Science of Synthesis: Cross Coupling and Heck-Type Reactions, Vols. 1–3; edited by Gary A. Molander, John P. Wolfe, Mats Larhed; Georg Thieme Verlag: Stuttgart, New York, **2013**, paperback/softback, 2606 pp, €649.00, $899.00, ISBN: 9783131734112

Preamble

I leaped at the opportunity to review these volumes because (a) they represent the premier recipe compendia of the most important cross-coupling reactions in organic synthesis of the last half-century and (b) they would instantly receive first-shelf, center display in our laboratories[1] for student browsing and immediate transfer to the bench. With the recognition that the word *browsing* has lost one of its original meanings ('to look through in a leisurely manner in the hope of finding something of interest'), a student of my generation would have sung, or attempted to sing, Georg Friedrich Händel's Hallelujah chorus on receipt of this three-volume, 2606 page (not counting indices) work.

First, the organic chemical community is deeply indebted to Gary Molander, John Wolfe, and Mats Larhed, all at the forefront of and knowledgeable in the subject matter, for their skill to herd together almost 100 authors in various areas of transition-metal-catalyzed cross-coupling and Heck-type[2] reaction activities to provide us with definitive, critical, state-of-the-art, and opportune reviews. As expressed by the volume editors, the foremost gratitude is, of course, to the authors for gathering, sifting, eliminating and finally choosing the material for inclusion from the vast and persistently unmanageable literature. As also expressed by the editors, well-deserved praise is due to Fiona Shortt de Hernandez and the meticulous *Science of Synthesis* associate editors and editorial team for shepherding this series into its conclusive corral.

On scanning the introductions by the volume editors and the introductory paragraphs of a few of the separate chapters, I came to the conclusion that this colossal *oeuvre* deserved more than pick-and-choose, random reading and commentary for the following reasons: (a) the authors deserved better treatment; (b) an appreciation and extraordinary knowledge of the complete field of cross-coupling and Heck chemistry would be acquired; and (c) perhaps of additional personal significance, an opportunity presented itself to think conceptually of *la nouvelle chimie* in context of retrosynthetic analysis, and therefore modernize teaching. Therefore, I turned the pages of the three volumes (i.e., browsed, in the traditional sense) and advise this now primeval technique to all – at least in part – as the reward is a richer knowledge base of this immense field. I also answered the (at least to me) significant questions, which should be asked about reviews, especially for *Science of Synthesis*: What is the coverage? How thorough is, of course, presumptuous to ask of experts. Does

it have a user-friendly organizational structure? What are some unique, unusual features? Is there an impression that the examples, whether methodological or in context of total synthesis of biologically active or natural product molecules, are well chosen? How is the writing? Importantly, can the chosen experimental procedures be taken by a reasonably competent student or professional chemist to the bench for direct execution? Are the searches, both paper and electronic, straightforward and convenient?

What is very useful to read? Start with the introductions of the volume editors who set the stage with useful 'snapshots' of all chapters. They justifiably present the key discoveries, set in historical context, with references which should be cited by all who write papers in the cross-coupling areas. Mats Larhed very appropriately gives homage to the history of Heck, the chemist and Heck, the reaction! The abstracts of all chapters provided at the beginning of each volume are also useful but a *must*-read are the concise, one- or two-paragraph introductions of each chapter. Although in these introductions mechanistic discussion and schemes are always presented to the best of the knowledge and perhaps with some uncertainty, there is no consistent organization of the contents of the chapters, as expected by the very nature of the diversity of the topics. Thus, to highlight a selected organizational format: the nature of the alkene → nature of the electrophile → carbocycles, heterocycles, and type of stereocenter; single C–H activation sp^2, sp^3 → double C–H activation is very individual and not followed in other chapters.

What does one learn in overview? Although the birth of this transition-metal chemistry in the early 1970s is cited, literature coverage before 2000 is minimum, not surprisingly since the floodgates broke open only in the late 1990s, and undoubtedly there was a determined wish (almost a necessity) of the group of 100 to follow the 'best practices' approach. The patent literature is unevenly covered, evidently based on the familiarity of the authors; certainly for the same reason, scale syntheses are exemplified to a higher degree in the chapters of industrial chemist authors. Nevertheless, numerous citations to *Org. Process Res. Dev.* throughout the volumes give an awareness of industrial application.[3] A relatively small number of references are to medicinal, bioorganic, and green chemistry journals; hence, as expected, the synthesis of labeled compounds are not exemplified (but must be known). Commendable of the obviously well-disciplined authors (and editors), there is little overlap of reactions – and where overlap exists, there is justification, for example in the several kinds of C–N couplings. Focusing on any chosen examples discussed, there are associated equations, schemes, and tables with clear, simply relayed information, and the very amiable feature to avoid short-range memory loss – the appearance of the text and the graphic on the same page. As is well recognized by chemists

working in cross-coupling areas, ligands are the key to unlocking clean, high-yielding reactions. In many chapters, they are provided in both structural and acronym form, which is duplicated in a comprehensive list at the end of the volume. However, to single out a superb general feature that is repeated in the individual reviews to follow, we feel that the authors of the volumes are standing behind us at our desk or bench with data that has been thoroughly experienced or researched, giving us the benefit of advice on which set of conditions and, more significantly, which ligand to choose first. They offer practical tips and other unknown gems of information that had heretofore been hidden in the literature or existed only in their own crania.

Negatives? I found only two mistakes (Volume 3, pages 255 and 428) and I cannot find the full names and affiliations of the 96 authors and volume editors.

At the risk of blasphemy, the *Science of Synthesis* compendia represent the King James Version of the Bible or, to paraphrase for our science, the most influential version of the most influential book in the practice of chemical synthesis, in what is now its most influential language.[4] The three-volume distinguished work *Cross Coupling and Heck-type Reactions,* appearing at a moment in time of the evolution of synthetic organic chemistry which represents still the maiden voyages of the various reactions (as many of the contributing authors have noted), will provide cold daylight recognition of their roots, guide their reproduction, extension, or application in practice, and chart their future routes.

I hope that, in what follows, you will agree, in contrast to the excessive trend in the primary research literature today, that all forms of hyperbole for these distinguished contributions are defensible. I hope that my less than concise review of Volume 1 will act as a catalyst to encourage reading those for Volumes 2 and 3 which will follow in the next sequential issues of SYNTHESIS.

References and Notes

(1) Together with commodity chemical catalogues as the only other books on the current student bookshelf.

(2) Although the result would complicate the present title of the volumes, to include the Heck reaction in the cross-coupling terminology may be worthy of debate.

(3) The continuing torrent waterfalls of the various fields of cross-coupling chemistry are evident by listening and viewing the periodical scientific update webinars at http://scientificupdate.co.uk/webinars/scheduled-workshops.html and reading specialist reviews in commercial journals. For examples, see: (a) Bruno, N. C.; Buchwald, S. L. *The Strem Chemiker* **2014**, *XXVII*, 1. (b) Board, J. C.; Cosman, J. L.; Rantanen T., Singh, S. P.: Snieckus V. *Platinum Metals Rev.* **2013**, *57*, 234.

(4) http://en.wikipedia.org/wiki/King_James_Version

Science of Synthesis: Cross Coupling and Heck-Type Reactions 1, C–C Cross Coupling Using Organometallic Partners; workbench edition, edited by Gary A. Molander, Georg Thieme Verlag: Stuttgart, New York, **2013**, paperback/softback, 1006 pp, €259,99, $298.99, ISBN: 9783131728715

In Volume 1, the journey begins with a chapter by A. S. Guram, J. E. Milne, J. S. Tedrow, and S. D. Walker on boron, the element of the 21st century, and purposely, on arylboronic acids coupling reactions, an area which certainly 'has become a mainstay in organic synthesis' as unmistakably evident even from a cursory key word search of the current literature (more than 1200 papers per year). The chapter is organized according to leaving groups from $C(sp^2)$–X to alkynyl sulfides and significantly, both traditional Suzuki–Miyaura and oxidative cross-coupling reactions are reviewed. Already in the presentation of the accepted (but not completely proved) mechanism of the reaction, the authors (four chemists from Amgen) set the tone of the chapter: Discussed are selected examples which showcase, whenever possible, practical aspects including catalyst cost, recovery, and residual metal removal from product. The chemist, academic, industrial, professional, or student, will enjoy a superb learning experience. To choose an example of the rich descriptive chemistry, ligandless couplings are introduced early on and shown to be advantageous in the synthesis of a clinical drug candidate (Figure 1).
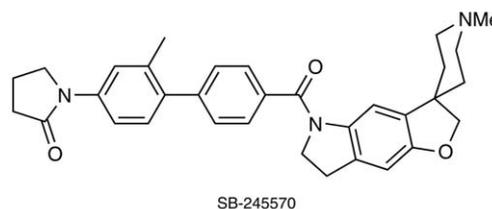

SB-245570

Figure 1 SB-245570: a clinical candidate for treatment of depression (all graphic materials are direct reproductions of the relevant *Science of Synthesis* volumes).

In reading, one learns about the achievement of <6 ppm residual palladium, dramatic solvent effects, and the choice between – what to the inexperienced eye is not undemanding – two different catalysts for optimum results. A systematic view of catalytic systems is structurally delineated (when to use a Beller, Buchwald, Hartwig, Nolan, or Organ ligand; when to switch from palladium to nickel catalysis), examples of aryl, heteroaryl, and vinyl chloride electrophiles are considered, the impact of coupling of ArCl and ArF are emphasized, leaving group [from halides, to triflates, carbamates, to more bizarre, and so far less used, phosphates, (potentially explosive) diazoniums, phosphoniums, sulfamates, triazenes] are given their due course, and block-buster illustrations (e.g., the BASF synthesis of boscalid on >1000 t/annum scale) are provided. More recent and not as widely used couplings which involve $ArSO_2Cl$ (with loss of SO_2Cl), $ArCO_2H$ derivatives

(acylative Suzuki–Miyaura reactions), benzylic (notably cyanohydrin triflates), and alkynyl electrophiles, terminate this massive chapter (146 pages) of rich and well-organized chemistry. As expected of a review from hardcore industrial chemists, the chosen procedures are carefully detailed to give a fair chance of reproduction, and NMR data for characterization are given, although in some cases one notes the lack of the increasingly disappearing physical parameter, the melting point. The reference list includes a handful of *Org. Process Res. Dev.* and patent citations which undoubtedly will increase as the Suzuki–Miyaura arylboronic acid coupling reactions further mature in scale-up processes.

In an important following section, M. Suginome and T. Ohmura deal with the known problems of arylboronic acids (e.g., difficult to purify, unsuitable for use under strong basic conditions, uncertain stoichiometry in weighing because of equilibrium with boroxins) and lessons on how to overcome these problems with derivatives such as pinacolates (now widely used) and related cyclic boronates, trifluoroborates, and triolborates. Valuable information abounds in the various sections of boronate-derivative cross-coupling reactions, for example practical [relative chromatographic stability, requirement of adventitious water (for hydrolysis to the reactive boronic acids)] and conceptual (umpolung realization via the Miyaura B_2pin_2 conditions) aspects. Examples for the illustration of scope are well chosen and include popular heterocycles, complex natural products, and polymers. Special emphasis is given to topics of *meta*-selective iridium-catalyzed borylation, the complementary and widely used directed *ortho* metalation (DoM)–borylation processes, and the not yet fully evaluated boron-masked and -protected derivatives [naphthalene-1,8-diamine (DAN), *N*-methyliminodiacetic acid (MIDA), and anthranilamide (AAM)] which provide opportunities for iterative and orthogonal boronation sequences (Scheme 1).
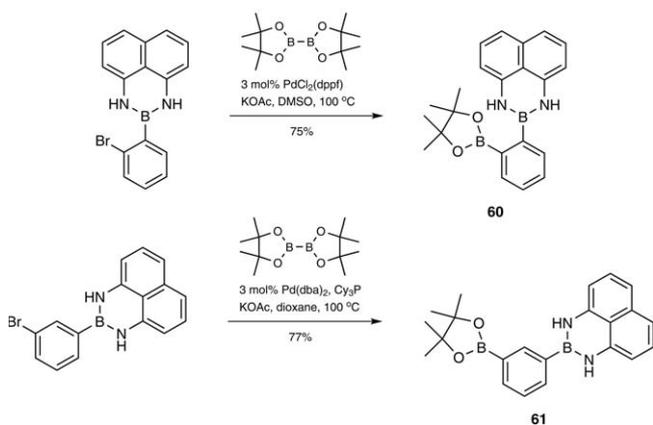
Scheme 1 DAN-protected arylboronic acid Miyaura borylation

A. Littke considers hetarylboronic acid derivatives from the known special perspectives which are due to this class of molecules that are significant in pharmaceutical and materials sciences: limited commercial availability and cost (rapidly changing), greater instability to protodeboronation compared to aryl systems, and lack of reproducible preparative procedures. He then leads the interested chemist through the major classes of five-membered (pyrroles, pyrazoles, imidazoles, furans, thiophenes, oxazoles, isoxazoles) and six-membered (mainly pyridines, and a sparse number of pyrazines, pyrimidines, and pyridazines) cyclic hetarylboronic acid coupling reactions. In the five-membered-ring series, as indicated by the mediocre amount of tabular data, comparative systematic studies on the relative coupling efficacy of boronic acids versus other boron derivatives (for example fluoroborates) are still required. Furthermore, the relative instability of boronic acids (for example, 2- over 3-furylboronic acid) can only be judged by experimental procedures in which an excess of reagent is used to obtain a reasonable yield of product. Commendably, comparative tables of various boron-derivative couplings are presented and an example of a 50 kg scale Suzuki–Miyaura cross-coupling is included. In the six-memberd-ring series, the notorious instability of pyridine 2-boronic acid to protodeboronation (compared to the corresponding 3- and 4-boronic acids) has been addressed by the use of an additive (CuCl) or switch to pinacolate, MIDA, and most recently, lithio borate derivatives, the latter two systems still necessitating proof of robustness on scale. The sections on 5,6- and 6,6-fused hetarylboronic acids belong, with minor exceptions, to indoles, benzofurans, thiophenes, and quinolines respectively, pointing to areas open for further research. With a similar potential, flow Suzuki–Miyaura processes in this area are in the early stages of study.

Of parallel importance to industry, the class of alkenylboron cross-coupling reactions, discovered concurrently with arylboron cross-coupling processes by Suzuki and co-workers, are addressed by B. Carboni and F. Carreaux. The statement 'There is no ideal reactant and the best way to choose the most efficient partner… will be to test various organoboron derivatives under their optimized conditions…' made by these two industrial chemists has a biblical ring. The poor atom-economy of DAN and MIDA derivatives and the corrosive nature of KHF_2 used in trifluoroboronate salt preparation are heedful and valid commentary. The described coupling chemistry for stereoselective diene and enyne synthesis has great value; problems of protodeboronation, partial alkyl group transfer and, thereby, partial isomerization, reported in the original work have been largely overcome by the variety of new catalytic systems and, as advised, procedures and may be ameliorated by re-examination of the early literature coupling conditions. The standard sp, sp^2, and sp^3 electrophiles are systematically covered, but also included are interesting diborylethene, carbonylative and acylative Suzuki–Miyaura reactions. All given experimental procedures are on a mmol scale.

D. L. Sandrock places the alkylboron cross-coupling reaction as a 'platform of choice' compared to the corresponding reactions of toxic alkyltin reagents and highly

reactive, unselective, air- and moisture-sensitive corresponding magnesium and zinc species. Surmised from this section are these instructive points: the use of alkylborons requires careful Schlenk-tube manipulations, and protodeboronation and β-hydride elimination propensities need superstoichiometric quantities of the reagent; however, these are issues that may be overcome by the recently developed trifluoroboronate and MIDA derivatives which perhaps paves the way to a broader validation of the Suzuki–Miyaura process for sp³ boron reagent couplings. With forecast for greater synthetic utility are results provided by the couplings of α-amino, α-amido boronates and sp³ trifluoroboronates with diverse functionality.

Before the discovery of Suzuki–Miyaura and Sonogashira reactions, how else would a chemist propose to make cross-conjugated enediynes? The answer lies, in part, in the relatively short section on alkynyl and allylboron cross-coupling reactions prepared by F. Colobert and F. R. Leroux, which shows the strong position of the air- and water-stable alkynyl and allyl fluoroborates in Suzuki–Miyaura cross-coupling reactions with the second position being occupied by lithio alkynyl borates. The highly selective and less well appreciated and functional-group-tolerant 9-MeO-9-BBN reagent is placed in context.

From boron to silicon. A herculean 140 page chapter, successfully executed by S. Denmark and W.-T. T. Chang on arylsilicon cross–coupling reactions, begins with an instructive introduction on their mechanistic understanding which has assisted in the development of catalytic systems, triggering the expansion of this now-named Hiyama–Denmark reaction into a bourgeoning area of activity. As one progresses through this section, one begins to appreciate the features of silicon- and boron-coupling chemistries which may drive greater future utilization of the former as it is further explored and rigorously tested. Especially prone to this evolution appear to be arylsilane coupling processes, highlights of which include intramolecular silicon activation to silicate by proximal oxyanion before the aryl group transfer to give biaryls (Scheme 2), oligoarene synthesis on gram scale by such activation, an allyl for fluoride group surrogate tactic, the advantages of using silanolates over silanols due to the dimerization of the latter to form inactive species, trialkoxy silane coupling with 2-bromopyridine, and sterically demanding couplings, among other aspects. The expanding list of cross-coupling partners from common halides through allylic carbonates to aryl sulfonates bodes well for future
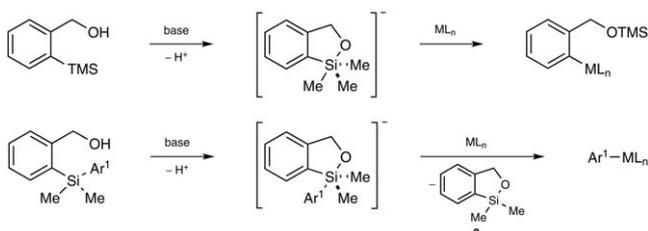
demonstration of the generality of silicon-based coupling chemistry.

The subsequent short chapter on hetarylsilicon cross-coupling also by S. Denmark and W.-T. T. Chang instructs that this reaction may overcome Suzuki and Negishi protocols because of the stability and easy isolation of the substrates as well as a lack of protodesilylation under the aprotic reaction conditions. The development of hetarylsilinol and -silanolate derivatives (e.g., pyridines, indoles, and thiophenes) appears to be advancing apace in this only just evolving field.

Alkenylsilicon cross-coupling chemistry (yes, also covered by S. Denmark and W.-T. T. Chang) has the inherent advantage of the stereoselective synthesis of silanes, and is a stereospecific cross-coupling process. It is in this class of silicon derivatives that comprehensive mechanistic work has been carried out. Among noteworthy illustrations of synthetic value are: intramolecular activation by pendant carbinols, two-directional synthesis of butadienes by sequential silanol and silane activation, and combinations with Heck–Mizoroki and ring-closing-metathesis reactions. Some examples of the construction of polyfunctionalized natural products and bioactive molecules strongly anticipate further value in complex synthesis.

The section dealing with alkylsilicon cross-coupling reactions is brief because sp³-hybridized organosilane donors are much more challenging than the sp²- and sp-hybridized counterparts due to the difficult transmetalation step of the strong σ-alkylsilane bonds and the reactivity of the corresponding allylsilanes via an S_E2'-type mechanism (Scheme 3). An even briefer section is relegated to alkynyl and acylsilicon couplings which appear to be at the initial stages of development, although it is difficult to ascertain if these will compete with other acetylenic metal couplings, for example the dominant Sonogashira process.
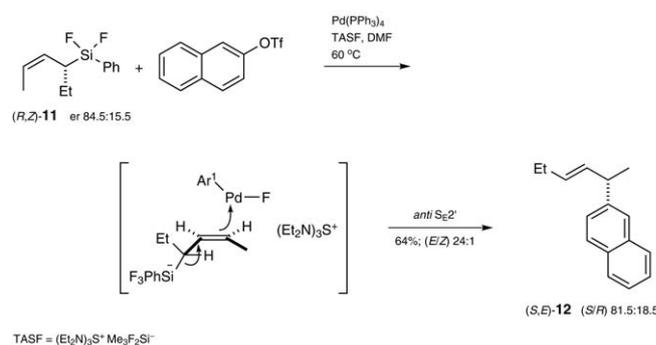
Scheme 3 *syn* S_E2' transmetalation mechanism to rationalize the stereospecificity of the allylsilane cross-coupling

In these contributions by S. Denmark and W.-T. T. Chang devoted to silicon-coupling chemistry, variations of procedures and silicon derivatives abound to stimulate the synthetic chemist to test the non-waters of these reactions. Commendably, all of their chapters conclude with advice

Scheme 2 Intramolecular silicon activation for Hiyama–Denmark cross-coupling

to the practitioner as to the major niches of silicon-coupling reactions, provide thought on their current strengths, and by implication signal their potential.

The early publications of seminal mechanistic work by Stille and his co-workers on the reaction that now bears his name changed the way synthetic chemists think about C–C bond formation. The section by A. Pitaval and A. M. Echavarren is rich in well-chosen examples and condition variations for adaptation and application. Improvement in ligand choice, development of ligandless reactions, and rate enhancement by additives [e.g., copper(I) and fluoride] combined with organostannane stability and broad tolerance of functional groups have placed the Stille reaction as a method of choice (especially in heterocyclic systems) in spite of the associated toxicity issues. Although toxic aspects of organotin derivatives are stated and well known throughout the synthetic community, a summarizing table of relative toxicities of most widely used derivatives together with procedures for immediate treatment would have been appropriate. Methodological data and biological and natural complex molecule synthesis are appropriately highlighted with some appreciation of scale-up (10–20 g) and green processes.

The first of the five organozinc chapters begins with a review by C. Gosmini and M. Corpet on arylzinc cross-coupling reactions whose size is commensurate with their equal synthetic significance to the corresponding arylboronic acid cross-coupling processes. Although organozincs, generated from corresponding lithium and magnesium species by transmetalation or by activated zinc metal insertion into carbon–halogen bonds, are sensitive to moisture, their tolerance of a spectrum of functional groups (ester, nitro, ketone, aldehyde, nitrile, halide, amide) places their cross-coupling (Negishi) above the Grignard (Corriu–Kumada) cross-couplings in general utility. Similarly to Suzuki–Miyaura coupling, the more expensive palladium catalyst tends to be more widely used in comparison to nickel because of greater selectivity. Results of increasing TONs by recently introduced ligands, use of organozinc ester (Scheme 4), high-yielding 2:1 coupling with 1,2-dichlorobenzene, use of pyridine 2-trimethylammonium salts, tolerance of boranes in coupling with alkenyl halides, and increasing use of iron catalysis are some randomly selected, arguably less commonly known, facts obtained by page-scanning of this chapter. A rapid scan of experimental procedures shows no scale-up processes, although a selection of organozinc reagents are commercially available in small and large quantities (Rieke, BASF) and industrial Negishi reactions are known. Synthetic chemists will appreciate the provided indication of conditions requiring Schlenk and glovebox conditions.

Hetarylzinc Negishi cross-coupling reactions, expertly reviewed by K. Undheim, commences with a refresher tutorial on the fundamental properties of π-excessive (for example pyrrole) and π-deficient (for example pyridine) heterocycles. It is appropriately noted that π-deficient systems undergo S_NAr reactions with halogen derivatives in
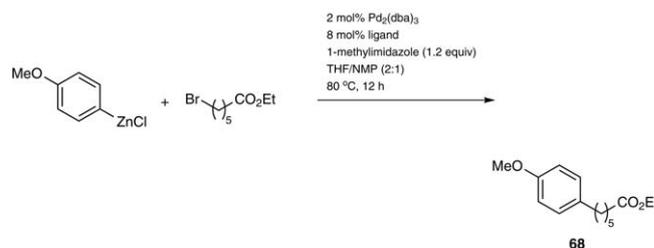
Scheme 4 Palladium-catalyzed sp²–sp³ Negishi cross-coupling

competition with transition-metal-catalyzed processes: a significant caveat which requires control experiments. Aside from the historically developed RZnX and R_2Zn coupling reagents, considerable work has been carried out on zinc amides (for example TMPZnX) for the direct formation of organozincate species of the type R_3ZnM (M = Li, MgX) by direct insertion into the C–H bond. The organozincates are more reactive and therefore less chemoselective because of the higher nucleophilicity of the R substituent as a result of a greater negative charge at the zinc center. Hence, examples of hetarylzincates are less prevalent than the corresponding HetArZnX and (HetAr)$_2$Zn reagents. Among interesting tidbits of information gained from reading Undheim's review are: bromolysis or iodolysis can be confidently used to determine concentration of organozinc reagents, the possibility of inversion of the metal and leaving group reaction partners of ArZnX and an A^1X electrophile is a useful mnemonic in coupling chemistry, finding empirical reactivity relationships in, for example, dihalopyridine and -purine reactivity has been used to achieve regioselective coupling, the activation of commercial zinc powder by lithium chloride to prepare a broad range of HetArZnX reagents is an important recipe, acidic H-bearing substances (amines, amides, alcohols, phenols) in couplings are tolerated, the outcome of 2-pyridylzinc coupling reactions are more favorable compared to the corresponding boron derivatives, the regioselective zincation of iodo- over bromopyridine derivatives invites orthogonal coupling chemistry, the Negishi process for the synthesis of polyaza heterocycles, for example triazines and nucleosides (Scheme 5), and the regioselective oxidative zincation of heterocycles using TMP·ZnCl·LiCl complex in the presence of sensitive (aldehyde and nitro) groups are successful procedures. One 20 g scale reaction (arylpyrimidine) is noted.

Many introductory sections of the various chapters of Volume 1 of this *Science of Synthesis* publication are repetitive in justly praising the value of cross-coupling reactions discovered in the early 1970s which provided the synthetic chemist with the first simple, general, and direct method for C–C bond formation (for example, for olefins, think of your first organic course which taught chemistry of Grignard addition to C=O compounds followed by dehydration). Calling on their considerable experience with alkenyl metal species in general, T. Mejuch and I. Marek
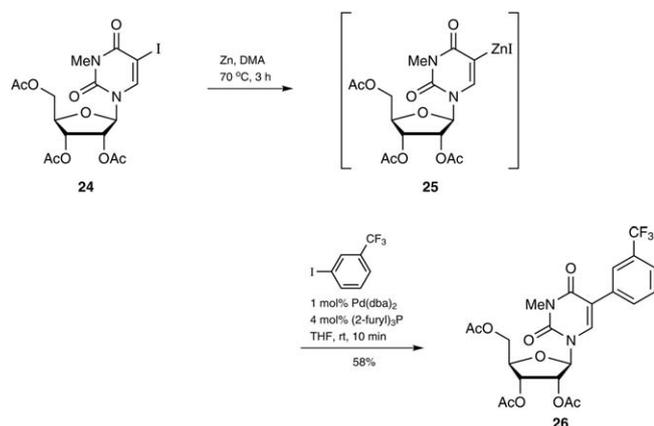
Scheme 5 Negishi coupling of nucleosides

begin their chapter on Negishi alkenylzinc coupling reactions by asking a fundamental, sometimes insufficiently considered question: why do unreactive zinc reagents produce reactive organometallic species which are capable of undergoing reactions with electrophiles that are unreactive towards organozinc reagents? The question is answered in the summarized rich synthetic chemistry of this chapter. Among the standard methods of alkenylzinc preparation, Mejuch and Marek are mindful to note the B–Zn and the Zr–Zn transmetalations and the direct zincation using TMPZnX·LiCl bases. To this reviewer, new or relearned reactions surfaced during the preparation of this review, including vinylboron–vinylzinc cross-coupling to dienes, the advantage of alkenylzinc over the corresponding zirconium, copper, magnesium, lithium, and boron species in cyclic ketone couplings, a type of comparative study which should be highly encouraged to those undertaking synthetic methodology studies. Practical aspects of the preparation of alkenylzinc bromides versus the chlorides and use of diethylzinc reagents perhaps deserved comment.

'β-Hydride elimination?' is the first question one asks when facing the chapter by L. Li and M. R. Biscoe on alkylzinc cross-coupling reactions. The answer is that efficient nickel- and palladium-catalyzed processes have been developed for the practical use of primary and secondary alkylzinc reagents but that tertiary alkylzinc species remain elusive (Scheme 6).
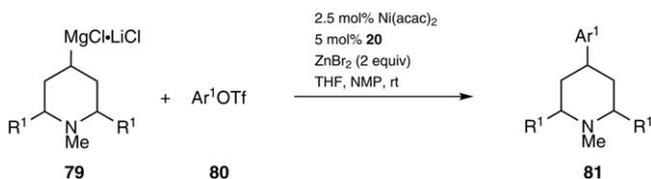
Scheme 6 Nickel-catalyzed sp^3–sp^2 Corriu–Kumada cross-coupling

As noted for other organometal species, lithium chloride has a remarkable effect on the reactivity of alkylzinc reagents although the procedures for formation of some of the double Mg–Li species are experimentally challenging (for example activation of lithium chloride and magnesium turnings with a heat gun at 400 °C). Three- and higher-carbon sp^3-zinc synthons bearing various functional groups, for example masked aldehydes and amino acids, are useful coupling partners but the venerable Reformatsky coupling reagent is missing (the inverted counterparts of coupling of alkenylzincs with α-bromo amides and α-chloro ketones are reviewed as are the corresponding α-bromo esters with arylzinc reagents in the relevant sections).

The chapter on alkynyl-, benzyl-, and propargylzinc cross-coupling reactions by I. J. S. Fairlamb and A. R. Kapdi begins with a useful refresher on the differences of alkynyl-Li, -MgX, -SnR$_3$, and -Zn reagents: the nucleophilicity of the lithium and magnesium halide species which leads to palladium-catalyst poisoning, the difficulty of separating tributyltin and magnesium salt by-products, and the reminder that alkynylcopper reagents are part of the broadly used Sonogashira process. Thus, even though alkynylzincs are intrinsically nucleophilic and air- and water-sensitive, they are increasingly the reagents of choice for selective (including stereoselective), fast cross-coupling processes. Usefully introduced, a comparison of alkynylmagnesium bromide, -tributyltin, -boronate, and -zinc bromide couplings clearly demonstrate the superiority of the latter species in forming arylalkyne derivatives. As expected of a good review for practicing industrial chemists, highlighted are the best methods for in situ alkynylzinc halide preparation, hetaryl electrophile coupling examples, and gram-scale procedures (Scheme 7). Although several cases of syntheses of alkynyl-containing natural products are given, surprisingly, complex oligomeric materials science related cases are not provided.
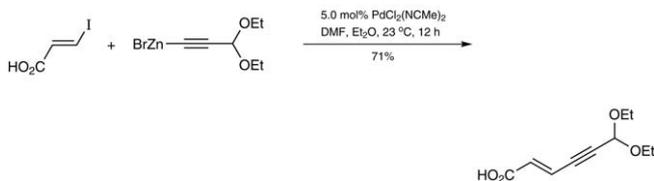

Scheme 7 Synthesis of a functionalized eneyne by Negishi coupling

C. Wolf leads us into the rather short section on aryl-, hetaryl-, and alkenylmagnesium halide coupling, recalling the seminal experiments of Kharash in 1943, followed by the independent discoveries of Kumada and Corriu 30 years later, in this class of reactions. Although the functional-group incompatibility and side-reaction propensity has somewhat discouraged the use of arylmagnesium halide coupling processes, mild protocols for the formation and some commercial availability of these reagents, which tolerate a variety of functional groups (for example

esters, thus upsetting the undergraduate dogma), are on the path of changing the status of applications of the Corriu–Kumada reaction. Interesting components which surface in the presentation include the facts that aryl Grignard couplings may be achieved not only with aryl halides (ArX; X = I, Br, Cl, *and* F) but also a variety of other functional groups including sulfones, nitriles, carbamates, phosphates, and sulfamates, among several others, and that the use of in situ generated, air- and water-stable palladium and nickel complexes incorporating phosphinous acid ligands are available. Alkenyl and alkynyl electrophile couplings are more rarely explored but the advent of cryogenic methods for the preparation of functionalized Grignards with the assistance of lithium chlorde and the introduction of new iron- and cobalt-based catalytic systems has overcome b-hydride elimination problems in all classes of electrophile coupling to afford useful building blocks. A response to atroposelective synthesis of axially chiral biaryls is perhaps still most adequately answered in the arylmagensium halide coupling area by the work initiated by A. I. Meyers in the S_NAr (not coupling) chemistry with chiral 2-methoxyaryl oxazolines and the parallel studies of Hayashi in the enantiotroposelective coupling of prochiral biaryls (Scheme 8).

In passing, a table of 2-pyridylmagnesium bromide–aryl electrophile coupling reactions demonstrate better yields than the corresponding boronic acid (ester) coupling procedures.
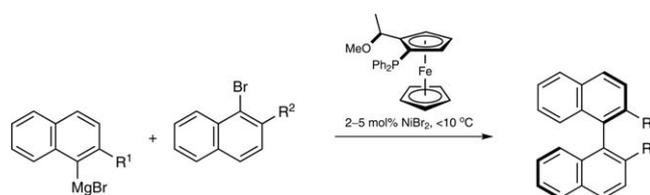
Scheme 8 Atropenantioselective Corriu–Kumada coupling

To conclude the massive Volume 1 of this *Science of Synthesis* series, K. Park and H. Jo present a short section on alkyl- and alkynylmagnesium halide cross-coupling protocols. For large-scale synthesis, preference is given to O-electrophiles (i.e., OTf, O-carbamate, phosphate, and most recently, some sulfur derivatives) over organic halides due to cost and toxicity. Issues of stability, inadequate storage, and β-hydride elimination of sp^3-Grignards have not been completely overcome. Iron catalysis in hetaryl electrophile coupling reactions appears to be suggesting a strong case for use in synthesis, and since 2002, the arrival of sp^3-Grignard–sp^3-electrophile coupling reactions are some aspects to be noted in this chapter. Gramscale experimental procedures for Corriu–Kumada reactions are included.

Victor Snieckus, Department of Chemistry, Queen's University, Kingston, ON, Canada