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 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.

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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 desulfinylative Heck coupling

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 nonfluorobutanesulfonates and alkylboronate 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 Homoolylic alcohol Heck coupling; the double-bond walk to carbonyl products
The as yet mechanistically uncertain and meagerly investigated coupling of homoallylic alcohols with aryloboronic 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 arliboronic 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 3.1.2.1.1.2 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 aroylations 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).

β-Selective arylation 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 aryloboronic 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 + enamine (p 245, 85% yield of enamine product), ArB(OH)₂ + enamine (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 enamines 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).

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 acetal.

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).

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 dihydronfurans. 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 metatation (DoM) processes which has noteworthy impact in academic and industrial organic synthesis via linking DoM to Suzuki–Miyaura and related cross-coupling reactions. 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
Case 5: The failure in the construction of a spiro nicotine analogue involving the cyclization of a pyridyl triflate–enamide tether combination using a set of standard palladium catalysts, several ligands and bases, and different temperatures; the eventual uncovering of the right ligand produced the desired result, albeit in moderate yield (still affected by proton–OTf exchange) (Scheme 11).

The appreciated lesson of our experimental science – ‘screen, screen, screen’ – is learned again. Case 6: Disfavored endo cyclization, which occurs by a carbopalladation step at long C–C-bond distance within the coordination sphere of palladium, may violate Baldwin’s rules, and in fact proceeds by a 5-exo-trig/3-exo-trig process although this process is furtive in the structure of the observed endo-cyclization product. This reviewer resists describing other remarkable cases (Matsuda–Heck reaction, C–H activations which are truly SNAr-based reactions, and Catellani norbornene relay processes among others) with apologies to the authors and invitation to read this chapter thoroughly.

Similarly daunting to the above review is the mission of covering the literature on the intramolecular Mizoroki–Heck reaction for the formation of heterocycles which is undertaken by S. G. Stewart. It bears the additional burden of choice since the derived heterocycles, especially the indoles, are very common natural product cores and biologically interesting systems. In considering mechanistic aspects of these reactions, the chemist reader visualizes the common steric, electronic, and entropic factors, and the geometry for ring closure according to Baldwin’s rules, whether they are followed or not. In the indole section, both simple and complex aromatic ring heteroannulation methods are presented with highlights, randomly chosen by Stewart, enamine Heck coupling (Scheme 12), a substantial number of ‘disallowed’ 5-exo-trig cyclizations, and acetylenic hydroamination routes. A substantial number of tables also represent indoline, oxindole, and much less, isoidoline construction modes which include domino Heck–anion capture of propanylanilines and a double Heck process (Scheme 13).

Pyrrolidines, both simple and fused systems, pyroles, and imidazoles are represented. In 6-exo-cyclization paths to isoquinoline and quinoline derivatives at two different oxidation states, significantly lower yields that the 5-exo reactions and double bond isomeric mixtures are complicating factors in attempts to attain clean results. Multi-component and complex indole alkaloid skeleton-forming reactions are notable inclusions. Usually difficult to access by classical chemistry (e.g., Friedel–Crafts reaction), azepines, azocines, and larger ring annihilations to aromatic rings by Heck reactions have witnessed substantial success and may become the method of choice. Hence, 7-exo and 8-exo modes of ring formation, including an oxidative Heck process, appear to be reliably achievable. In this chapter, an efficient Tsuji–Trost/Heck domino reaction may elicit special interest, although mechanistic evidence for most of these reactions is not available. Heteroannulation to form furans and pyrans and their respective sulfur series appear to be less investigated. Surprisingly, no large-scale experimental descriptions are noted. Finally, I italicize here domino and cascade in order to liven the debate regarding the meaning and usefulness of these terms, as well as tandem.3

Circa mid-1990s, chemists began to recognize the surprising facility with which the Heck reaction provides access to sterically congested systems, especially tertiary and
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 skeletons, 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 alkenes 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 quagridegame C, and consecutive (or, if you prefer, domino) Heck steps in the equally impressive construction of a halaquinone 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-catalyzed meta and para arylation, 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...
prevailing 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(sp3)–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 annihilation case in gram quantities), and conditions for enantioinduction 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, acylyzed intramolecular hydroarylations which proceed via 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 unfor-}

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).

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).

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 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, pyroles, 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 \( \pi \)-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 regional 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 annihilations 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.

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.


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