
Volume 2 opens with a succinct introduction by J. P. Wolfe on C–N bond-forming reactions, the earliest studied and now most widely applied carbon–heteroatom coupling reaction. Then the chapter by M. Tomás-Gamasa reflects on the fact that, before 1997, in spite of the seminal work of Ullmann and Goldberg in the early 1900s, aryl C–N bond formation was restricted to classical arene nitration–reduction, S$_N$Ar and benzyne, and reductive amination processes, with the concomitant predicaments of scope limitation, expensive reagents, and environmental concerns. She then posits the two main palladium- and copper-catalyzed methods and shows, respectively, the use of the former metal (broad use but considerable expense) and the special features of the latter metal (low toxicity and cost, different reactivity profile). Since 2000, the high temperatures of the Ullmann–Goldberg conditions have been systematically decreased to provide ambient temperature and greener (ligandless, solvent-free, polymer-supported) copper-catalyzed couplings in addition to fundamentally new protocols [primary amine synthesis with ammonia and its surrogates and arylboronic acid coupling partners – the Chan–Lam–Evans reaction (Scheme 1)].

The >40 ligands to promote the copper-catalyzed N-arylation of alkylamines are conveniently displayed and then each is separately exemplified in sections that allow evaluation of the advantages and limitations as required by the synthetic chemist. Among the various features presented are: chemoselective coupling of aliphatic amine over aniline and primary amine over secondary amine, functional-group tolerance (including unprotected alcohols and phenols), methods for aryl chloride coupling, and decreased copper catalyst loading. Analogous to the discussion of the copper-catalyzed section, the palladium-catalyzed coupling section, initiated by the discoveries in the Buchwald and Hartwig laboratories in 1995, presents a graphic of a similarly large number of ligands for consideration with advice on more useful and popular ligands and benefits of pre-formed, frequently air-stable palladium systems. A smaller set of examples of various palladium–ligand systems follows, perhaps offering opportunity for additional work on this broadly applied protocol. As expected by the experimental chemist, Schlenk tube, glove box, and screw-cap vial use is presented when required. All examples are small-scale reactions.

The extensive chapter by U. Scholz, W. Dong, J. Feng, and W. Shi dealing with alkyamine–hetaryl electrophile C–N bond-forming reactions is subdivided according to the hetaryl halide used. From this, one obtains an overview of the extensive playground of heterocycle coupling reactions and, along the way, appreciates the advances and advantages of this palladium- and copper-catalyzed methodology over classical protocols. Thus, among many valuable facts, the alert synthetic chemist learns: the simple synthesis of 3-aminothiophenes and -benzothiophenes (but not the corresponding pyrroles and indoles) compared to the difficulties of the enamine method; a practical procedure for introduction of volatile amines; the gap in knowledge and lack of optimized protocols in patent references (e.g., carbazole electrophiles); selective coupling of Br over Cl electrophiles and positional Cl sites [e.g., purines and pyrimidines (Scheme 2)]; extensive exploration of all isomeric halopyridines for amine couplings, with the exception of 4-iodopyridine; the lack of testing of halopyridinone coupling; and the escalating use of micro-wave procedures.

The copper-catalyzed amination section, lacunae in knowledge are apparent, for example lack of reactions with thiophene, benzothiophene, pyrazole, and chloropyridine electrophiles, among others. The caveat of potential S$_N$Ar reactions, rather than catalytic coupling processes occurring, to be overcome by undertaking control experiments, is not frequently mentioned. Difficulties in trans-

**Scheme 1** The Chan–Lam–Evans copper-catalyzed coupling of arylboronic acids with amines (all graphic materials are direct reproductions of the relevant *Science of Synthesis* volumes)

**Scheme 2** Selective amination of purine derivatives

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formations, as surmised from the literature, are duly noted and a significant number of patent references are cited.

M. B. Hay and J. D. Hicks introduce the subject of aryl/hetarylamine–aryl/alkenyl electrophile cross-coupling by a detailed discussion of our current mechanistic knowledge of the palladium catalytic cycle of amination reactions which can guide and avoid error in laboratory practice for the uninitiated. Key experimental considerations are defined. Limitations and advantages of copper-catalyzed aminations are presented in tabular form, and clear practical advice is given. The Chan–Lam–Evans copper-mediated oxidative C–N coupling with boronic acids is given separate treatment, and its advantages (milder conditions, broader scope for heterocycles, insensitivity to oxygen) over the copper- and palladium-catalyzed processes carried out with aryl halides are noted. The authors, obviously experienced experimentalists (affiliation unfortunately not given), provide a tour through the various types of aryl and alkenyl electrophiles in which gems of commentary appear with respect to the commonly asked questions: What is the minimum catalyst loading that can be used? How does solvent choice affect solubility of formed inorganic salts and therefore cause reaction inhibition? Which are the best two or three ligands for copper-catalyzed couplings? Why use Cs₂CO₃ over t-BuONa as a base? Should precatalysts be given increasing favor? What is the best base to avoid complications of coupling with molecules containing acidic C–H bonds? What is a good example in which palladium and copper catalysis are complementary for aromatic over aliphatic amines? What are the conditions for selective coupling at two positionally different aromatic bromide groups? What is the best ligand for coupling of sterically demanding substrates? When is there expectation of O–Tf bond cleavage as opposed to coupling? Does the Chan–Lam–Evans protocol fail with some boron partners? In view of recent encouraging results, should N-heterocyclic carbene (NHC)-based catalysts be given priority consideration (Scheme 3)?

When an E/Z-alkenyl isomeric mixture is used, is there isomeric enrichment under the coupling conditions? An extensive question: Which is more reliable, a copper- or palladium-catalyzed coupling for complex primary heterocyclic amines? What is the best set of conditions for formation of tertiary amines? Of course, this surfeit of questions then triggers the comment attributed to a famous chemist: ‘Five minutes in the (e-)library will save you five hours in the lab’ the first part of which now deserves the prefix ‘With Science of Synthesis’.

A concisely reviewed chapter by Q. Shen, F. Guo, and J. F. Hartwig on aryl/hetaryl–amine coupling with hetaryl electrophiles delineates the challenges faced for success of these reactions vis-à-vis the corresponding aryl–electrophile couplings. The problem, which became evident after failure of the original Hartwig and Buchwald methods of 1995 that were successful in aryl electrophile coupling reactions, was the displacement of the ancillary ligands of the catalyst by basic heterocycles (e.g., pyridine, pyrazole, and imidazole). Synthetic need, especially by medicinal chemists, drove this area, and catalysts were developed which bear chelating phosphines not binding to palladium; however, subsequent third-generation catalysts containing sterically encumbered, electron-rich phosphines that are strong palladium binders showed that chelation via two P-donors is not a requirement for effective coupling reactions. The third-generation catalysts have had a prevalent, general impact in improving yields of coupled products, including those originating with aryl chlorides. While six-membered-ring hetaryl electrophile coupling may be considered at a robust state of synthetic application, the corresponding five-membered-ring systems are still in the developmental stage bursting with potential imminent breakthroughs. Perhaps, a bold generalization based on examples cited in this chapter, ligands of the Josiphos-type which offer structures of tight chelation by the rigid backbone, sterically bulky, and electron-rich bisphosphines and – on the basis of similar electronic and steric properties, the NHCs – are most suitable for aryl and hetarylamine cross-coupling reactions (Scheme 4).

The chapter concludes with hetarylamine–hetaryl electrophile couplings, leading to chemoluminescent compounds (apparently as yet without significant patent references) and the copper-catalyzed Ullmann-type reaction which ‘remains an unsolved problem’.

O. K. Amhad and M. Movassaghi provide the first chapter of a sequential triumvirate on N-arylation of functional organic molecules which deals with N-arylation and N-vinylation of heterocycles. Various liganded copper catalysts dominate in these reactions of imidazoles, pyrroles, triazoles, and carbazoles in which, where applica-
ble, N-coupling appears to occur at the sterically more accessible site to give single regioisomeric products. The Chan–Lam–Evans protocol for N-arylation via aryboronacid coupling shows the advantage of ambient temperature reaction conditions in comparison to the elevated temperature requirement for the corresponding aryl halide coupling reactions. Palladium-catalyzed N-arylations have been less explored; other arylmetal compounds (Pb, Bi, Cd) as well as Fe–Cu co-catalysis, initially stealthily introduced but subsequently intentionally, appear to be worthy of further investigation.

In the next chapter, A. Klapars of Merck immediately defines as a generalization that there is only partial complementarity of palladium- and copper-catalyzed couplings of amides with aryl and vinyl halides, sulfonates, and boronic acids. Among the many useful accumulated facts are: Copper-selective arylation of primary amides over anilines versus the opposite selectivity using palladium; in lists of ligands which improve coupling of amides, many reports give only the reactions for straightforward substrates and fail to provide direct ligand comparisons; the emergence of copper(I) iodide (CuI) as the catalyst of choice in differentially reactive o-chloro-bromobenzene derivatives; a favored C–N coupling may be followed by intramolecular S$_n$Ar reaction to give a benzoazole derivative [and the caveat that most likely the S$_n$Ar process is not copper-catalyzed (Scheme 5)]; and the very successful results of intramolecular amidation, examples of which are almost exclusively the favorable five-membered-ring-size type.

Turning to palladium catalysis, insight into the simplified mechanism of the palladium-catalyzed coupling of amides with aryl halides provides rationalization of the poor reactivity of aryl iodides and poor binding of hindered amides in the first (transmetalation) step. The rest of the section shows that ligand development is a never a stationary target and is a function of the perceived bench needs of chemists. Such a need, the introduction of an ammonia equivalent, is en route to one satisfactory synthetic solution by the development of arylation using tert-butyl carbamate which has the additional advantage of being a dependable directed ortho metalation group. Coupling with aryl and heterocyclic sulfonates is delineated and their relative stability and reactivity is evaluated. The copper-catalyzed coupling with alkynyl and allenyl electrophiles to produce acyl enamines is represented by simple, intramolecular, and complex natural product examples. The corresponding palladium-catalyzed coupling uses mainly alkyl sulphonates, which allows a facile and advantageous link to precursor carbonyl compounds. The Chan–Lam–Evans oxidative coupling of amides with aryloboronic acids is placed in comparative perspective with the corresponding coupling with halides. Cross references to differences and similarities for palladium- and copper-catalyzed processes by sections are conveniently provided. In the N-arylation of amides, the alternative dissection of the classical acylation of an aryl amine should, of course, be given consideration.

J. Duan, H. Chen, X. Hong, and M. Harmata develop the theme of C–N bond formation of sulphonamides, sulfoximides, guanidines, and ureas. To begin, the authors note that the classical sulphonamide alkylation with alkyl halides, which produces waste organic halide or metal halogen salt products, is being superceded by N-alkylation with alcohols using Ru, Cu, Ir, Ag, Fe and transition-metal catalytic "borrowing hydrogen" methods. Interesting molecules such as alkyl and alkenyl sulphonamides and dihydropyroles thereby become available. In another noteworthy feature, palladium-catalyzed sulfoximide N-arylation may be connected with intramolecular aldol-type reactivity to afford benzothiazines. As noted in the commentary of other chapters (e.g., that by O. K. Amhad and M. Movassaghi), iron-catalyzed reactions are influenced by trace amounts of contained copper which greatly control their outcome. The as yet limited synthetic work on coupling of sulfamate, sulfonimidamide, guanidine, and urea derivatives already point to utility for modern methods of benzimidazole and benzimidazolone construction which avoids the classical and wasteful one-carbon bridging 1,2-diaminobenzene procedures (Scheme 6). A change of retrosynthetic mind-set is required to understand the discovery of reactions in which the normal C-halogen electrophile for C–N bond formation is simply a C–H bond. T. G. Driver addresses these minimized functional group substrate reactions for the construction of C(sp$^2$)–N and C(sp$^3$)–N bonds. The well-known rhodium-catalyzed synthesis of pyrroles and indoles from dienyl and aryl vinyl azides has been supplemented for indoles by the recent method starting from nitrostyrenes by palladium-catalyzed/CO reductant procedure.
the amines, either N-acylated or in the neutral state for C–N bond formation, leads to carbazoles, indazoles, and quinolones. The N-arylamidine-to-benzimidazole conversion by a copper-catalyzed C–N bond-formation process overcomes, as in the previously discussed reaction from guanidine derivatives, the deficiencies for the synthesis of this class of molecules from 1,2-diaminobenzenes. C–N bond formation via C(sp³)–H bond activation does not have the advantage of a π-system for electrophilic substitution and must rely on metal–nitrene or transition-metal complex C–H activation events. Progress in these area focuses on catalytic rhodium-derived iminoiodinanes as reactive intermediates, with some impressive early consequences in synthesis including asymmetric C–H bond amimation.

Although full appreciation of the significance of organophosphorus compounds cannot be denied by the catalysis chemist, their application for the synthesis of extractants, flame retardants, and various metal-organono compounds should be given due consideration. C. Petit and J.-L. Montchamp use their expertise to delineate methodologies for catalytic C–P bond formation, limiting discussion to reactions of P–H phosphines, P–H phosphate oxides, phosphine–borane complexes, phosphorines, among other P-derivatives, with electrophiles bearing aryl sp²-carbons, because alkenylphosphorus compounds are more easily prepared by other well-known means. Thus, formation of binaphthalene-2,2′-diphosphines from the nickel-catalyzed coupling of Ph₂PH with BINOL ditriflates is an example of a simple, general procedure. Although not noted, the stable, easily handled phosphine–borane complexes are perhaps of practical convenience in handling. Experimental procedures for reactions with 10–40 grams are cited, but much greater scale processes are undoubtedly involved in current industrial plant operations.

As described by C. C. Eichman and J. P. Stambuli in the next chapter, synthetically useful C–O and C–S bond-forming cross-coupling reactions once followed the catalyst technology for C–N bond-forming reactions and reached advanced stages only after side-reactions specifically pertinent to the former couplings were overcome. The synthesis of diaryl and alkyl aryl ethers (the traditional Ullmann-type reactions) by palladium- and copper-catalyzed silicon-directed oxylation of aryl halides with phenols and (primary, tertiary, and secondary) alcohols may now be declared to be efficient and well-established methodologies. (I would add, with a smiley face, one missed report.) The catalytic Chan–Lam–Evans reaction using boronic acids includes the use of an unusual synthesis of a TBDMS-O-vinyl derivative. The sections on the synthesis of diaryl, alkyl aryl, and aryl vinyl sulfides provide important advice on the avoidance of interference, with proper choice of ligands, and of catalyst poisoning by thiols in both palladium- and copper-catalyzed processes. The provision of such commentary in the introduction and tabular data would have been welcome. As emphasized in the chapters concerned with the synthesis of benzimidazoles and benzoxazoles, the corresponding process to prepare benzothiazoles from thioamides has the similar advantage of easily available starting materials. In the coupling of disulfides, it appears that a full equivalent of the disulfide partner is required.

K. Inamoto reviews the new, rapidly evolving area of C–O and C–S bond-forming reactions by directing group (DG) C(sp³)–H and C(sp³)–H activation processes. Palladium(II)-catalyzed acetoxylation of both types of C–H bonds in the presence of stoichiometric (diacetoxyiodo)benzene appears to be common practice, and site selectivity occurs by using 2-pyridyl, pyrazole, oxime ether, and 2-pyrollidinone, among other DGs. Peroxide and oxone oxidants appear to be less widely used. The removable DG disisopropyl(2-pyridyl)silyl in an aromatic C(sp³)–H process deserves further attention. Other aspects of value for the modern synthetic chemist include silicon DG oxygenation to yield catechols after fluoride-mediated desilylation (Scheme 7).

Copper-, rhodium, and gold-catalyzed acetoxylations appear to be in the embryonic states. C–S bond-forming processes by DG activation are known by the Buchwald–Hartwig protocol but are rare by C–H activation–functionalization routes, with the exception of expected intramolecular reactions which furnish benzothiazoles.

The new wave of C–B and C–Si bond-forming reactions by use of B–B and Si–Si as well as B–H and Si–H compounds may be projected to supersede the classical construction modes involving the combination of organolithiums and -magnesium with XS₁ and XB (X = halogen, OR) reagents in view of the inefficient step economy and required protection of electrophilic and protic functional groups in the latter classes of reactions. With acknowledgment of the continuing required consideration of the traditional procedures in industry, M. Murata brings this new perspective to the forefront of attention in this chapter. The palladium-catalyzed coupling of aryl halides with the no-longer-expensive B₂pin₂ to furnish ArBpin derivatives, most appropriately named the 'Miyaura borylation', has received, since its discovery in 1995, substantial work in catalytic system variation and thereby deserves a robust status emblem. In spite of scant knowledge of the catalytic cycle (one isolated intermediate and density functional theory calculations), tabular results show that the method is broadly applicable to structurally diverse organic molecules. Now equally robust, more atom-eco-
nomical and widely applicable is the method devised by the author of this chapter and Masuda which uses pinacolborane HBpin as the boron source. A comparison of the two reagents, which should be a general requirement in synthetic method development, shows that HBpin is a more efficient coupling partner than B$_2$pin$_2$ in several cases. A cited large-scale preparation of aryl boronates is not experimentally described. New procedures involving coupling of easily prepared and less expensive neopentylglycolborane and subsections on alkanyl, allyl, and benzyllic electrophiles may be noted. The synthesis of aryl(trialkoxy)silanes, among other organosilicon derivatives, and their coupling reactions concludes this chapter from which one can predict that further advances in methodology for C–Si bond formation will be discovered (Scheme 8).

Contrasting with the chapter by M. Murata on C–B and C–Si bond-forming reactions using C–X electrophiles, K. J. Szabó evaluates the recently and rapidly evolving field of reactions involving C–H functionalization. The M. Murata and K. J. Szabó chapter introductions are advisable comparative reading, no matter if on the same topic, since they provide somewhat different perspectives depending on the experience of the chemist. Somewhat in contrast from other chapters of all three Science of Synthesis volumes, substantially more mechanistic discussion is presented, indicating key experiments in the C–H borylation area which have been performed partially in the author’s laboratories. Appreciation of differences in borylation of arenes and alkynes (C–H cleavage and formation of C–Ir bonds without π-bond participation versus cis insertion), atom economy (both boron atoms of B$_2$pin$_2$ are consumed per only one hydrogen-atom loss from a C–H bond), and avoidance of prefunctionalization are all helpful factors for synthetic design. Data is tabulated for selected numbers of arene, hetarene, and alkene borylation reactions that provide alternative routes to metalla–electrophilic boron substitution to furnish substrates which are ready for Suzuki–Miyaura coupling [achievable in a one-pot procedure (Scheme 9)].

The uncited complementarity between ortho borylation of benzamides and other directed metalla–electrophilic group (DMG)-bearing aromatics by directed ortho metalla–iridium-catalyzed meta borylation appears to also be a valuable synthetic path deserving inclusion in future updates of this Science of Synthesis volume. Of specific value is the fact that the derived meta-substituted arylboronates may be converted into the corresponding anilines by C–N coupling, thereby leading to contra-S$_2$Ar substituted products. C(sp$^3$) borylates, (e.g., allyl, benzyl, and arguably the Holy Grail, alkyl) are challenging synthetic substrates requiring additional concentrated effort. In contrast, Szabó points out that the corresponding C–Si bond-forming processes have not received mechanistic scrutiny. Thereby perhaps, catalytic C–H silylation is as yet underdeveloped, requiring, it appears, more highly reactive catalysts than for the corresponding borylation reactions. A welcome ‘outlook’ section closes this fine chapter.

The formation of a C–CN bond by nucleophilic substitution on alkyl halides and related derivatives is learned (or at least presented) in the first organic course. Before the era of palladium catalysis, direct ArBr into ArCN conversion could only be achieved by the classic Rosenmund–von Braun reaction using copper(I) cyanide in an inert solvent at high temperatures. As a modern foil, G. Yan, Y. Zhang, and J. Wang present useful procedures for the palladium-, nickel- and copper-catalyzed cyanation of Ar–X bonds as well as oxidative cyanation of arylboronic acids and direct cyanation of sp$^3$ C–H bonds. The advantages of various catalytic methods are provided, with the expected emphasis on those which require nontoxic promoters and catalysts; thus, K$_4$[Fe(CN)$_6$] (non-toxic), zinc(II) cyanide, and thiocyanates in the presence of copper(I)thiophene-2-carboxylate (for arylboronic acid into ArCN conversion) appear to be the more useful cyanide sources. The delineated slow release of cyanide from acetone cyanohydrin (to avoid palladium poisoning) at 150 °C is a somewhat intimidating procedure for the uninitiated. Direct C–H cyanation of heterocycles (e.g., 3-cyanoindole synthesis) appears to be a potentially useful but mechanistically unclear reaction. Cyanation by direct activation of aryl, heteroaryl, and tertiary amine C–H bonds appear to be fruitful areas for further study.

As explained by K. B. McMurtrey and M. S. Sanford in the chapter on C–F bond-forming reactions, the low kinetic reactivity of aryl(fluoro)metal complexes to undergo
C–F bond-forming reductive elimination has been the challenge for advances in this field. Two approaches are documented in this short review, one of which involves either stoichiometric palladium- or silver-mediated reaction of arylboronic acids and arylsilanes using Selectfluor as the F⁺ source or silver-catalyzed fluorination of aryl stannanes. The very apparent deficiencies of these methodologies may be contrasted with the second approach via palladium-catalyzed directing group activated fluorination of 2-pyridylaryl, benzylamine, and benzylamide systems (Scheme 10), the latter providing functionalized fluorinated aromatics of potential value.

The challenges faced in the development of F⁻ reagents, which are especially useful in ¹⁸F PET imaging, due to the low nucleophilicity and poor solubility of fluoride salts is at the tip of being met by the design of new ligands, a comment appropriate for all of reviews of cross-coupling chemistry.

C–C cross-couplings of mono-activated and doubly activated enolates comprise the last two chapters of this monumental Volume 2 of Science of Synthesis Cross Coupling and Heck-Type Reactions. S. P. Marsden has the unenviable task of placing into organized context those reactions which involve formation of key sp³–sp² bonds (e.g., α-arylation of enolates) which has been the classical domain of the limited SₓAr chemistry, among other and less pleasant methods such as those involving aryl lead compounds. Truly revolutionary in concept and practical in execution is the palladium-catalyzed α-arylation of carboxyl derivatives and other α-C–H acidic species, for example nitriles, sulfones, and ketimines, among many others. Reformatsky reagents, although excluded from the discussion, are known coupling partners. Although not fully elucidated as yet, but rational as presented, is the mechanism of the coupling which, as expected, features electronic and steric control and shows reactivity as a function of the departing group and the introduced aryl group (lowering pKₓ of the remaining C–H, thereby promoting double arylation). The questions that synthetic chemists are prone to ask – can aryl chloride systems be used, is double arylation achievable if desired, is acetone monoarylatable, and is it possible to create quaternary carbons? – are all answered in the positive. High turn-over numbers with very low catalyst loading may be achieved in some α-arylations. For intramolecular reactions, a new umpolung methodology is retrosynthetically established, for example indole C-3 C–C bond formation not involving the classical SₓAr methodologies from aniline derivatives. After considerable systematic study, it appears that asymmetric α-arylation reactions still do not consistently achieve high enantioselectivity but that the interfering aldol condensation of aldehyde α-arylation substrates has been solved. Other electron-withdrawing groups that acidify α-sites, for example esters, amides, nitriles, imines, and more sophisticated (e.g., dioxanones) substituents in inter- and intramolecular versions, both racemic and stereoselective, offer considerable new playground area for this chemistry (Scheme 11).

The advance provided may be appreciated by giving pause to a retrosynthetic analysis for arylglycinates, before and after α-arylation methodology development (Scheme 12).

The corresponding C–C couplings of doubly activated enolates (malonates and related derivatives) reviewed by Y. Wu, J. Wang, and F. Y. Kwong similarly places the significance on the α-arylation process for bioactive molecule synthesis. Malonates constitute the major substrates, with one example (α-F) indicating biosignificance and reminding us that the standard SN₂ alkylation can be a preamble to the palladium-catalyzed α-arylation reaction. As rightly stated, the copper-catalyzed version dates to the 1970s and before (Hurtley reaction), but is now relatively convenient and carried out under much milder conditions. The positioning of ortho functional groups in the aryl halide can lead to cyclizations to heterocycles. Enantioselective α-arylation may be achieved (Scheme 13).

Scheme 10 Palladium-catalyzed direct aromatic C–H fluorination

Scheme 11 γ-Arylation–Michael addition route to indolenine derivatives

Scheme 12 Palladium-catalyzed α-arylation of glycinate imines

Scheme 13 Copper-catalyzed enantioselective α-arylation to quaternary carbon derivatives
One-pot decarboxylative $\alpha$-arylation is feasible. Although implied in the concluding scope and limitations section, an example of large-scale application of copper-catalyzed direct $\alpha$-arylation in the pharmaceutical industry would have been valuable. The indication of literature coverage (to 2011) found in this chapter is a rare comment in this Science of Synthesis series.

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