oxides have some mention. These and other more bizarre heterocycles have received meager attention. Throughout these given examples, modest yields, non-ambient temperature conditions, and test of only the prototype, unfunctionalized cases prevail and therefore invite further investigation.

E. Suna and K. Shubin from Latvia, a Baltic state, engage the difficult topic of intramolecular coupling via C(sp²)–H activation by carefully defining the scope and limitations of coverage. Thus, herein the interested reader will find reactions involving formation of C–C bonds between a non-functionalized C-atom of an (hetero)aryl compound and a carbon that is part of a multiple bond or a carbon connected to a leaving group. Rather late in recognition by this reviewer is the fact that careful reading of the general introductions of all chapters is a must for the chemist before search for specific examples to take to the lab. The Fujiwara–Moritani annulation (or oxidative Heck-type) reaction, touched upon in the chapter by E. W. Werner and M. S. Sigman above, receives considerable coverage for the formation of five-, six-, and eight-membered rings (not necessarily in harmony with Baldwin's rules) especially for indole and pyrrole C–H coupling partners. Conditions are carefully analyzed for the cases given, with emphasis on ligand types and catalyst/ligand ratio. Yields are modest in general, some unusual heterocycles (e.g., thienopyrroles) are available, the requirement for stoichiometric palladium is noted (including a pyrrole annulation case in gram quantities), and conditions for enantio-induction appear to be at an early stage of development. Next is the coverage of rhodium- and ruthenium-catalyzed intramolecular hydroarylations which proceed via hetero functional group driven chelation and may be, according to the given mechanism, better named as C–H activation or insertion reactions. These are also most prevalent in the indole series, although some benzimidazoles and dihydrobenzofuran (and their pyrido analogues) have surfaced. The reactions also appear to be in early stages of evolution and suffer from the requirement of more than catalytic amounts of silver salts. Similar heteroatom chelation-driven annulation reactions of ketones by iridium catalysis, essentially a Friedel–Crafts complement, have limited data but, based on the single table of results, are high-yielding processes (including an unforgivably described 100% yield). Alkyne additions into aromatic and heteroaromatic C–H bonds appear to have already considerable scope for the synthesis of fluorenes,

3-ylidene oxindoles, and indanones, the latter under rhodium and not palladium catalysis. For indanones, the retention of a 3-TMS substituent in the product begs further chemistry. In the following section dealing with C–X (X = halogen, OTf) couplings, an important table (p 676) appears, to the immense credit of Suna and Shubin. This table surveys the seven key variables that influence the outcome of such reactions and concludes that all variables are 'critical' to the success of optimization studies. Organic synthesis *is* an experimental science. Flipping through pages for the construction of dibenzofurans, carbazoles, and various more usual systems leads naturally to the synthetic practitioner's question 'How else would you make this molecule?' with the ready answer 'not easily' or 'with many more steps'. Another observation is that our retrosynthetic analysis hat requires re-adjustment from the modern cross-coupling transformations (Suzuki–Miyaura, Migita–Stille, Negishi, Hiyama) in which two groups (one in each partner, metal and leaving group) are required for the formation of a C–C bond to a single group which, of course, transforms the analysis into a much simpler single substituent precursor. A caveat is that the regioselectivity of the cyclization event may not be easily predicted, as evidenced by the tabular data. A not as yet widely recognized reaction, intramolecular C–C bond formation between an aryl C–H and alkyl chloride, for example from chloroacetylanilides to oxindoles and chloromethylbiphenyls to fluorenes appears primed for further application to the construction of polycondensed aromatics (Scheme 17).

Scheme 17 Palladium-catalyzed double C–H activation–cyclization to a polycyclic aromatic molecule

Since the time that the C(sp³)–H activation process was pronounced 'the Holy Grail in chemistry', we have journeyed far. Although early work was purely curiosity-driven without hyperbole, recent times have increasingly witnessed papers and grant proposals in which the terms 'atom-economical, cost-effective, and environmentally friendly' have become the standard, almost cliché, language. D. Kalyani and L. V. Desai undertake the subject of palladium-catalyzed coupling via C(sp³)–H activation by defining the difficulties (absence of π -electrons in alkyl C–H substrates for catalyst coordination, propensity for β -hydride elimination) and then demonstrate, via five sections of reactivity type, the very early state of synthetic methodological and application development of this field. For each section, a mechanistic scheme, postulated or supported to various degrees, is available to assist the reader

to think in non-traditional retrosynthetic terms. For example, in the discussion of palladium(0)/(II)-catalyzed intramolecular arylation, a prefunctionalized aryl halide undergoes oxidative addition and snaps into a non-activated *ortho* side-chain C(sp³)-H bond to form functionalized benzocyclobutenes in reasonable yields. Other examples (dihydrobenzofurans, indolines, indanes, and more unusual cases) quickly lead to the conclusion that this reaction may be the most effective approach to at least the benzocyclobutene-type molecules (e.g., compared to benzyne reactions). An amazing multiple C-H activation reaction leading to a dibenzopyran discovered in 1992, which reinforces the need for the non-traditional retrosynthetic thinking (as does the Catellani reaction), is mentioned presumably to stimulate a revisit and further investigation (Scheme 18).

Scheme 18 Multiple C-H activation, oxidative addition, and reductive elimination to a dibenzopyran: a mechanistic conundrum

For intermolecular arylation according to the palladium(0)/(II)-catalytic manifold, the initial results, only six to seven years old, show a critical requirement of highly electron-deficient aryls on the chelating group (e.g., amide) or special functionality (*N*-oxide) to promote the reaction in even modest yields. Expectedly, the ultimate goal in C(sp³)-H bond activation, to achieve unfunctionalized arylation, is shown by two cases studies and is clearly primed for future research (Scheme 19).

Scheme 19 Palladium-catalyzed C-H activation/C-C bond formation in bioactive molecule synthesis

Similarly, C(sp³)-H activation followed by carbonylation or alkenylation leading to simple lactams appears to be a scantily explored approach. Perhaps the reason is that the palladium(II)/(IV)-catalytic cycles are not yet fully mechanistically understood. C(sp³)-C(sp³) bond formation by C(sp³)-H activation appears, according to Kalyani and

Desai, to have not yet overcome undesired and dominating homocoupling and β -hydride reductive elimination reactions. The first reports on the allylic C-H alkylation of β -dicarbonyl systems, proceeding via π -allyl-palladium species, and therefore reminding us of the well-known Tsuji-Trost reaction, and giving modest yields of linear/branched mixtures of products, are reviewed with the concluding statement 'Despite the potential synthetic utility of enantioselective C-H functionalizations, their development has been extremely slow.' which requires little further comment. Similarly, a four-page discussion on applications of C(sp³)-H activation/C-C coupling reactions (one on scale) prior to the closing summary and future outlook reinforces the theme this reviewer has attempted to emphasize: C-H activation reactions dramatically change our traditional retrosynthetic thinking by pointing to unprecedented disconnections, and their mechanistic understanding will assist in formulating the currently known and future discovered transformations.

With the last chapter, cross coupling by double C-H activation by C. S. Yeung, N. Borduas, and V. M. Dong, we are appropriately placed at the pinnacle of the perfect C-C bond-forming reaction, where neither coupling partner is preactivated or prefunctionalized. Significant advantages of such processes, all of recent 2007 vintage, are evident, including use of simpler starting materials and absence of stoichiometric quantities of waste products; on the other hand, since overall loss of H₂ is involved, a sacrificial oxidant is required for the regeneration of the palladium(II) catalyst. From the chosen examples given, it may be surmised that this reaction has a long road to travel in order to achieve results that can be attained by the traditional (both substrates prefunctionalized) cross-coupling procedures. Intermolecular double C-H activation processes are limited to various combinations of aryl and hetaryl partners. Bringing together bare, nonchelating-group-containing (het)aryl starting materials involves, besides careful control of conditions including, it appears, the acidity of the reaction medium, avoiding homocoupling by using large excess (e.g., up to 100 equivalents of the carcinogen benzene) of the less expensive coupling partner. With limited mechanistic evidence being available, empirical data is depended upon (p 786) to predict successful reaction for certain heterocycles. The tabulated data for a variety of heterocycles (indoles, pyrroles, benzofurans, xanthenes) in a sea of simple aromatic substrates shows the requirement for silver salts in excess, poorly understood regioselectivity results, and modest and variable yields of products. The requirement for pivalic acid in many of these processes is rationalized by its 'role in promoting C-H activation by a concerted metalation-deprotonation mechanism' and provision (with AgOAc) of 'a suitable buffer for promoting the desired cross coupling over acid-mediated decomposition', statements which have not, to the best of this reviewer's knowledge, been proved. Some results, exemplified by C-2 benzimidazole-thiazole coupling, carried out with only a modest excess of one of the coupling partners, are

of obvious unique synthetic advantage. The recognition that a change from a π -deficient heterocycle to its corresponding *N*-oxide will prevent palladium catalyst binding and therefore not affect catalyst turnover has shown encouraging results for pyridine and pyrazine and in selected natural product syntheses. More promising results are observed for the double C–H activation of systems that incorporate DGs which, by Lewis basicity, enhance regio- and chemoselectivity and improve reactivity. To date, such groups are limited (p 797), provide uneven yields of products, and are mostly encumbered by the inability to excise the DG for further synthetic transformations. In certain structural types (e.g., pivaloyl anilides and the *N*-methoxy benzamides), the formation of the corresponding biaryl products constitutes initial results which promise at least complementarity of these reactions to the established directed *ortho* metalation/Suzuki–Miyaura cross-coupling strategy.² Intramolecular double C–H activation processes involve heteroatom-tethered biaryls and therefore, of course, avoid the issue of excess of one of the partners. These have been demonstrated to robust extents for carbazoles, dibenzofurans, phenanthridinones, and more unusual heterocyclic systems. Larger-ring annulations are still rarities in the double C–H activation regimen (Scheme 20).

Commendable in this chapter is the provision of noteworthy comparisons of the covered methodology with classical (e.g., Borsche–Dreschel and Graebe–Ullmann) approaches, an aspect which should be mentioned by all chemists who write papers on new, general, less limited in scope, robust milder, more efficient, and environmentally friendly methodology developments in their laboratories.

Scheme 20 Macrocyclization synthesis by palladium-catalyzed double C–H activation

In a future issue of SYNTHEsis, a sampling of comments on e-SoS 4.0 from students and postdocs in my research group will be reported.

- (1) Heck, R. F. *Synlett* **2006**, 2855.
- (2) (a) Board, J. C.; Rantanen, T.; Singh, S. P.; Snieckus V. *Platinum Metals Rev.* **2013**, 57, 234. (b) Snieckus, V.; Anctil, E. J. G. In *Metal-Catalyzed Cross-Coupling Reactions and More, Vol. 3*; de Meijere, A.; Bräse, S.; Oestreich, M. Eds, Wiley-VCH: Weinheim, **2014**, 1067–1134.
- (3) Fuhrhop, J.-H.; Li, G. *Organic Synthesis*, 3rd ed.; Wiley-VCH: Weinheim, **2003**, 468.
- (4) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, 28, 154.

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